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WARFARIN VERSUS DOACS IN THE PREVENTION OF THROMBOEMBOLIC STROKE IN PATIENTS WITH AFIB.

Allen Szabon, DMSc, MPAS, CCPA
Physician Assistant; Calgary, Alberta Foothills Medical Centre
Department of Clinical Neurosciences, Physical Medicine and Rehabilitation

A Narrative Review

ABSTRACT

Purpose: Preventing thromboembolic (TE) events "such as stroke" is an essential part of managing patients with non-valvular atrial fibrillation (Afib). Over the last 50 years, oral anticoagulant treatment with the Vitamin K Antagonist (VKA) Warfarin has played a crucial role in the secondary prevention of Stroke for Afib patients. Research suggests the new direct oral anticoagulant (DOACs) appears to have dominance over Warfarin for Afib treatment in the context of stroke prevention, and for the most part, superior to Warfarin in the secondary stroke prevention in patients with non-valvular Afib. Nevertheless, what does the evidence tell us about risk versus benefits?

Method: This literature review conducts a systematic review of the advantages and disadvantages of DOACs, namely dabigatran, rivaroxaban, apixaban and edoxaban, compared with Warfarin in patients with (non-valvular) Afib. The review's search terms included *Oral Anticoagulants, Anticoagulants, Direct Oral Anticoagulants, New Oral Anticoagulants, Warfarin, and secondary prevention non-valvular Afib, Afib, Stroke prevention and Stroke.* The search resulted in sixty articles selected. Following a full-text review, twenty articles were excluded. The excluded articles included six non-English languages, eight previously identified, and six others did not fulfill the inclusion criteria of "*Warfarin versus DOACs prevention of Stroke in Patients with Afib*." The remaining articles were reviewed to analyze the advantages and disadvantages of DOACs versus Warfarin in patients in preventing TE stroke in people with non-valvular atrial fibrillation.

Conclusion: The findings of this systematic literature review suggest that in the secondary prevention of stroke in patients with non-valvular Afib, DOACs, demonstrate a significant advantage and enhanced safety profile over Warfarin in reducing the risk of thromboembolic stroke compared with Warfarin. As such, DOACs should be considered first-line therapy in the secondary prevention of stroke in patients with non-valvular Afib. Compared with Warfarin, the advantages of DOACs indicated that DOACs are associated with lower life-threatening and intracranial bleeding rates. DOACs rapid onset with peak effect within a few hours, predictable dose responses, reduced or elimination of routine monitoring, and few, if any, important food or drug interactions, and simplify management.

Keywords: *Oral anticoagulants, Anticoagulants, Direct Oral Anticoagulants, New Oral Anticoagulants versus, Warfarin, Rivaroxaban, Apixaban, Dabigatran, Edoxaban, prevention of non-valvular Afib, Afib, Stroke prevention, stroke.*

INTRODUCTION

Over the last 50 years, the oral anticoagulant warfarin has played a pivotal role in the secondary prevention of stroke in patients with non-valvular Afib. Warfarin's long half-life and narrow therapeutic range necessitates regular INR monitoring and is a common cause of iatrogenic hospital admission.[1] DOACs including Dabigatran, Rivaroxaban, Apixaban and the newly introduced Edoxaban allow for fixed dosing, do not require routine monitoring, they have a rapid onset and relatively short half-life. However, they are sensitive to changes in renal function. Recent research indicates DOACs, and their dominance over Warfarin appears positive, but what does the evidence tell us? In this

literature review article, the author looked at the relative advantages and disadvantages of Warfarin versus DOAC use in preventing TE stroke for assisting in risk stratification and therapy selection for various patient populations.

Atrial Fibrillation and Stroke

Atrial fibrillation is an irregular heart rhythm shown to increase the risk of thromboembolic events, heart failure and other cardiac-related complications. During non-valvular Afib, the heart's atria beat chaotically, out of coordination

with the heart's ventricles. A significant concern with non-valvular Afib is blood's potential to coagulate to form thrombi within the heart's atria. These thrombi can travel through the arteries leading to the brain occluding a cerebral artery, leading to a thromboembolic stroke.

Non-valvular Afib affects 33-million people worldwide and is the most common sustained arrhythmia encountered in clinical practice, increasing global incidence and prevalence. An estimated 250,000 people have non-valvular Afib in Canada. An incidence of up to 4.5% per year and a potential lifetime risk of 25% among those older than 40years of age.[4] This number is likely underestimated since many people do not know that they have non-valvular Afib until they develop symptoms or present with a cardioembolic stroke. Non-valvular Afib is defined as Afib that occurs in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.[4]

Stroke is the third leading cause of death in Canada, costing people and the health system billions annually. Roughly 62,000 people in Canada have a non-valvular Afib-related stroke each year, and about 742,000 Canadian adults, aged 20 years or older, live with the effects of a stroke.[5] People with non-valvular Afib are five times more likely to have a stroke than those who do not have Afib, and among adults with non-valvular Afib, females have a significantly higher risk of stroke than males. Non-valvular Afib may recur despite the use of medicines or treatment to restore heart rhythm. For this reason, an oral anticoagulation medicine is prescribed to reduce the risk of thrombi developing in 55% of the total population of high-risk non-valvular Afib patients and in 35% of patients over 85 years old. Long-term oral anticoagulant therapy is a cornerstone of stroke prevention, and until a few years ago, the therapeutic standard was dose-adjusted Warfarin. However, in recent years, there have been multiple Randomized Controlled Trials (RCT) indicating that DOACs provide better protection in secondary stroke prevention than Warfarin.

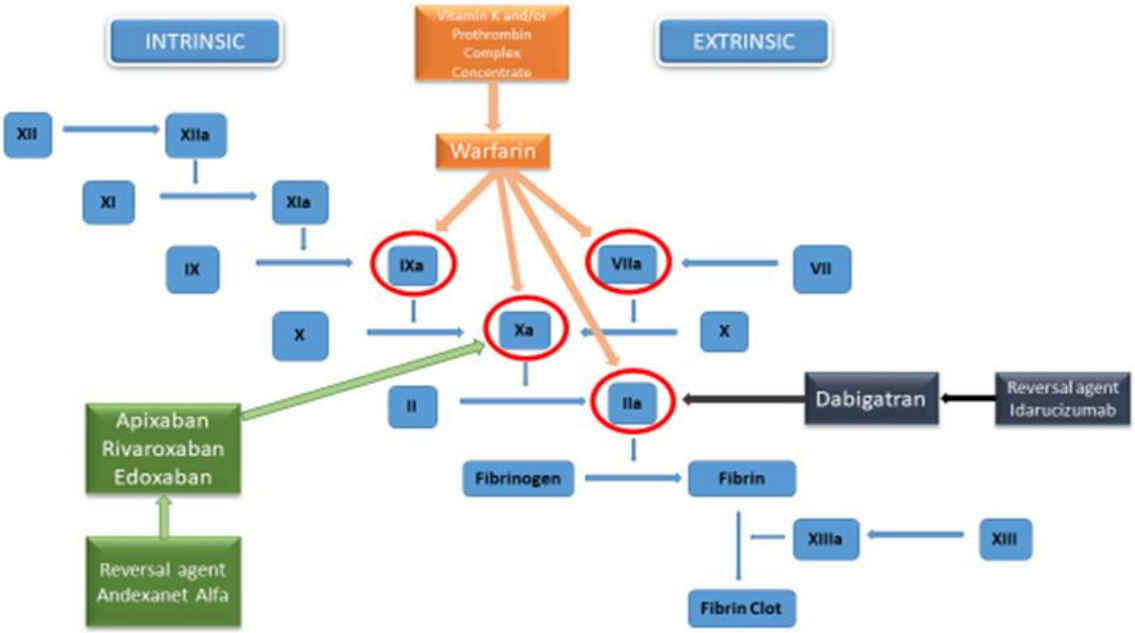
As the prevalence of non-valvular Afib approaches epidemic proportions, stroke prevention remains a cornerstone of management and thoughtful consideration. Patients may benefit from which anticoagulation is critical. Nevertheless, given our historical paucity of anticoagulant therapy choices, and the relatively novel class of DOACs, uncertainties remain, mainly revolving around the perceived risk of life-threatening bleeding with Warfarin versus the newer DOACs. Recommendations for anticoagulation therapy for patients with non-valvular Afib are based on guidelines from the 2014 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) task force on the management of patients with non-valvular Afib.

Vitamin K Antagonist, Warfarin

For more than 50 years, Warfarin is the primary prescribed antithrombotic agent for preventing TE stroke. Clinical evidence confirms Warfarin's effectiveness in preventing blood clots blocking cerebral blood vessel occlusion and systemic embolism in atrial fibrillation patients. Vitamin K epoxide reductase prevents the cofactor's formation for vitamin K-dependent coagulation factors such as Factor II, VII, IX, and X (See Table 1) anticoagulant factors Protein C & S causing a therapeutic Vitamin K deficiency to reduce clotting.

Warfarin therapy aims to decrease the clotting tendency of blood but not to prevent clotting completely. Research has shown that Warfarin reduces the risk of thromboembolic events by 65% and all-cause mortality by 22% compared with no treatment. The clotting test used to measure the effect of Warfarin is the prothrombin time (PT) and partial thromboplastin time (PTT). Patients who take Warfarin require regular laboratory international normalization ratio range (INR) monitoring for dose adjustment, which varies within patient populations. Some patients require low doses and others require high doses to achieve therapeutic INR (2.0-3.0/3.5).[15,17] If the INR is below the target range (i.e., under-anticoagulated), there is an increased risk of clotting and, hence, thromboembolic events. Conversely, if the INR is above the target range (i.e., over-anticoagulated), there is an increased risk of spontaneous or trauma-related hemorrhage. The dosing variation can be due to age, diet, disease state, genetics, other prescribed medications, and weight.[15]

Figure 1. Coagulation cascade



Overview of the coagulation cascade, indicating the sites of action of anticoagulant medications and their reversal agents.

Disadvantages when dosing Warfarin

The major complication (See Table 2) associated with Warfarin is severe and life-threatening bleeding such as bleeding into the brain or internal bleeding. Rare and minor bleeding such as easy bruising, gum bleeding, or nosebleeds is common.[18,19,20] Warfrins poor adherence to dosing regimens complicated by certain medications and polypharmacy requires diligent monitoring. Patients who eat green leafy vegetables (i.e. lettuce, spinach, broccoli) and certain drinks (i.e. Green tea, Grapefruit juice, Cranberry juice) may need higher doses of Warfarin because foods high in vitamin K can reduce the effects of Warfarin.[21] Changes in health status require increased INR monitoring. Warfarin has a longer half-life than DOACs, with the onset of therapeutic INR level taking three to six days. Warfarin is a relevant contraindication in pregnancy and classified as teratogenic from the risk of fatal bleeding due to the immature fetal liver.[22] An acute, advanced illness or liver disease may reduce the number of clotting factors leading to coagulopathy. Antacids or laxatives, certain antibiotics, antifungal medications, including fluconazole, cold or allergy

medicines, and Ibuprofen, can interact with Warfarin. Dietary or Herbal supplements, including Ginkgo-biloba, Ginseng, Coenzyme Q10, St. John's Wort, can interact with Warfarin by increasing or decreasing the Warfrin's action. Additionally, one in five doses administered are incorrect.[23] It is not surprising with these systemic changes, and polypharmacy requires frequent monitoring of the coagulation pathway. It is not surprising that the reviewed studies show patients are in the therapeutic INR range only approximately 50% to 65% of the time.[22] Maintaining the optimal anticoagulant effect and transient hypercoagulability requires constant attention and dose adjustment.

Advantages when dosing Warfarin

Warfarin has some advantages over DOACs (See Table 2), including its low cost, shared knowledge of side-effects. Warfarin has been the primary therapy for the prevention of TE events for over half a century. Warfarin has a high bioavailability and can be used in all age groups. In a bleed, reversal of anticoagulation factors can be achieved by stopping Warfarin or administering vitamin K, fresh frozen plasma or coagulation factor concentrates.[24] Alcohol in low or moderate amounts (one or two servings per day) is unlikely to affect the INR significantly.

Direct Oral Anticoagulants (DOACs)

The improved understanding of the intrinsic, extrinsic, and common coagulation cascades led to the development of DOACs. Knowledge of more predictable pharmacokinetics and pharmacodynamics provided DOACs distinctly different mechanisms of action. The new approaches, including direct factor Xa inhibitor or direct thrombin inhibitor, provide a change in the management options for patients at risk from thromboembolic diseases.

DOACs pinpoint a specific target for controlling the clotting cascade with maximum efficacy and minimum inconvenience. The approval of Dabigatran (Pradaxa) in 2010 led to the creation of the term "new oral anticoagulants" (NOACs).[25] When Rivaroxaban (Xarelto) came to the market in 2011, followed by Apixaban (Eliquis) in 2012, and finally Edoxaban (Lixiana) was introduced in 2016, the name changed to "direct oral anticoagulants" (DOACs). The four DOACs mentioned are approved for use in Canada for thromboprophylaxis of non-valvular Afib.

These approvals are based on the successful outcomes of four Phase-III dose-adjusted, warfarin-controlled randomized controlled trials (RCTs). The RE-LY trial for dabigatran, 25 the ROCKET AF trial for rivaroxaban, [26] ARISTOTLE for apixaban[27] and the ENGAGE AF-TIMI 48 study for edoxaban.[28] Each trial demonstrated similar or improved effectiveness compared with Warfarin, in addition to reduced rates of intracranial and life-threatening hemorrhage. Like Warfarin, DOACs reduce the risk of thrombus formation and growth. Avoiding the transient hypercoagulation due to the half-life of protein C and S. However, given their high affinity to a specific protein in the coagulation cascade, DOACs offer a more predictable response to therapy, making them both more effective and convenient to use.

Dabigatran (Pradaxa®) was approved by the Food and Drugs Act (FDA), for secondary prevention of stroke in patients with non-valvular atrial fibrillation in October 2010 following the RE-LY trial.[25] Pradaxa inhibits fibrin production and prevents thrombin-mediated activation of factors V, VIII, XI, and XIII and thrombin-induced platelet aggregation which is lower in the common coagulation pathway than the other DOACs. (See Table 1). The peak onset of action of Pradaxa occurs within one hour. Pradaxa's half-life is approximately 12 to 17 hours and is predominantly cleared by the kidneys.

Elimination of dabigatran after hepatic activation occurs (up to 80%) in the kidneys. Thus, patients with significant renal impairment are excluded from most clinical trials involving dabigatran. Pradaxa is associated with fewer drug to drug and drug to food interactions than warfarin[31]. If surgical intervention is planned, Pradaxa should be discontinued 1-2 days prior to the surgery. If medication reversal is indicated, Praxbind™ (idarucizumab) is a specific antidote for dabigatran's immediate reversal.[32] With Pradaxa, significant bleeding was typically gastrointestinal,

whereas in patients treated with Warfarin, the worst bleeds were intracranial and therefore more difficult to treat.[33] Approved labels in Canada and elsewhere recommend an arbitrary dose reduction in the setting of moderate renal dysfunction and recommend against use with severe renal dysfunction.

Following the multinational, double-blind ROCKET trial, Rivaroxaban (Xarelto®) received FDA approval in November 2011 to prevent stroke in patients with non-valvular Afib.[26] Xarelto inhibits Factor Xa and is metabolized predominantly in the liver (CYP3A4 & P-glycoprotein pathways) with a rapid onset of action peaking 2-4 hours after ingestion. (See Table 1) Clinical trial data have shown that Xarelto allows predictable anticoagulation with no need for dose adjustments or routine coagulation monitoring.[34] The identified risk of major bleeding was similar for Xarelto and Warfarin. However, a significantly lower risk of intracranial hemorrhage and fatal bleeding was seen with Xarelto when compared with Warfarin.[26] With planned surgical intervention, it is recommended to stop Xarelto at least 24 hours before surgery. If urgent medication reversal is indicated, Andexanet alfa (AndexXa) is effective.[29] Rivaroxaban is contraindicated in patients with a creatinine clearance of less than 30 mL/min, and caution is advised in patients with renal insufficiency.

Apixaban (Eliquis®) was approved by the FDA for the prevention of stroke in patients with non-valvular Afib in December 2012 following the ARISTOTLE trial.[27] Eliquis inhibits Factor Xa in the common coagulation pathway (See Table 1). Eliquis is an oral, selective, reversible, direct factor Xa inhibitor with high oral bioavailability. The onset of

action is approximately 3 hours, with a half-life of about 12 hours. Additionally, its absorption with food is not impacted. Eliquis is metabolized predominantly in the liver (CYP3A4 & P-glycoprotein pathways)[27] and is also partially excreted in the renal system, necessitating dosage adjustments with renal insufficiency in the presence of kidney disease.

The ARISTOTLE trial with 18,201 patients compared Eliquis with Warfarin to prevent stroke with non-valvular Afib and found that Eliquis was superior to Warfarin in preventing stroke, leading to fewer bleeding episodes, and resulted in decreased bleeding-related mortality.[27] When reversal of anticoagulation is indicated, prothrombin complex concentrate, recombinant Factor VIIa, and Andexanet alfa (AndexXa) are effective.[30] Apixaban does not induce or inhibit CYP enzymes and appears to have a low likelihood of drug-drug interactions.

Lastly, Edoxaban (Lixiana®) is the lastest direct oral anticoagulant approved for use in Canada for the prevention of stroke in patients with non-valvular Afib. Edoxaban was approved in November 2016 following the ENGAGE AF-TIMI 48 study.[28] Similar to Eliquis and Xarelto studies, Lixiana binds reversibly to the active site of free factor Xa or factor Xa incorporated into the prothrombinase complex. (See Table 1). Lixiana has a rapid onset of 1-2 hours and is sustained for up to 24 hours.[35]

Clinical trial data have shown that similar to Xarelto and Eliquis, Lixiana allows predictable anticoagulation with no need for dose adjustments or routine coagulation monitoring. The approval of Lixiana follows two phase 3 trials, ENGAGE, AF-TIMI 48 and Hokusai-venous thromboembolism which compared treatment with once-daily Lixiana to Warfarin.[36] Lixiana can be administered without concern for dietary interactions. If medication reversal is indicated, management of bleeding with Andexanet alfa (AndexXa) is effective.[29] The major side effect is bleeding and as Lixiana crosses the placenta, it is not used during pregnancy.[29]

Advantages of DAOCs over Warfarin

Evidence demonstrates several advantages of DOACs over Warfarin (See Table 2). DOACs cause fewer intracranial or gastrointestinal bleeds[35]. They are easier to manage around surgical and dental procedures with predictable pharmacokinetics and wide therapeutic windows. DOACS have a rapid onset with a short half-life. At the

same time, Warfarin may remain at therapeutic levels for more than 24-hours after final dosing and may take several days to reach therapeutic serum concentration on initiation of therapy.

With a rapid onset, the half-life of proteins C and S, anticoagulants are much shorter than the clotting factors. As a result, warfarin dosing will lead to a deactivation of all serum protein C/S well before the coagulation factors – which have a longer half-life – and lead to transient hypercoagulability until active coagulation factors have been excreted and replaced by inactive ones.[36] It is prudent for patients receiving DOACs to assess kidney function, hemoglobin, and platelet counts every 6-12 months.[37] Furthermore, regular INR monitoring of coagulation parameters is not required with DOACs, therefore, improving patient compliance.[38] Finally, DOACs have predictable pharmacokinetics and pharmacodynamics. They have fewer diet/drug/disease interactions and are convenient for rural patients with barriers to clinic visits.[38]

Disadvantages of DAOCs over Warfarin

DOACs are not without disadvantages (See Table 2). Higher out-of-pocket costs (20 times that of Warfarin) and twice a day dosing may negatively impact compliance. Currently, treatment with Warfarin, including regular INR monitoring costs less than C$300 per annum. The new DOACs examined in this report cost more than C$1,200 per annum.[39] Besides price, additional considerations include renal insufficiency, cognitive impairment and access to pharmaceutical dispensaries, as there are limited data regarding safety and effectiveness of DOACs in CKD and the shorter half-life may increase the risk of thrombus formation in individuals prone to missing doses or without access to timely medication refills. Managing DOACs can be a challenge as Pradaxa, and Eliquis need to be taken twice per day, where Xarelto and Lixiana are taken once-a-day.

This requires strict compliance, because missing just one dose places a patient at higher risk of thromboembolic complications as the shorter half-lives of DOACs will potentially result in more time without any degree of anticoagulation. There are no long-term safety data for dabigatran, rivaroxaban, apixaban or edoxaban and their safety profiles are still not fully understood and therefore are not suited for patients with valvular atrial fibrillation or compromised kidney function. None of the DOACs are approved for use during pregnancy or in pediatrics,[39] additionally, DOACs have not yet been used in patients with mechanical mitral valves issues limiting generalizability of data to non-valvular A-fib patients until further trials can be performed. Lastly, rivaroxaban and low dose apixaban were associated with increased risks of all-cause mortality compared with warfarin.[40]

CONCLUSION

DOACs offer important advantages over Warfarin for the secondary prevention of thromboembolism in patients with non-valvular Afib. DOACs are associated with lower rates of life-threatening and intracranial bleeding, and are more convenient because they can be given in fixed doses without routine coagulation monitoring. DOACs have a rapid onset with peak effect within a few hours, they have predictable dose responses, thus eliminating the need for routine monitoring; and they have few, if any, important food or drug interactions, thus simplifying management. Specific reversal agents will help to streamline the management of patients with uncontrolled bleeding and those who are requiring urgent surgery. Unfortunately, DOACs are more expensive than Warfarin, they are required to take twice-daily which could lead to poor compliance or availability and the long-term effects of these newer drugs are not as well-known as those of Warfarin.

At this point, the author concluded that overall, DOACs represent a safe, effective, and likely favorable alternative when compared to Warfarin as a first line therapy, in the secondary prevention of non-valvular Afib-related TE stroke. To fully elucidate the comparative advantages/disadvantages of these agents, rigorously conducted comparative RCTs or network meta-regression analyses of patient-level data are required. As practitioners gain

familiarity with these oral anticoagulant drugs and adapt to their use, DOAC use will likely increase substantially over time.

Figure 2 Overview of Oral Anticoagulants

Overview of Oral Anticoagualnts				
Subtances		**Mechanism of action**	**Advantages**	**Disadvantages**
Vit K Antagonist (Coumarins)	**Phenprocoumon Warfarin**	Inhibits Vitamin K regeneration and Vitamin K–dependent coagulation factors such as Factor II, VII, IX and X, along with Protein C & S and it causes a therapeutic Vitamin K deficiency to reduce clotting.	- Well-known effects and side effects. - Low costs - Direct reversal by replacement (e.g., with prothrombin complex concentrate, FFP, PCC) or Vit K. - High bioavailability - Test monitoring with PT (INR), dose adjustment dependent on INR value - Can use in all group ages - Long clinical experience with VKAs (these drugs have been used as anticoagulants for over 60 years)	- Difficult to manage - Long half-life - Regular monitoring of the PT/INR required - Requires bridging before surgery - Broad range of interactions - Not suited for acute therapy of pulmonary embolism or deep vein thrombosis - Unpredictable pharmacokinetics and individual (great variability of individual dose) - Great drug–drug interactions - Dietary restriction - Need for frequent monitoring of INR - Narrow therapeutic window - Slow onset and offset - Long half-life (this is a problem when required emergency surgery and in cases of bleeding due to accumulation of the drug in the blood) - VKAs-induced skin necrosis if started without LMWH
Direct oral thrombin inhibitors	**Dabigatran (Pradaxa)**	Pradaxa inhibits fibrin production and prevents thrombin-mediated activation of factors V, VIII, XI, and XIII and thrombin-induced platelet aggregation which is lower in the common coagulation pathway than the other DOACs.	- Easily manageable (similar to heparins) when administered orally - Regular monitoring of coagulation parameters is not required therefore improved patient compliance - Antidotes available in the case of life-threatening bleeding - Dabigatran: idarucizumab (Antidote) - Predictable pharmacokinetics and pharmacodynamics - Low drug–drug and food interactions - No dietary restriction - Rapid onset and offset - Short half-life - In general no need for laboratory monitoring, although in some cases it is required	- Costly - Limited clinical experience with these drugs - Not recommended, and partially contraindicated, in patients with artificial cardiac valves - Not suited for patients with valvular atrial fibrillation - Do not exist standardized test for monitoring of NOACs, when it is necessary for monitoring of these drugs, eg, in hepatic and renal disease - Sometimes rapid offset and short half-life may be considered as disadvantages - High cost - Not enough experience - DOACs therapy can be initiated without LMWH (no risk for induced skin necrosis) due to their rapid onset
Direct oral factor Xa inhibitors	**Apixaban (Eliquis)** **Rivaroxaban (Xeralto)** **Edoxaban (Lixiana)**	Eliquis, Xarelto and Lixiana inhibits Factor Xa and is metabolized predominantly in the liver (CYP3A4 & P-glycoprotein pathways).	- Easily manageable (similar to heparins) when administered orally - Predictable pharmacokinetics and pharmacodynamics - Low drug–drug and food interactions - No dietary restriction - Rapid onset and offset - Short half-life - In general no need for laboratory monitoring, although in some cases it is required - Wide therapeutic window - Switching patient from LMWH and VKAs to NOACs - Apixaban, Rivaroxaban and Edoxaban: andexanet alfa (Antidote)	

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