# Safety and Efficacy of New Oral Anticoagulant Agents

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**ANCC Accredited NCPD Hours – 2 Hrs**

**Target Audience: RN/APRN**

## Need assessment

New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists. Their pharmacokinetic characteristics make prescribing complex. Thus it is imperative that Practitioners/ Nurses are aware of specific treatments so as to maximise their benefits and minimise their pitfalls. It is the responsibility of medical community 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.

## Objectives

- Enlist the indications for Oral anticoagulant therapy.
- Discuss the Pharmacological action and types of Novel Anticoagulants.
- Discuss the efficacy of new oral anticoagulants when compared with Warfarin
- Discuss the safety and efficacy facets of new oral coagulants in general
- Describe the safety concerns and clinical issues with evidences from Phase III clinical studies on NOACs

## Goals

The goal of this article is to summarize the available clinical trial evidence and a proposed approach regarding the safety and efficacy of new oral anticoagulants.

## Introduction

Oral anticoagulants are highly effective for stroke prevention in patients with atrial fibrillation, but strict adherence to medication is crucial for maximizing treatment benefits. There is hope that non–vitamin K antagonist oral anticoagulants (NOACs) may improve adherence, because of less burden of treatment compared with warfarin. This is uncertain, however, as warfarin users may incur lower out-of-pocket medication costs and have frequent contact with the healthcare system. Expected adherence to therapy is often an important consideration in clinical decision-making; data on adherence rates can help physicians and patients choose between medications. [1, Rank 3]

Although poor adherence is a barrier to effective stroke prevention, it can provide researchers with a window into the risk-benefit balance of the therapy. Given the well-established efficacy for anticoagulation in stroke prevention, it is unlikely that a clinical trial would randomize patients at increased stroke risk to no anticoagulation, but pharmacy-linked administrative data may provide a critical tool to assess outcomes among candidates for anticoagulation who are taking and those who are not taking therapy. In this way, studying variation in adherence may contribute to the evidence of safety and efficacy of oral anticoagulants. Because not all patients benefit equally and, in some, the risks of therapy may outweigh the potential benefits, examining the impact of nonadherence across the range of risk is important to help guide therapy, particularly among patients with anticipated low incidence of cardioembolism and potential for bleeding. [2, Rank 4]

## Indications for Anticoagulant Therapy

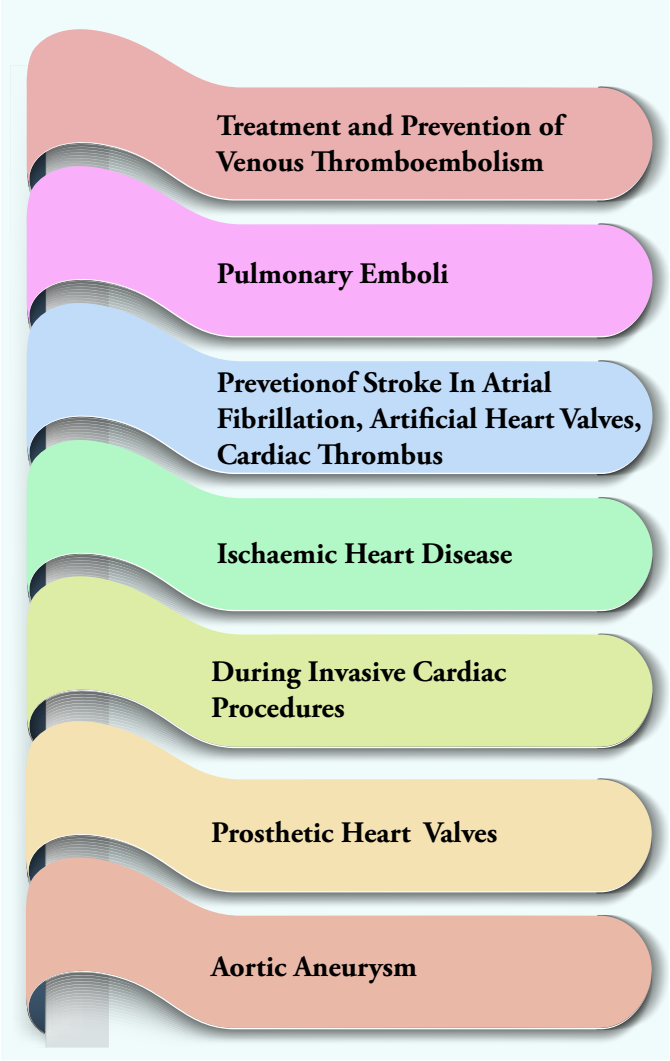


Figure 1: Anticoagulant therapy - Indications

## Venous Thromboembolism

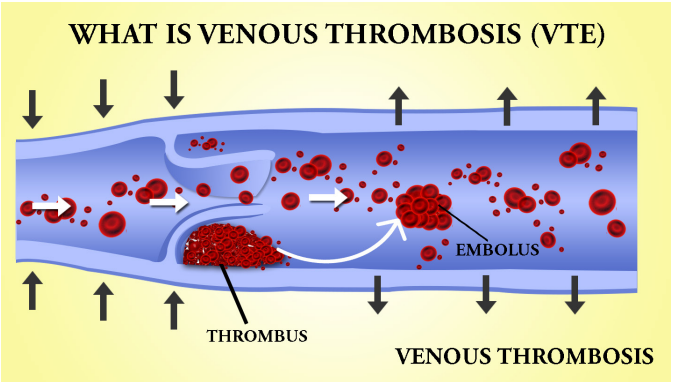


Figure 2: Venous Thromboembolism

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major healthcare concern that results in considerable long-term morbidity and mortality and affects more than 1.6 million individuals each year. Patients withsymptomatic Venous Thromboembolism have a high and persistent risk of recurrent events, including non-fatal and fatal PE. Estimates suggest a cumulative incidence of recurrent Venous Thromboembolism from 17.5 percent after 2 years of follow-up increasing to more than 30 percent after 8 years. [3, Rank 4]

Treatment with a NOAC (Novel Oral Anticoagulant Agents) would be an attractive alternative to either the standard vitamin K antagonist treatment or injection treatment, but it is unknown whether this therapy is effective and safe. [6, Rank 4]

> **"Standard treatment for venous thromboembolism has been the administration of heparin or low molecular heparin (LMWH), overlapped and followed by a vitamin K antagonist."**

The association of Venous Thromboembolism with cancer is well known and has been described in large cohort studies. Cancer combined with VTE is associated with a poor outcome in terms of recurrent thrombosis and survival. Despite vitamin K antagonist (VKA) therapy, cancer patients have twice as many relapses and 3 times as many bleeding cases as non-cancer patients in spite of careful treatment control with frequent INR measurements. Other challenges are the increased comorbidity, multi pharmacological treatment with potential interactions and the resulting difficulty in controlling INR, resulting in poor quality anticoagulation control, as reflected by reduced time in therapeutic range that has implications for the efficacy and safety of the vitamin K antagonist. In cancer patients, INRs may also be affected by nausea, for example in conjunction with chemotherapy. Furthermore, invasive procedures as part of the investigation or treatment of cancer, such as chemotherapy, increase the risk of complications and are likely to cause thrombocytopenia and other

serious side effects. This can lead to the need for delayed or reduced dosing in vitamin K antagonist therapy with implication of efficacy of the anti-thrombotic treatment. [4, Rank 5]

Standard regimen with heparin is effective but complex, especially in patients with cancer who are challenged by intensive surgical and medical therapy and by having periods of their disease characterized by changing appetite and food intake. To overcome some of these challenges, the first large multicentre, randomised, open-label clinical trial was performed to investigate whether LMWH (dalteparin) was more effective and safer than oral anticoagulant therapy in preventing recurrent venous thromboembolism in patients with cancer who have acute venous thromboembolism. This study showed that dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. Non-vitamin K antagonist oral anticoagulants (NOACs, previously referred to as new or novel oral anticoagulants) directed against factor Xa or thrombin overcome some limitations of standard therapy, including the need for injection and for regular dose adjustments on the basis of laboratory monitoring. The clinical trials investigating the effects of the NOAC's were not aimed at patients with Venous thromboembolism and cancer, although these patients were not excluded in the majority of the studies. [5, Rank 3]

## Anticoagulants: Pharmacological Action

The anticoagulant effect of warfarin results from the inhibition of the cyclic interconversion of vitamin K in the liver. The reduced form of vitamin K is necessary for the carboxylation of the terminal regions of the vitamin K proteins, factors II, VII, IX, and X. Without carboxylation, these vitamin K–dependent clotting factors do not become activated. Warfarin, similar in structure to vitamin K, interferes with the cyclic restoration of reduced levels of vitamin K. Therefore, warfarin indirectly reduces the synthesis of these clotting factors. The anticoagulant effects of warfarin are delayed for several days after dosing changes, including therapy initiation. This is because of the variable half-lives of previously formed circulating clotting factors. Carboxylation inhibition can also result in a paradoxical increased risk of clotting when warfarin is initiated because of decreased levels of the vitamin K–dependent anticoagulant proteins C and S.

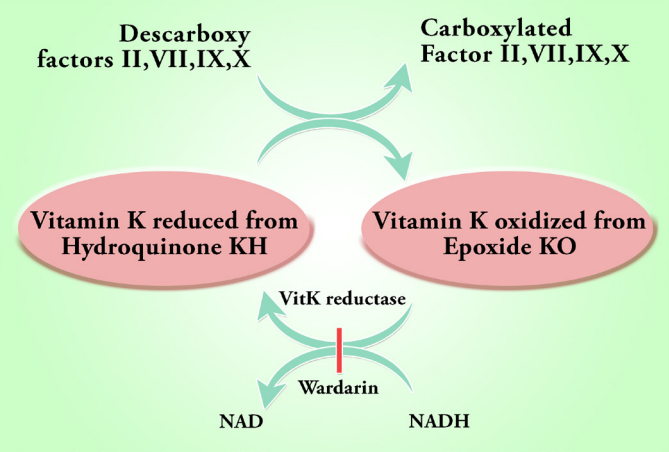


Figure 3: Action of Warfarin

**Novel Oral Anti-Coagulants (NOAC)**

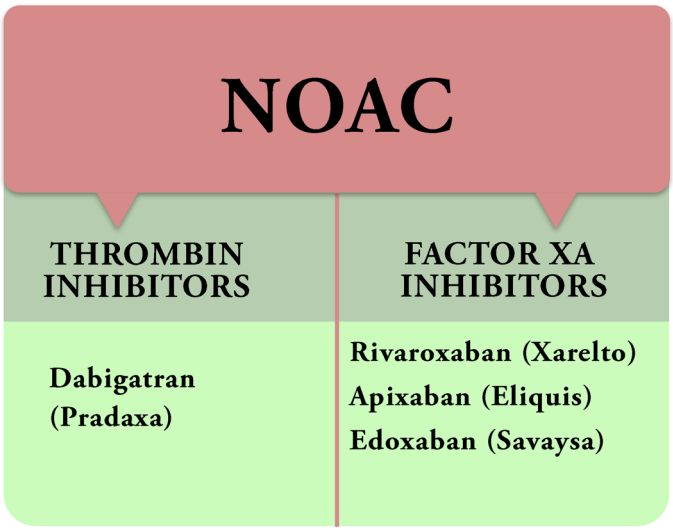


Figure 4: Classification of NOAC

Historically, vitamin K antagonists (VKAs; eg, warfarin) have been the standard of care and only oral option. Many limitations are associated with warfarin despite its widespread use. Warfarin has a narrow therapeutic window, requires frequent laboratory monitoring, and is affected by diet, genetics, and illnesses. Medications that do not require frequent monitoring and have

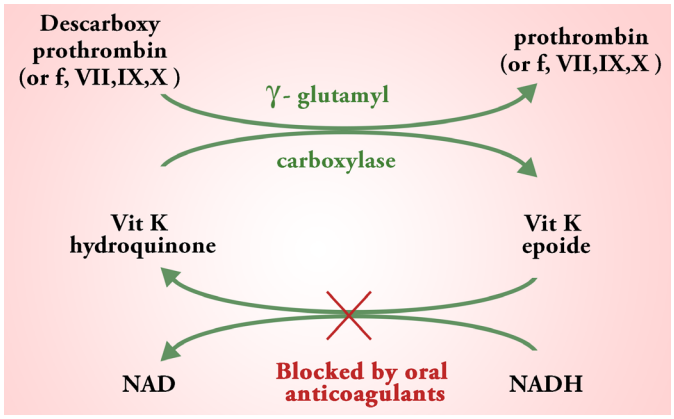


Figure 5: Action of Oral Anticoagulants

less inter- and intra-patient variability could offer great potential. Novel oral anticoagulants (NOACs) are relatively new medications that offer many of these potential benefits.

The 2 classes of NOACs are direct thrombin inhibitors and direct factor Xa inhibitors. Dabigatran (Pradaxa) is currently the only direct thrombin inhibitor and was the first NOAC approved in 2010. Factor Xa inhibitors include rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa).

## Pharmacology

The coagulation pathway is a cascade of events that leads to hemostasis. The coagulation cascade is an intricate pathway controlled by many factors. Inhibiting one element can turn off the entire process. The last steps of the coagulation pathway involve converting prothrombin to thrombin via prothrombinase and factor Xa

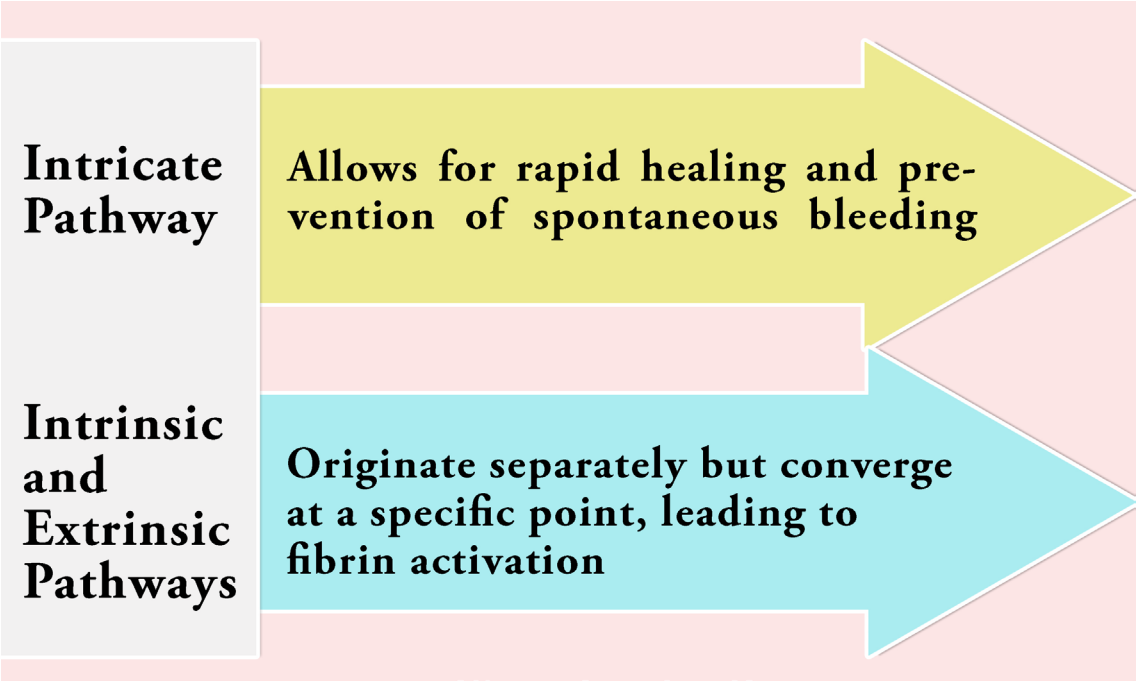


Figure 6: Coagulation Pathway

Thrombin then converts fibrinogen to fibrin, producing a clot. Direct factor Xa inhibitors reduce thrombin production by selectively inhibiting factor Xa and prothrombinase activity. Direct thrombin inhibitors, such as dabigatran, inhibit thrombin to prevent the formation of fibrin and the development of a clot.

## Therapeutic Use

Although nuances exist between specific medications, NOACs have overall similar indications such as to reduce the risk of stroke and systemic embolism (in nonvalvular atrial fibrillation) and to treat and prevent deep vein thrombosis and pulmonary embolism. The usual dosing and administration of each NOAC is less patient-specific than warfarin. Dabigatran 150 mg should be administered twice daily with a full glass of water. Rivaroxaban dosing varies based on indication, with a dose ranging from 10 to 20 mg and a frequency of once or twice daily. The 15- and 20-mg rivaroxaban tablets should be taken with food, although this is not a requirement for the 10-mg tablet. The apixaban dose and frequency varies based on indication, but ranges from 2.5 to 10 mg once or twice daily. Edoxaban is dosed at 60 mg once daily regardless of indication. Dosage adjustments for specific creatinine clearance or drug interaction are given in the package inserts.

The purpose is to ultimately stabilize the platelet plug with a fibrin mesh. Individual factors and interactions were

classified using the well-characterized extrinsic or intrinsic pathways. Transport reactions should be taken into account the blood flow and then only a coagulation model would more closely related to the physiological in vivo setting. [13, Rank 3]

The extrinsic core of a coagulation model covers all relevant interactions and factors, from the triggering of the cascade by Tissue Factor, to Factor II (Prothrombin) activation and Factor II a (thrombin) formation. The Prothrombin Time test best assesses coagulation activity in the extrinsic pathway. The intrinsic pathway consists of all relevant interactions and factors leading from Factor XII a to Factor X a. The aPTT test best assesses coagulation activity in the intrinsic pathway. [14, Rank 5]

A feedback loop for the activation of Factor XI and a reaction representing the cleavage of fibrinogen and kinetic data were added to the original model to define two independent thresholds for thrombus formation – one based on Factor II a and the other on the fibrinogen cleavage product named 'I a' in the model and being used as a representation of fibrin formation concentration, respectively. [15, Rank 3]

The protein C/S (endothelial protein C receptor system) and the coagulation factor adsorption reactions to lipids were developed. The species 'Phospho Lipid' represents protein-binding sites on phospholipid vesicles. Additional coagulation factor inhibition reactions were introduced based on published rate constants. [16, Rank 5]

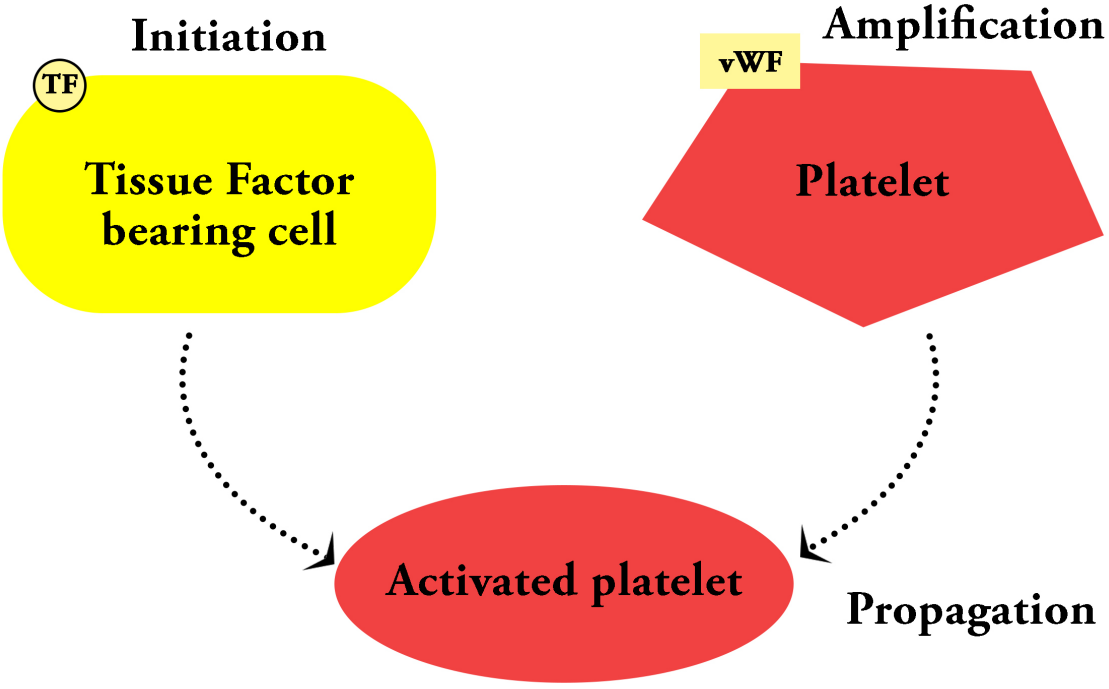


Figure 7: Coagulation: Factors

# Efficacy Facets of Oral Anticoagulant Therapy

## Anticoagulation Activity Measurement and Bleeding Management

Conventional anticoagulants require frequent clinic visits and subsequent dose adjustments to monitor and control anticoagulation intensity. Owing to their wide therapeutic window and predictable pharmacokinetic profile, such monitoring is not usually required with direct Oral Anticoagulants, and this can alleviate the excessive burden that regular clinic appointments can represent. However, this frequent monitoring can provide reassurance to both patient and physician and is therefore not always considered to be an inconvenience. Without the need to attend warfarin clinics, regular reviews should be considered to provide a means to reassure patients and to ensure that physicians are able to follow their clinical progress. This is particularly important in patients with comorbidities or those undergoing neuraxial anaesthesia (in which there is an increased risk of developing haematoma) and is already a recommendation in patients with renal insufficiency.

`In hospitals that are equipped with appropriate facilities, laboratory measurement of direct Oral Anticoagulants plasma concentration may be appropriate in certain situations. Examples include confirmation of compliance, suspected overdose, cases of life-threatening bleeding or cases in which imminent surgery is required. Clinically relevant drug–drug interactions can also alter bleeding risk and should be taken into account; however, known drug–drug interactions are rare for these agents.

Although there are no well-established methods of measuring the anticoagulant activity of direct Oral Anticoagulants (the INR is not a valid measure), alternative options have been studied. As a result of the direct linear relationship of anti-Factor Xa activity with apixaban plasma concentration, the Rotachrom Heparin chromogenic assay has been suggested for the indirect measurement of apixaban levels. Rivaroxaban has been measured over a wide range of plasma concentrations with appropriate calibrators and controls using a chromogenic Factor Xa assay. Plasma concentrations of dabigatran can be quantified using the HEMOCLOT dilute thrombin time assay. [23, Rank 3]

The half-life of direct Oral Anticoagulants is much shorter than that of traditional anticoagulants, such as Vitamin K

antagonists, but physicians remain concerned about the lack of specific reversal agents for the direct Oral Anticoagulants to be used when, for example, a patient is bleeding. However, a universal Factor Xa inhibitor antidote and neutralising fragment antibodies are in development. When an overdose is suspected, administration of activated charcoal may be considered. In cases of mild or local bleeding, the next dose should be delayed or treatment discontinued as appropriate, and local compression is suggested. In cases of severe or life-threatening bleeding, administration of blood products is also recommended. If bleeding cannot be controlled by these measures, administration of specific procoagulant reversal agents (prothrombin complex concentrate (PCC), activated PCC or recombinant Factor VIIa) should be considered. These suggestions are based on minimal clinical and non-clinical data. [24, Rank 4]

## Vitamin K Antagonist Control

Management of the International Normalized Ratio (INR) can be problematic. The European Society of Cardiology suggests a time in therapeutic range (TTR) for the INR (usually 2.0–3.0) of 70% as the minimum threshold that constitutes good management of patients with Atrial Fibrillation. Data from real-life practice suggest that this level of control is not achieved in many patients. Two possible reasons for suboptimal time in therapeutic range are poor patient adherence and/or the patient's INR being affected by concomitant medications, drug–food interactions or genetic polymorphisms. Patients who fall into these categories therefore represent groups that could benefit from fixed-dose therapy with the direct oral anti-coagulants.

Pivotal international phase III trials comparing Direct Oral Anticoagulants versus warfarin in patients with AF was done in groups of ROCKET (Rivaroxaban), RE LY (Dabigatran), Aristotle (Apixaban), ENGAGE AF TIMI (Edoxaban). Skjoth and colleagues compared the efficacy and safety end points of 4 clinical trials (ENGAGE-AF, RE-LY, ROCKET-AF, and ARISTOTLE) comparing NOACs with warfarin. Compared with edoxaban (60 mg), apixaban was similar in efficacy but was associated with lower clinically relevant or major bleeding (HR 0.79; 95% CI, 0.70-0.90). In trials of the direct oral anti-coagulants for the prevention of arrhythmia related stroke and for the treatment and secondary prevention of venous thrombo embolism, patients receiving warfarin had a mean time in therapeutic range between 55% (ROCKET AF) and 65% (RE-MEDY). In subanalyses of the RE-LY

and ARISTOLE trials in patients with AF, it was found that the overall profiles of dabigatran and apixaban were consistent against warfarin regardless of time in therapeutic range. However, the composite outcome of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death and major bleeding favoured dabigatran when the time in therapeutic range was ≤57%, but above this level, the composite outcome was not significantly different between dabigatran and warfarin. Similarly, the composite of stroke/ SE, all-cause death and major bleeding favoured apixaban for time in therapeutic range <60.5%, but for higher time in therapeutic ranges, apixaban was not significantly different from warfarin. These data may provide a guidance time in therapeutic range threshold below which patients receiving VKA could be switched to dabigatran or apixaban. [17, Rank 5]

## Direct Oral Anticoagulants

The pharmacokinetic profiles of direct oral anti-coagulants influence dose and regimen. Peak plasma concentrations of the direct OACs are reached within 4 h of oral administration, which is considerably quicker than among the VKA-based therapies. The half-lives of the direct Oral anti-coagulants range from 5 to 15 h; however, in renally impaired patients, slower elimination can affect drug exposure. Approximately one-third of an orally absorbed rivaroxaban dose is eliminated unchanged in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and the faeces. Apixaban has multiple elimination pathways, with approximately 27% of total clearance via renal excretion. Dabigatran is administered as an oral pro-drug that is converted into its active form in the liver; the majority (85%) of the unchanged drug is excreted by the kidneys. [18, Rank 4]

Although limitations exist, indirect comparisons can be helpful in determining differences between new Oral anti-coagulants. Dabigatran demonstrated greater efficacy than edoxaban, although it was also associated with more "other location bleeding." There was no difference between edoxaban and rivaroxaban in regard to efficacy or mortality, but rivaroxaban was associated with more major or clinically relevant bleeding.

## Comparative Efficacy

A lack of direct head-to-head trials makes it difficult to compare the efficacy and safety of Novel oral antocoagulants. However, clinical trials used for the basis of approval were similar, and each study was a

multinational non-inferiority study comparing the medication to warfarin (dosed to a target international normalized ratio of 2:3) and using a primary composite end point of the occurrence of first stroke or systemic embolic event. Although non-inferiority margins varied between studies, each new medication significantly demonstrated non-inferiority to warfarin. Each study also examined the safety of each new medication compared with warfarin, specifically addressing various bleeding risks.

## Novel Oral Anticoagulants versus Warfarin

Large phase III trials for stroke prevention in patients with non-valvular AF have been completed for dabigatran (RE-LY), rivaroxaban (ROCKET AF), apixaban (ARISTOTLE and AVERROES), and edoxaban (ENGAGE AF-TIMI 48). Results from all trials point to an efficacy similar or superior to warfarin or ASA (Acetylsalicylic acid).

Dabigatran, rivaroxaban, apixaban, and edoxaban all demonstrated non-inferiority to warfarin with respect to the primary efficacy endpoint, the composite of stroke and systemic embolism. Dabigatran 150 mg twice daily (bid) and apixaban 5 mg bid also demonstrated superiority to warfarin for the primary efficacy endpoint in the intention-to-treat (ITT) population (hazard ratios [HRs], 0.65 and 0.79, respectively). Rivaroxaban 20 mg once daily (od) was superior to warfarin while patients were receiving treatment (HR, 0.79; p = 0.02) and was non-inferior in the ITT analysis, which included events occurring after early discontinuation of the study drugs. For edoxaban, a modified ITT analysis, including all patients receiving at least one dose of the drug, showed that both the 30 mg and 60 mg od regimens of edoxaban were non-inferior for the primary efficacy endpoint compared with well-managed warfarin (median time in therapeutic range = 68.4 % of the treatment period) (p for non-inferiority=0.005andp<0.001, respectively). Overall, for the prevention of ischemic stroke, only dabigatran 150 mg bid was superior to warfarin. All agents significantly reduced rates of hemorrhagic stroke relative to warfarin. [27, Rank 3]

AVERROES, the superiority phase III trial of apixaban versus ASA in patients considered 'unsuitable' for VKAs, demonstrated that apixaban is an effective alternative to ASA. AVERROES was stopped after 1.1 years of follow-up because of the clear superiority of apixaban over ASA for the primary endpoint,with similar rates of major bleeding (including intracranial hemorrhage [ICH]). The benefit–risk

profile of apixaban versus ASA, as demonstrated in the AVERROES trial, reinforces the latest guideline recommendations that ASA should no longer be considered a suitable alternative to OACs for stroke prevention in the majority of patients with non-valvular AF.

One in four patients who experience an AF-related stroke die within 30 days of the index event. VKA treatment reduces overall mortality by 26 % relative to placebo, and it is notable that all NOACs tested in phase III trials also demonstrated a strong trend towards reduced all-cause mortality in the ITT population compared with warfarin; this was statistically significant only for apixaban versus warfarin (HR, 0.89; p = 0.047) and was close to statistical significance for the 150 mg bid dose of dabigatran (relative risk, 0.88; p = 0.051).

A meta-analysis of all 71,683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials found that allocation to a NOAC significantly reduced the composite of stroke or systemic embolism by 19 % compared with patients receiving warfarin. This overall reduction was largely driven by the 51 % reduction in the incidence of hemorrhagic stroke among patients treated with a NOAC. Compared with warfarin, NOACs were also associated with a significant 10 % reduction in all-cause mortality. [28, Rank 5]

Other than edoxaban 30 mg, the remaining New Oral Anticoagulants demonstrated numerically lower hazards of stroke or systemic embolism, and any stroke compared with warfarin. It reached statistical significance for apixaban and dabigatran 150mg in prevention of stroke or systemic embolism and any stroke, whereas edoxaban 60mg only in stroke or systemic embolism. All Novel Oral Anticoagulants were associated with a significant reduction in the risk of hemorrhagic stroke. Compared with warfarin, dabigatran 150 mg could significantly reduce the risk of ischemic stroke, whereas edoxaban 30mg could significantly increase the risk of ischemic stroke. Dabigatran 150mg and apixaban could significantly reduce the risk of disabling and fatal stroke. All-cause mortality was numerically reduced by all Novel Oral Anticoagulants, especially by apixaban and edoxaban 30mg. Only dabigatran 150 mg could increase the risk of myocardial infarction significantly. Concerning the safety results, apixaban, dabigatran110mg, and both doses of edoxaban exhibited lower rates of major bleeding and any bleeding compared with warfarin. A significantly lower hazard for dabigatran 150mg in any bleeding was also observed. All Novel Oral

Anticoagulants demonstrated significant reductions in Intracerebral hemorrhage compared with warfarin. Dabigatran 150 mg, rivaroxaban, and edoxaban 60 mg were associated with significantly increased gastrointestinal bleeding; however, edoxaban 30 mg was the opposite. [7, Rank 2]

## Indirect Comparison among Novel Oral Anticoagulants

Compared with dabigatran 150 mg, rivaroxaban showed significantly higher hazards of stroke or systemic embolism, any stroke, and hemorrhagic stroke. The hazards of stroke or systemic embolism, any stroke, ischemic stroke, and disabling or fatal stroke were significantly higher for edoxaban 30 mg compared with dabigatran 150 mg. A similar pattern in any stroke was observed for edoxaban 60 mg compared with dabigatran 150 mg. There were significantly higher risks of stroke or systemic embolism, any stroke, ischemic stroke, and disabling or fatal stroke for edoxaban 30 mg compared with apixaban. A similar pattern, with the exception of stroke or systemic embolism, was seen in the comparison of edoxaban 30 mg and rivaroxaban. The results of efficacy achieved no statistical significance for edoxaban 60 mg compared withapixaban, rivaroxaban, and dabigatran 110 mg, respectively. Edoxaban 60 mg had significantly lower risks of stroke or systemic embolism, any stroke, and ischemic stroke, than edoxaban 30 mg. [8, Rank 1]

> **"The function of the coagulation pathway is to keep hemostasis. Primary hemostasis is an aggregation of platelets forming a plug at the damaged site of exposed endothelial cells. Secondary hemostasis includes the two main coagulation pathways, intrinsic and extrinsic, that meet up at a point to form the common pathway. The common pathway ultimately activates fibrinogen into fibrin. These fibrin subunits have an affinity for each other and combine into fibrin strands that bind the platelets together, stabilizing the platelet plug."**

Lower risks of stroke or systemic embolism, any stroke, and ischemic stroke were observed in dabigatran 150 mg compared with dabigatran 110 mg. Apixaban, rivaroxaban, and edoxaban 60 mg could significantly reduce the risk of MI compared with dabigatran 150 mg. Regarding the bleeding outcomes, the hazards of major bleeding, gastrointestinal bleeding, and any bleeding were significantly higher for rivaroxaban vs.

apixaban and edoxaban 30mg. A similar pattern was observed for both doses of dabigatran vs. edoxaban 30mg and for dabigatran 150mg vs. apixaban. The hazards of major bleeding, ICH, and any bleeding were significantly higher for rivaroxaban vs. dabigatran 110mg. The hazards of major bleeding were significantly lower for edoxaban 30mg than apixaban, and similar results were observed in edoxaban 60mg vs. rivaroxaban. The hazard of ICH was significantly lower for edoxaban 30mg than for rivaroxaban. The hazard of any bleeding was significantly higher for edoxaban 60mg than for dabigatran 110mg, and similar results were observed in rivaroxaban vs. dabigatran 150mg, edoxaban 60mg vs. apixaban, and rivaroxaban vs. edoxaban 60 mg. The hazards of major bleeding, gastrointestinal bleeding, and any bleeding were significantly higher for edoxaban 60mg than edoxaban 30mg; the hazard of any bleeding was significantly higher for dabigatran 150mg compared with dabigatran 110mg. [9, Rank 3]

## Safety and Efficacy of Novel Oral Anticoagulants

The results comparing Novel Oral Anticoagulants and warfarin from the current analysis were consistent with the direct ones and confirmed the findings from direct analysis. The application and development of anticoagulant drugs aim at seeking balances between hemorrhage and thrombosis, as higher efficacy in stroke prevention is related to higher risk of major bleeding events. Therefore, when researchers evaluated new treatments, both results of stroke prevention and bleeding had to be carefully considered, rather than estimating clinical efficacy in isolation. According to the results of the NMA, apixaban, edoxaban 60mg, and dabigatran 150mg were found to have significantly better efficacy in prevention of stroke or systemic embolism than warfarin. Similarly, apixaban, both doses of edoxaban, and dabigatran 110mg have significantly demonstrated lower hazards of major bleeding. [10, Rank 5]

Moreover, a meta-analysis including the four randomised control trials demonstrated similar results for the four Novel Oral Anticoagulants compared with warfarin, but there were no comparisons among Novel Oral Anticoagulants. Although an indirect comparison analysis among Novel Oral Anticoagulants has been recently published, it used the so-called Bucher method, which can only be used for testing with two arms. However, the Bayesian model used in the Network meta-analysis did not have such a limitation. Moreover, in the four

included trials, there were direct comparisons between two doses of dabigatran and edoxaban. Other early published Network meta-analyses only provided comparisons in the outcomes of stroke or systemic embolism and major bleeding. According to the results from indirect comparisons, edoxaban 60mg and apixaban were better than dabigatran 150mg and rivaroxaban in bleeding events, and were more favorable compared with dabigatran 110mg and edoxaban 30mg with respect to stroke prevention. Apixaban significantly revealed better results than edoxaban 60mg in any bleeding events. In conclusion, apixaban was considered to have an advantage over the other Novel Oral Anticoagulants in terms of safety. [11, Rank 3]

## Safety Concerns of New Oral Anticoagulants

All anticoagulants are associated with an increased risk of bleeding. There have been a number of case studies showing serious bleeding events associated with dabigatran use. However, in phase III studies, 30-day mortality after the first major bleeding event tended to be lower with dabigatran (9.1%) than with warfarin (13.0%; p=0.057). In an investigation of postmarketing reports, the risk of bleeding was found to be consistent to that reported in

> **"The Novel Oral Anticoagulants are effective alternatives to Vitamin K antagonists, and rivaroxaban, dabigatran, and apixaban are recommended by the European Society of Cardiology guidelines for the prevention of thromboembolism in patients with non-valvular Atrial Fibrillation and a CHA2DS2-VASc score of ≥1."**

RE-LY, when dabigatran was used according to recommendations. This highlights the importance of adhering to the recommended dose. However, bleeding may still cause anxiety to patients and be of concern to physicians. It is important to minimise the risk by advocating the proper use of anticoagulants within the hospital setting and understanding procedures for the optimal management of bleeding. Additionally, there is a need to consider the dosing of these drugs in certain patient populations, strategies for switching between anticoagulants and how to deal with emergency situations. [19, Rank 3]

Although all patients with atrial fibrillation are at an elevated risk of stroke, some groups are considered more difficult to treat than others. The typical patient with atrial fibrillation is elderly with multiple co-morbidities. These patients may be at higher risk of bleeding events than other

groups and may, therefore, be less likely to receive Vitamin K antagonists treatment, even if their stroke risk is also higher. [28, Rank 5]

***Elderly Patients***

Patients with Atrial Fibrillation who are elderly are at a higher risk of both thromboembolic and bleeding events during anticoagulation treatment, but when the risks of anticoagulation are weighed against the advantages, these patients gain the greatest net clinical benefit from treatment. Guidelines recommend anticoagulants over antiplatelet agents for elderly patients (≥75 years) because the thromboembolic efficacy of antiplatelet agents decreases with age.

In the phase III studies of Novel Oral Anticoagulants, 31–44 % of enrolled patients were aged ≥75 years. As expected, rates of ischemic and hemorrhagic events were numerically higher in older patients than in younger patients, regardless of the treatment arm. In general, the benefits of Novel Oral Anticoagulants in elderly patients were consistent with those observed in the overall study populations. In RE-LY, patients experienced similar rates of stroke/systemic embolism and intra cerebral haemorrhage, regardless of age category. There was a significant interaction between age and treatment ($p \leq 0.001$) for major bleeding with both dabigatran doses, although this was observed only for extracranial bleeding. Younger patients (<75 years) experienced fewer major bleeding events with dabigatran relative to warfarin, whereas elderly patients (≥75 years) experienced similar or increased rates of bleeding with dabigatran relative to warfarin. Owing to this increased risk of bleeding in the elderly population, the European Union Summary of Product Characteristics for dabigatran etexilate recommends a dose reduction to 110 mg bid in patients ≥80 years. In ROCKET AF, no significant interaction between age and treatment effect was observed for the primary efficacy endpoint, major bleeding, mortality, or intra cerebral haemorrhage. A small but significant interaction between age and treatment effect was, however, observed for clinically relevant non-major bleeding (rivaroxaban vs warfarin; patients aged ≥75 years, HR, 1.15; patients <75 years, HR, 0.94; interaction p=0.01). Nevertheless, no dose adjustment for age is recommended in patients receiving this drug.

In ARISTOTLE, no significant interaction between age and treatment effect was observed for the primary efficacy endpoint (stroke or systemic embolism) or principal safety outcome (major bleeding). Prespecified outcomes in ARISTOTLE were investigated in relation to age in a separate analysis, demonstrating that apixaban

was effective and well tolerated across all age groups (<65 years, 65 to <75 years, and ≥75 years), including patients ≥80 years (13 %). As per the study design for ARISTOTLE, the Summary of Product Characteristics for apixaban recommends a dose reduction to 2.5 mg bid in patients with at least two of the following risk factors: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. In the ENGAGE AF trial, the efficacy and safety of both doses of edoxaban compared with warfarin were consistent across age groups (<65 years, 65 to <75 years, and ≥75 years); consequently, no dose adjustment of edoxaban is required on the basis of age alone. In summary, elderly patients may derive similar or even greater benefits from Novel Oral Anticoagulants compared with the general population [28, Rank 2]

***Renal Impairment***

Chronic renal disease is present in 10–15 % of patients with AF (Atrial Fibrillation) and may increase the risk of AF-related cardiovascular complications. Clinical guidelines recommend baseline and subsequent regular assessments of renal function in patients after initiation of Novel Oral Anticoagulants. Phase III trials of Novel Oral Anticoagulants included 17–21 % of patients with moderate renal impairment (creatinine clearance [CrCl] 30–49 mL/min), but excluded patients with severe renal impairment (CrCl <30 mL/min for RE-LYROCKET AF, and ENGAGE AF; CrCl <25 mL/min for ARISTOTLE and AVERROES). There was no dose adjustment in RE-LY, and patients were randomized to either the dabigatran 110 mg or 150 mg bid doses. ROCKET AF prespecified a reduced dose for patients with moderate renal impairment (rivaroxaban 15 mg od), whereas in ARISTOTLE, patients with renal impairment (serum creatinine ≥ 1.5 mg/dL) received a reduced dose (apixaban 2.5 mg bid) only when ≥1 additional factors were present (age ≥80 years or body weight ≤60 kg). In ENGAGE AF, patients were randomized to either edoxaban 30 mg od or 60 mg od, and the edoxaban dose was subsequently halved in patients with an estimated CrCl of 30–50 mL/min at randomization or at any time during the study. Patients with moderate renal impairment experienced numerically higher rates of ischemic and hemorrhagic events than patients with normal renal function, regardless of treatment. In the RE-LY, ROCKET AF, and ARISTOTLE trials no significant interactions between renal function and treatment effect were observed for stroke/systemic embolism prevention. However, in ENGAGE AF, patients with CrCl >95 mL/min receiving edoxaban 60 mg od experienced twofold higher rates of ischemic stroke than those

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receiving warfarin; consequently, the US Prescribing Information states that edoxaban should not be used in patients with CrCl >95 mL/min and, according to the European Summary of Product Characteristics, edoxaban should only be used in patients with a high CrCl after careful evaluation of thromboembolic and bleeding risks. [25, Rank 3]

In RE-LY, no statistically significant interaction between treatment and renal function (calculated using the Cockcroft–Gault Formula) was observed for major bleeding; however, when renal function was calculated using either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or the Modification of Diet in Renal Disease (MDRD) equation, significant interactions were observed: patients with high renal function (glomerular filtration rate ≥80 mL/min) experienced a greater relative reduction in major bleeding with either dabigatran dose compared with warfarin. In ROCKET AF, no significant effects of renal function were observed for the principal safety outcome (interaction p = 0.45) or major bleeding (interaction p=0.48). Fatal bleeding rates were also significantly lower in patients receiving rivaroxaban versus warfarin irrespective of renal function. In ARISTOTLE, there was a greater reduction in major bleeding with apixaban compared with warfarin among patients with moderate or severe renal impairment (CrCl 25–49 mL/min) versus mild (CrCl 50–79 mL/min) or no renal impairment (p=0.03 for interaction).

Among the NOACs, renal excretion of the active unchanged drug ranges from 27 % to 85 %. Because of decreased clearance and elevated plasma levels in patients with renal impairment, dabigatran is contraindicated in patients with creatinine clearance <30 mL/min in the European Union. In 2010, the US Food and Drug Administration (FDA) approved dabigatran for the prevention of stroke and systemic embolism in patients with AF in two doses: 150 mg bid and, for patients with creatinine clearance 15–30 mL/min, 75 mg bid. For rivaroxaban, the approved dose in patients with AF and moderate (creatinine clearance 30–49 mL/min) or severe (CrCl 15–29 mL/min) renal impairment is 15 mg od. The approved dose of edoxaban in patients with moderate or severe renal impairment is 30 mg od. However, data on new oral anticoagulants in patients with estimated creatinine clearance <30 mL/min are limited. For this reason, the latest ESC guidelines on AF recommend that none of the new oral anticoagulants are used in this group of patients and that renal function is regularly monitored in all other patients. Renal function should be assessed annually in patients within the normal creatinine

clearance range (≥80 mL/min) and in those with mild (creatinine clearance 50–79 mL/min) impairment, and perhaps 2–3 times per year in patients with moderate (i.e., creatinine clearance 30–49 mL/min) impairment. [22, Rank 4]

***Patients with Acute Coronary Syndrome (ACS)***

Antiplatelet therapy, including ASA (acetylsalicylic acid) and dual antiplatelet therapy (ASA plus clopidogrel/ prasugrel/ ticagrelor), is indicated in patients with a recent acute coronary syndrome (ACS). Approximately 15 % of patients with AF have concomitant Acute Coronary Syndrome. Standard antithrombotic therapy in the year after an Acute Coronary Syndrome event currently comprises dual antiplatelet therapy (ASA plus a P2Y12 inhibitor), so patients with AF who have experienced an Acute Coronary Syndrome event have indications for both anticoagulant and antiplatelet therapy. Because the addition of antiplatelets to VKA therapy increases the risk of bleeding, safer options are needed for patients with concomitant AF and Acute Coronary Syndrome. Although no clinical trial data are currently available to inform real-world practice with Novel Oral Anticoagulants in this population, three studies, PIONEER AF-PCI, REDU-AL-PCI, and AUGUSTUS, are currently underway. PIONEER AF-PCI is an exploratory, open-label, randomized, multicenter clinical study assessing the safety of two rivaroxaban strategies compared with Vitamin K Antagonist therapy in patients with AF who have undergone percutaneous coronary intervention with stent placement for Acute Coronary Syndrome. REDU-AL-PCI is a randomized, open-label, blinded endpoint study currently recruiting patients with atrial fibrillation who have undergone percutaneous coronary intervention with stenting, to assess the efficacy and safety of two strategies of dabigatran therapy compared with Vitamin K Antagonist therapy. Lastly, AUGUSTUS, a randomized, open-label study with a 2×2 factorial design, is investigating the efficacy and safety of apixaban versus Vitamin K antagonists and ASA therapy versus ASA placebo in patients with non-valvular AF who have undergone percutaneous coronary intervention with stent placement in the previous 14 days; all patients will also receive a P2Y12 inhibitor. [24, Rank 3]

The relative benefit of dabigatran 110 mg bid versus warfarin for stroke/systemic embolism prevention was not affected by concomitant antiplatelet therapy; however, a trend was observed for reduced efficacy with dabigatran 150 mg bid compared with warfarin (HR, 0.52 vs HR, 0.80; interaction p=0.058). The relative efficacy of rivaroxaban and apixaban versus

warfarin for prevention of stroke/systemic embolism was not affected by concomitant acetylsalicylic acid therapy; likewise, concomitant antiplatelet therapy did not influence the relative efficacy of edoxaban versus warfarin. As expected, in all four trials, concomitant treatment with a Novel Oral Anticoagulants and antiplatelet therapy was associated with an increased incidence of bleeding events; however, there was no evidence of heterogeneity of safety outcomes between any of the Novel Oral Anticoagulants versus warfarin. [24, Rank 4]

## Phase III Clinical Studies: Results and Recommendations

Large Phase III studies have investigated the efficacy and safety of apixaban, dabigatran, edoxaban, and rivaroxaban, compared with warfarin or ASA, in patients with nonvalvular AF. [24, Rank 3]

In the studies comparing the direct oral anticoagulants with warfarin, high-dose dabigatran (150 mg twice daily [bid]), and apixaban were shown to be superior to warfarin for the prevention of stroke and systemic embolism in the intention-to-treat population; in this setting, rivaroxaban, low-dose dabigatran (110 mg bid), and both doses of edoxaban (60 mg once daily [od] and 30 mg od) were shown to be noninferior to warfarin. The AVERROES study was terminated early

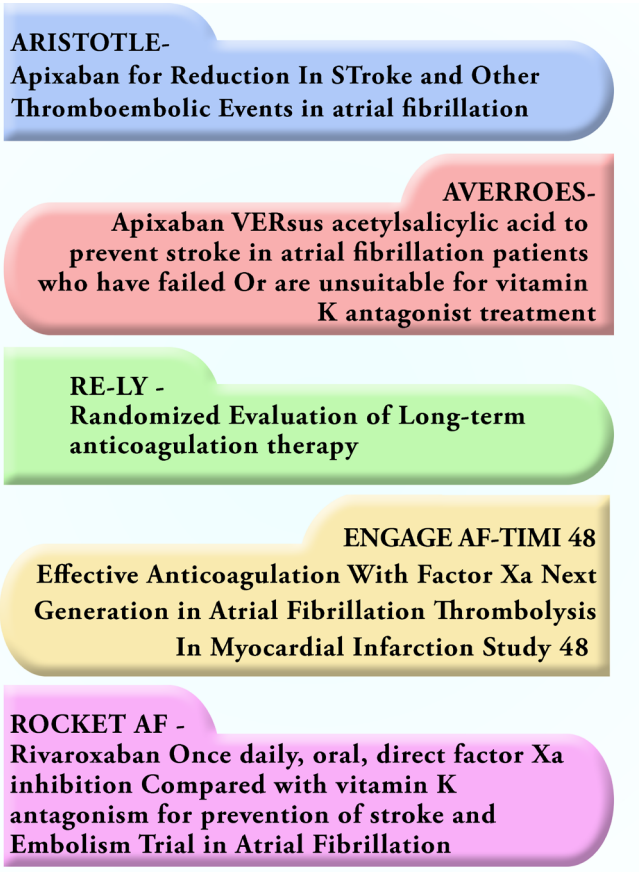


Figure 8: Phase III Clinical Studies on NOACs

owing to a clear benefit of apixaban over ASA for the prevention of stroke and systemic embolism. [20, Rank 5]

Different major bleeding definitions were used in the Phase III clinical studies of the direct oral anticoagulants, and enrolled patients had different baseline bleeding risks. Nonetheless, the direct oral anticoagulants were associated with a similar or lower incidence of major bleeding compared with warfarin or aspirin. The risk of intracranial hemorrhage was 33%–70% lower in patients treated with a direct oral anticoagulant than in those treated with warfarin. Fatal bleeding rates were also lower in patients treated with

apixaban, rivaroxaban, edoxaban, and low-dose (110 mg bid) dabigatran compared with patients treated with warfarin; similar rates of fatal bleeding were seen in patients treated with high-dose (150 mg bid) dabigatran. In the AVERROES study comparing apixaban with ASA, rates of ICH and fatal bleeding were comparable in both treatment groups.

The incidence of major gastrointestinal (GI) bleeding varied with the use of the different direct oral anticoagulants. Compared with warfarin, a lower incidence of major GI bleeding was observed in the low-dose (30 mg od) edoxaban group; a similar incidence was observed in the apixaban and low-dose dabigatran (110 mg bid) groups; and a higher incidence was observed in patients treated with high-dose (150 mg bid) dabigatran, rivaroxaban, or high-dose edoxaban (60 mg od). Similar rates of major GI bleeding were observed between patients treated with apixaban and acetyl salicylic acid.

Non-bleeding-related adverse events occurred at a similar rate in direct oral anticoagulant-treated and warfarin-treated patients in the ROCKET AF, ARISTOTLE, and ENGAGE studies. In the RE-LY study, a significantly greater incidence of dyspepsia was observed in dabigatran-treated patients compared with warfarin-treated patients; rates of other non-bleeding-related adverse events were similar in the two treatment groups. [17, Rank 3]

***Dabigatran***

The efficacy and safety of the direct thrombin inhibitor, dabigatran (150 mg twice daily and 110 mg twice daily) were investigated in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. The approved dosages of dabigatran vary between markets; the FDA-approved dose is 150 mg (75 mg in patients with severe renal impairment), while both the 150 mg and 110 mg doses are approved in Europe. Dabigatran 150 mg twice daily was superior to warfarin ($P<0.001$) for reduction of the risk of stroke or systemic embolism, with a similar risk of major bleeding between groups ($P=0.31$). The dabigatran 110 mg twice daily dosage was noninferior to warfarin in reducing the risk of stroke or systemic embolism ($P<0.001$), with a significantly lower risk of major bleeding ($P=0.003$). The risk of ischemic stroke was significantly lower with dabigatran 150 mg than with warfarin (relative risk 0.76, 95% confidence interval [CI] 0.60–0.98; $P=0.03$), but was similar in both groups when dabigatran 110 mg was compared with warfarin (relative risk 1.11, 95% CI 0.89–1.40; $P=0.35$). Compared with warfarin, the risk of intracranial hemorrhage was lower ($P<0.001$) for both

dabigatran doses. The risk of gastrointestinal bleeding was higher with dabigatran 150 mg twice daily than with warfarin (P<0.001), but was similar in the dabigatran 110 mg twice daily and warfarin groups (P=0.43). There was a nonsignificant trend toward reduced risk of mortality with dabigatran 150 mg versus warfarin (P=0.051); however, this trend did not occur with the dabigatran 110 mg twice daily dosage (P=0.13). The only adverse event significantly more common with dabigatran than with warfarin was dyspepsia (11.8%, 11.3%, and 5.8% for the dabigatran 110 mg, 150 mg, and warfarin groups, respectively). The risk of myocardial infarction (MI) was higher with dabigatran than with warfarin, but was not statistically significant for either comparison (P=0.09 and P=0.12, respectively, for the 110 mg and 150 mg twice daily dosages). A meta-analysis of seven dabigatran trials across indications also found a nonsignificant increase in the risk of MI or acute coronary syndrome (27% higher in dabigatran-treated patients; P=0.05). Another analysis of the RE-LY data found no statistically significant differences in event rates with either dabigatran dosage versus warfarin when using aggregated cardiac events (eg, MI as well as unstable angina, percutaneous coronary intervention, and cardiac arrest). [15, Rank 2]

***Rivaroxaban***

Rivaroxaban is an oral, direct Factor Xa inhibitor approved for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery and is in advanced clinical development for the treatment of thromboembolic disorders. Its mechanism of action is antithrombin independent and differs from that of other anticoagulants, such as warfarin - a vitamin K antagonist, enoxaparin (an indirect thrombin/Factor Xa inhibitor) and dabigatran (a direct thrombin inhibitor). A blood coagulation computer model has been developed, based on several published models and preclinical and clinical data. Unlike previous models, the current model takes into account both the intrinsic and extrinsic pathways of the coagulation cascade, and possesses some unique features, including a blood flow component and a portfolio of drug action mechanisms. Rather than reproducing known standard clinical measurements, such as the prothrombin time and activated partial thromboplastin time clotting tests, the anticoagulant benchmarking was based on a simulation of physiologically plausible clotting scenarios. Compared with warfarin, rivaroxaban showed a favourable sensitivity for tissue factor concentration inducing clotting, and a steep

concentration–effect relationship, rapidly flattening towards higher inhibitor concentrations, both suggesting a broad therapeutic window. The predicted dosing window is highly accordant with the final dose recommendation based upon extensive clinical studies. [12, Rank 4]

The efficacy and safety of the factor Xa inhibitor rivaroxaban were investigated in 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. Patients who were enrolled in ROCKET-AF were at a higher risk of stroke than those in RE-LY or ARISTOTLE (CHADS2 [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke, transient ischemic attack, or central nervous system thromboembolism {doubled}]; score 3.5 versus 2.1 in RE-LY and ARISTOTLE). A once-daily dose of rivaroxaban (20 mg) was used, with a dose reduction (15 mg) in patients with a creatinine clearance of 30–49 mL per minute. Rivaroxaban was noninferior to warfarin (P<0.001) for reduction in the risk of stroke or systemic embolism in the intent-to-treat population; however, superiority was not shown (P=0.12). The risk of major bleeding was similar in rivaroxaban-treated and warfarin-treated patients (P=0.58). The risk of intracranial hemorrhage was significantly lower with rivaroxaban, but the risk of gastrointestinal bleeding was significantly higher (P=0.02 and P<0.001, respectively). The risks of mortality and MI were not significantly different between groups (P=0.15 and P=0.12, respectively). [13, Rank 1]

***Apixaban***

The efficacy and safety of the factor Xa inhibitor apixaban were investigated in the AVERROES (Apixaban Versus Acetylsalicylic acid [ASA] to Prevent Strokes) and ARISTOTLE trials. In both Phase III trials for apixaban (5 mg twice daily), a reduced dose of 2.5 mg (twice daily) was used if patients met two of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL. It should be noted that only a limited number of patients received the lower apixaban dose (AVERROES, 6.0%; ARISTOTLE, 4.7%). In AVERROES, the risk of stroke or systemic embolism was significantly lower in the apixaban group than in the aspirin group (P<0.001 for superiority); however, the risk of major bleeding was comparable in the two groups (P=0.57).12 A trend toward lower risk of mortality was observed with apixaban (P=0.07), and the risks of intracranial hemorrhage and gastrointestinal bleeding were similar between groups (P=0.69 and P=0.71, respectively). In ARISTOTLE, the risk of stroke or systemic

embolism was significantly lower with apixaban than with warfarin (P<0.01 for superiority), and this reduction was primarily driven by a reduction in the risk of hemorrhagic stroke (hazard ratio [HR] 0.51, 95% CI 0.35–0.75; P<0.001). The risks of major bleeding (P<0.001), intracranial hemorrhage (P<0.001), and mortality (P=0.047) were significantly decreased with apixaban compared with warfarin. In AVERROES and ARISTOTLE, the risks of gastrointestinal bleeding (P=0.71 and P=0.37, respectively) and MI (P=0.37 and P=0.59, respectively) were similar with apixaban versus the two comparators. [14, Rank 2]

***Edoxaban***

The efficacy and safety of the factor Xa inhibitor edoxaban (60 mg and 30 mg once daily) were investigated in the ENGAGE AF-TIMI 48 trial (Edoxaban versus Warfarin in Patients with Atrial Fibrillation). The edoxaban dose was halved (30 mg and 15 mg once daily) if any of the following conditions were present at the time of randomization or at any point during the study: estimated creatinine clearance 30–50 mL per minute, body weight ≤60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors). A protocol amendment mandated similar dose modification in the event of concomitant dronedarone use. Both doses (60 mg and 30 mg) were found to be noninferior to warfarin for reduction in the risk of stroke or systemic embolism (modified intent-to-treat population, P<0.001 and P=0.005 for noninferiority, respectively; intent-to-treat population, P=0.08 and P=0.10 for superiority, respectively) and were associated with significantly lower risks of major bleeding (P<0.001 and P<0.001). The risk of all-cause mortality was significantly reduced with edoxaban 30 mg versus warfarin (P=0.006) but was similar in the edoxaban 60 mg and warfarin groups (P=0.08). The risk of major gastrointestinal bleeding was significantly higher with edoxaban 60 mg than with warfarin (P=0.03), but was lower with edoxaban 30 mg (P<0.001 versus warfarin). Edoxaban is not discussed further in this review, because neither dose has yet been approved by the Food and Drug Administration agency or European agencies. [13, Rank 3]

## Drug Adherence and Tolerability

Ease of administration influences patient adherence and outcomes, and an advantage of direct oral anticoagulants is that they are administered orally. This could help to reduce the length of hospitalisation, for example, when patients are treated for venous thromboembolism (VTE) and have no need for initial subcutaneous heparin

subanalysis of the EINSTEIN PE and EINSTEIN DVT trials, hospitalised patients who received initial treatment with rivaroxaban for deep vein thrombosis or PE had a significantly shorter length of stay compared with patients who received enoxaparin/VKA across regions and countries ($p<0.0001$ for both groups). Rivaroxaban can also be administered as a crushed tablet and given mixed with food or via a nasogastric tube in patients who struggle to swallow whole tablets; however, no similar studies have been performed for apixaban administration, and dabigatran capsules should not be crushed or chewed before swallowing. [20, Rank 2]

For long-term use, rivaroxaban is given once daily (for AF and long-term venous thromboembolism reatment), whereas other direct oral anticoagulants are given twice daily. Edoxaban, if approved, would also be given once daily in this indication. For many cardiovascular diseases, once-daily medication administration has been shown to be more convenient for patients, resulting in improved patient compliance and persistence. Once-daily dosing may confer further advantages in terms of outpatient management, patient outcomes and pharmacy management. However, the impact of a missed dose on pharmacological effect may be greater than for a drug dosed more frequently. Product packaging can also play a role in patient compliance. Dabigatran etexilate must be stored in airtight bottles to protect it from moisture and maintain its pH; this is a requirement for sufficient adsorption. Dabigatran administration may therefore be an issue for some elderly patients in whom compliance is improved by the use of dispensers, in which the other direct oral anticoagulants can be stored. [21, Rank 3]

Postsurgical venous thromboembolism prophylaxis requires only short-term anticoagulation, whereas patients with AF will often receive lifelong anticoagulant treatment. For venous thromboembolism treatment, however, the duration of anticoagulation must be considered carefully. The length of venous thromboembolism therapy was 3, 6 or 12 months in the EINSTEIN trials, 6 months in AMPLIFY and the RE-COVER studies, and 3–12 months in Hokusai- venous thromboembolism. Data from a study of patients receiving Oral Anticoagulant Agents therapy after a second venous thromboembolism suggest that indefinite treatment resulted in a lower rate of recurrence than treatment for 6 months; however, a higher risk of bleeding was also noted with extended treatment. The duration of therapy should therefore be individualised after assessment of the benefit–risk profile. Three months of anticoagulant treatment is recommended for acute

venous thromboembolism associated with reversible risk factors or in cases of unprovoked venous thromboembolism in which bleeding risk is high. In cases of unprovoked venous thromboembolism with low or moderate bleeding risk, or in patients suffering from active cancer (in which the risk of venous thromboembolism recurrence is threefold higher), extended therapy is recommended. [22, Rank 4]

Balancing stroke prevention against the risk of major or severe bleeding is complicated by the fact that several stroke risk factors (such as hypertension, prior stroke, and chronic renal dysfunction) are also bleeding risk factors. Vitamin K antagonists treatment increases the risk of intra-cerebral haemorrhage approximately twofold compared with acetylsalicylic acid (aspirin), but a key finding from all of the phase III trials was that the incidence of major bleeding events with new oral anticoagulation treatment was similar to or lower than with warfarin.

The principal safety outcome was major bleeding (RE-LY, ARISTOTLE, AVERROES, ENGAGE AF) or the composite of major bleeding and non-major clinically relevant bleeding (ROCKET AF). In RE-LY, dabigatran 150 mg bid demonstrated similar rates of major bleeding compared with warfarin, whereas dabigatran 110 mg bid demonstrated improved safety outcomes compared with warfarin, reducing rates of major bleeding by 20%. In ROCKET AF, the rates of major and non-major clinically relevant bleeding were similar in patients receiving rivaroxaban compared with those given warfarin. Apixaban demonstrated superiority in terms of primary safety outcomes compared with warfarin in the ARISTOTLE trial, reducing the rate of major bleeding by 31%. [29, Rank 3]

Not all patients with AF should be treated with Novel Oral Anticoagulant Agents for stroke prevention. Dabigatran, rivaroxaban, apixaban, and edoxaban are contraindicated in patients with active pathologic bleeding or with a lesion or condition considered to be a significant risk of major bleeding, e.g., gastrointestinal (GI) ulceration. GI bleeding accounts for approximately 90 % of major bleeding events in patients with AF receiving Vitamin K antagonists. Dabigatran 150 mg bid and rivaroxaban significantly increased rates of GI bleeding (1.5-fold) compared with warfarin in RE-LY and ROCKET AF, respectively. Apixaban was associated with GI bleeding rates that were similar to those with warfarin in ARISTOTLE ($p = 0.37$). GI bleeding also occurred more frequently with edoxaban 60 mg od than with warfarin in ENGAGE AF ($p=0.03$),although edoxaban 30 mg od demonstrated

significantly lower rates of GI bleeding compared with warfarin ($p<0.001$). A pooled analysis of phase III trials of the Novel Oral Anticoagulant Agents found that, compared with warfarin, Novel Oral Anticoagulant Agents were associated with a 25 % increase in the incidence of GI bleeding ($p = 0.04$).

The most devastating major bleeding complication associated with Vitamin K antagonists treatment is intra-cerebral haemorrhage; the annualized hospitalization rate for warfarin-associated intra-cerebral haemorrhage is approximately 0.5 %.Furthermore, the majority of warfarin-associated deaths are from intra-cerebral haemorrhage, and most intra-cerebral haemorrhage survivors have severe functional disability at discharge. Patients taking Novel Oral Anticoagulant Agents have a lower risk of intra-cerebral haemorrhage compared with those prescribed warfarin. In phase III studies, dabigatran, rivaroxaban, apixaban, and edoxaban all significantly reduced the rate of intra-cerebral haemorrhage (by 33–70 %) compared with warfarin. It is probable that the decrease in intra-cerebral haemorrhage contributed to reductions in fatal/life-threatening bleeding and to the overall trend towards reduced mortality. A meta-analysis demonstrated that, overall, Novel Oral Anticoagulant Agents reduced ICH by 52 % compared with warfarin ($p < 0.0001$) [30, Rank 1]

## Side Effects


Figure 9: Signs of Haemorrhage in NOAC clients

Novel Oral Anticoagulant Agents are usually well-tolerated with few side effects. The main side effect is bleeding, which can range from minor - slight bruising or occasional bleeding from the gums to serious bleeding - vomiting blood, blood in the stools/urine, or intracerebral haemorrhage

## Use of Co-medications with New Oral Anticoagulants

Patients requiring anticoagulant treatment often receive comedications to treat comorbidities, and patient exposure to direct Oral Anticoagulant Agents can be influenced by drugs that interfere with their metabolism. It is important for practitioners to be mindful of any interactions that may alter plasma concentrations of direct Oral Anticoagulant Agents; however, several widely used drugs have been demonstrated to have no interaction with these agents.

Apixaban and rivaroxaban are all substrates for cytochrome P450 (CYP) isoforms, such as CYP3A4, and for the cell efflux transporter P-glycoprotein (P-gp). Apixaban and rivaroxaban plasma concentrations have been shown to increase to a clinically relevant degree in the presence of ketoconazole and ritonavir, which are strong inhibitors of CYP3A4 and P-gp. In view of the associated increased risk of bleeding, concomitant treatment with systemic azole antimycotics or HIV protease inhibitors is not recommended. For apixaban or rivaroxaban, the concomitant use of less potent inhibitors of CYP3A4 and/or P-gp results in smaller increases in plasma concentrations that are not considered clinically relevant. CYP3A4 inducers should be administered with caution. Edoxaban elimination is only slightly dependent on CYP3A4 mechanisms and is mostly mediated by P-gp.

Dabigatran is not metabolised by Cytochrome enzymes but is dependent on P-gp transporters. Consequently, strong P-gp inhibitors are expected to increase dabigatran plasma concentrations, and dose adjustments and caution are therefore required for dabigatran with the use of P-gp inhibitors and inducers. Particular care is also needed in patients with renal impairment who are taking comedications, owing to the high dependence of dabigatran on renal elimination and consequent possible increases in exposure.

Caution is needed in the treatment of patients in whom direct Oral Anticoagulant Agents are administered concomitantly with antiplatelet regimens or non-steroidal anti-inflammatory drugs (NSAIDs), owing to these agents' influence on haemostasis and increased bleeding risk. Coadministration of these agents was allowed within certain limits in some studies. Data from the RECORD and EINSTEIN programmes

found that concomitant use of NSAIDs resulted in an increase in bleeding events with both rivaroxaban and enoxaparin. [22, Rank 5]

## Managing the Switch between Other Anticoagulants

Patients can be started on direct Oral Anticoagulants treatment immediately after diagnosis of the appropriate indication; therefore, switching from one anticoagulant to another is rarely required. For patients with a condition that is well controlled by Vitamin K Antagonist therapy, there is little reason to switch between anticoagulant treatments. However, situations may arise that call for switching medication. If a transition between treatments is required, it is important to adhere to product guidelines to maintain an optimal anticoagulant effect during transition.

For patients who are unable to maintain INR in the therapeutic range, it might be necessary or beneficial to switch to a direct Oral Anticoagulants. Switching from Vitamin K Antagonist to a direct Oral Anticoagulants is relatively simple; Vitamin K Antagonist therapy should be stopped and direct OAC therapy started when the INR reaches <2.0 for apixaban and dabigatran, and ≤2.5 for DVT and PE treatment and prevention of recurrence and ≤3.0 for stroke prevention, for rivaroxaban. When switching from a direct OAC to warfarin, coadministration of both drugs is required during the transition due to the slow onset of action of Vitamin K Antagonist: continue co-administration until the INR is ≥2.0. INR measurement is best performed at the time of trough direct oral anticoagulant drugs concentration (ie, immediately before the next dose is due) to minimise any interference by the direct oral anticoagulant drugs on the measurement.

Requirements for switching from direct oral anticoagulant drugs to a parenteral anticoagulant are rare. One example might be the diagnosis of cancer, for which the recommended antithrombotic treatment is Low molecular weight heparin. Parenteral anticoagulants should be started at the next scheduled dose of rivaroxaban or apixaban. In the case of dabigatran, the parenteral anticoagulant should be withheld until 12 h after the final dose of dabigatran was administered. For the conversion from a parenteral anticoagulant, the first dose of direct oral anticoagulant drugs should be administered 0–2 hour prior to the next scheduled dose of parenteral anticoagulant. In the case of continuously administered parenteral anticoagulants such as intravenous UFH (Unfractionated Heparin), the first dose of apixaban, dabigatran or rivaroxaban should be administered at the time

of discontinuation of parenteral anticoagulant treatment.

In clinical practice, it is rare to switch from one direct oral anticoagulant drugs to another. One review suggests that, when converting from one direct oral anticoagulant drugs to another, the new treatment should begin at the next scheduled dose; however, in certain circumstances, for example switching from rivaroxaban to dabigatran in patients with creatinine clearance 30–50 mL/min, rivaroxaban should be started 2–4 days after the final dose of dabigatran. [23, Rank 3]

## General Contraindications and Dose Adjustments with New Oral Anticoagulants

There are limited data on the use of direct Oral Anticoagulants in some patient populations. Currently, none of the direct oral anticoagulant drugs are approved for use in paediatric populations, pregnant individuals or those who are breastfeeding. For patients with cancer, the guidelines prefer Low Molecular Weight Heparin. The maintenance of sufficient anticoagulation by dose adjustment can be a challenge in some groups. For most cases in which direct oral anticoagulant drugs are administered, no dose adjustment is required. In certain cases—for example, in patients who have renal or hepatic insufficiency, elderly patients or those at higher risk of bleeding—dose adjustments are recommended. [23, Rank 4]

Apixaban and rivaroxaban are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Apixaban treatment is contraindicated in cases of severe hepatic impairment (eg, Child–Pugh class C), whereas cirrhotic patients with Child–Pugh class B or C should not be treated with rivaroxaban. A study of apixaban in healthy subjects or those with mild or moderate hepatic impairment (Child–Pugh class A and B) demonstrated similar anti-Factor Xa activity and International Normalized Ratio between the groups. Consequently, dose adjustment of apixaban is not necessary, but it should be used with caution in cases of mild-to-moderate hepatic impairment. Patients with liver disease were excluded from clinical trials of dabigatran; consequently, dabigatran use is contraindicated in cases in which hepatic impairment or liver disease is expected to have any impact on survival. [24, Rank 3]

Given that apixaban, dabigatran and rivaroxaban are all associated with some degree of renal clearance, impaired renal function can result in increased plasma concentrations. For long-term drug therapy, particularly in elderly patients (because

renal function declines with age), renal function and detection of chronic kidney disease should be determined before therapy is initiated. Additionally, recent practical guidelines on the use of new oral anticoagulant drugs in patients with non-valvular AF recommend 6-monthly monitoring of renal function in patients who have creatinine clearance (CrCl) 30–60 mL/min, are >75 years old or are fragile, and at 3-monthly intervals if the creatinine clearance is in the range 15–30 mL/min. Clinical studies of the direct oral anti- coagulants usually define renal function in terms of creatinine clearance (in mL/min). It is important to determine renal function using the Cockcroft–Gault formula, which provides a more accurate estimate of renal function compared with measuring plasma creatinine alone or relying on the estimated glomerular filtration rate reported by the laboratory, especially in patients with extreme weight and age characteristics. [25, Rank 3]

In clinical trials of direct oral anticoagulant drugs in stroke prevention, venous thrombo embolism and orthopaedic surgery, patients with creatinine clearance <30 mL/min were generally excluded. Patients with creatinine clearance <25 mL/min were excluded from ARISTOTLE. The direct oral anticoagulants are not recommended for patients with creatinine clearance <15 mL/min; for patients with severe renal insufficiency (creatinine clearance 15–29 mL/min), risk assessments by the physician are necessary. Dabigatran is not recommended in patients with severe renal insufficiency and apixaban is to be used with caution in these patients, whereas certain dose adjustments are required for rivaroxaban use in atrial fibrillation but not in venous thrombo embolism treatment. [26, Rank 5]

## Clinical Issues

Real-world experience and postmarketing data are providing additional insights into the use of new oral anti-coagulants in patients with nonvalvular AF. Since its approval in late 2010, reports have associated dabigatran with serious adverse events, particularly bleeding, most commonly in patients with low body weight, advanced age, or impaired renal function. The information from these reports is consistent with data from a RE-LY subanalysis that identified older age (≥75 years) and poor renal function as key predictors of bleeding events with dabigatran treatment. Subsequent investigations by the Food and Drug Administration and the European Medicines Agency's Committee for Medicinal Products for Human Use concluded that the bleeding risks were consistent with the bleeding rates reported in RE-LY, and

the dabigatran prescribing information recommends assessing patient renal function before beginning treatment and as clinically indicated thereafter. Furthermore, the Food and Drug Administration concluded in a Mini-Sentinel pilot analysis that observed bleeding rates associated with new use of dabigatran were lower than bleeding rates associated with new use of warfarin.

A larger study was conducted by the Food and Drug Administration to assess the efficacy and safety of dabigatran versus warfarin in 134,000 Medicare patients, aged 65 years or older, who had received a diagnosis of nonvalvular atrial fibrillation within the 6 months prior to the first dispensing of medication. The results showed that dabigatran (combined data for 150 mg and 75 mg dosages) was associated with a lower risk of ischemic stroke (adjusted HR 0.80, 95% CI 0.67–0.96), intracranial hemorrhage (HR 0.34, 95% CI 0.26–0.46), and death (HR 0.86, 95% CI 0.77–0.96) compared with warfarin. The investigators found that there were similar risks of stroke or systemic embolism and major bleeding with both doses (150 mg and 110 mg) of dabigatran and with warfarin, and that the risks of mortality, intracranial hemorrhage, pulmonary embolism, and myocardial infarction were all lower in dabigatran-treated patients. The mean age of the 244 patients recruited was 70.1 years, 54.1% were male, their mean CHADS2 score was 2.4, and the median treatment duration was 310 days. The investigators found that the risks of stroke and bleeding (any degree) were similar in dabigatran-treated and warfarin-treated patients. The investigators also found that there was no significant difference in treatment compliance rates between the two groups. [10, Rank 4]

Real-world data on bleeding with rivaroxaban and apixaban are limited, as these therapies have been available for less time than dabigatran, but trial subanalyses are available. In ROCKET-AF, predictors of major bleeding with rivaroxaban included older age, male sex, increased body mass index, diabetes, chronic obstructive lung disease, and worsening renal function. Risks of major adverse outcomes, including death following a major bleeding event, were similar in patients treated with rivaroxaban and warfarin in ROCKET-AF. Additionally, rivaroxaban was associated with a lower risk of intracranial hemorrhage. A subgroup analysis of ARISTOTLE found a lower risk of bleeding in all age categories for apixaban-treated versus warfarin-treated patients, including those aged ≥75 years. In addition to observing a reduced risk of stroke or systemic embolism regardless of renal function, another analysis from ARISTOTLE found a greater reduction in the

relative risk of major bleeding in the apixaban arm versus warfarin arm with worsening renal impairment (creatinine clearance <50 mL per minute). When considering these data, it is important to note that patients with a creatinine clearance <30 mL per minute (RE-LY and ROCKET-AF) or <25 mL per minute (ARISTOTLE) were excluded from the trials; new oral anti-coagulants should not be used in patients with creatinine clearance <15 mL per minute, as there are limited clinical outcomes data to inform on the use of new oral anti-coagulants in such patients. A separate analysis of the ARISTOTLE trial found that, compared with warfarin, apixaban was associated with a 31% reduction in risk of a first major bleeding event, and was associated with fewer intracranial hemorrhages. Additionally, apixaban was associated with fewer adverse consequences following extracranial hemorrhages, fewer trauma-associated hemorrhages, and a 50% reduction in fatal events at 30 days in the case of a major hemorrhage.

The EHRA guide states that current recommendations on bleeding management are not so much based on clinical experience as expert opinion on laboratory endpoints. For bleeding that is not life-threatening, the guide suggests that time is the most important reversal strategy for the anticoagulant effects of new oral anti coagulants because of their short half-lives; however, standard supportive measures should also be used, including mechanical compression, surgical hemostasis, fluid replacement, and other hemodynamic support. [8, Rank 3]

## Conclusion

Because the incidence of AF is increasing in a rapidly aging global population, AF-related stroke and its associated economic burden are expected to increase. Encouragingly, emerging data from real-world clinical practice suggest that the increasing availability of the new oral anti-coagulants is correlated with a higher proportion of patients with non-valvular AF receiving new oral anti-coagulants for stroke prevention, that there is improved treatment persistence with new oral anti-coagulants versus VKAs, and importantly, that real-world effectiveness and safety of the new oral anti-coagulants mirrors the findings of the phase III trials. These data include recently published results from XANTUS, the first completed non-interventional phase IV study investigating the safety and efficacy of new oral anti-coagulants in routine clinical practice, which showed that unselected patients with non-valvular AF treated with rivaroxaban experienced low rates of major bleeding (2.1 %/year) and stroke (0.7 %/year) over

1 year of follow-up. Introduction of the new oral anti-coagulants is simplifying patient management, improving guideline adherence and increasing persistence. This is likely to increase the number of patients showing a favorable benefit–risk profile with new oral anti-coagulants, compared with warfarin, including a concomitant benefit regarding bleeding, especially ICH. Familiarization of cardiologists with the new oral anti-coagulants , and further information deriving from the large phase III trials and real-world studies, should help towards achieving this goal. [5, Rank 5]

***Important information for post-test is highlighted in red letters, boxes and diagrams.**

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