# BARRIERS TO LONG-TERM ANTICOAGULATION

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# Barriers to Long-term Anticoagulation

**ANCC Accredited NCPD Hours: 1 hrs**

**Target Audience: RN/APRN**

## Need Assessment

Long-term anticoagulant therapy is being used frequently in the management of certain vascular and thromboembolic diseases. Prolonged survival and decreased morbidity have been reported from use of anticoagulants. However, there has not been adequate evaluation of the ease or difficulty with which a satisfactory and practical program of prolonged anticoagulant therapy can be carried out. The relative benefits and risks of anticoagulant therapy have not been adequately quantified for many thromboembolic disorders, and the decisions as to whether, for how long, and how intensely to administer anticoagulation are often complex and controversial.

## Objectives

- Identify the types of anticoagulants commonly used.
- Analyse the common barriers of long term anticoagulation therapy.
- Describe how direct oral anticoagulants associated bleeding affects anticoagulation therapy
- Discuss how drug-drug interactions influence anticoagulation therapy
- Discuss the patient and physician related barriers in long term anticoagulation.
- Adapt to the recommendations on overcoming barriers of Anticoagulant therapy.

## Goal

The goal of this article is to provide the reader with an overview on barriers to long term anticoagulation therapy for stroke prevention

## Introduction

The availability of the new direct oral anticoagulants (DOACs) has significantly changed the therapeutic landscape of anticoagulation and these agents may eventually displace conventional VTE treatment with a rapid-acting parenteral anticoagulant overlapped with a vitamin K antagonist (e.g. warfarin) in appropriately selected patients. As a class, the DOACs exhibit comparable efficacy and a significantly lower bleeding risk compared to warfarin among patients with acute symptomatic VTE. For patients who need extended anticoagulation for secondary VTE prevention, the safety record of the DOACs is strong. [1, Rank 5]

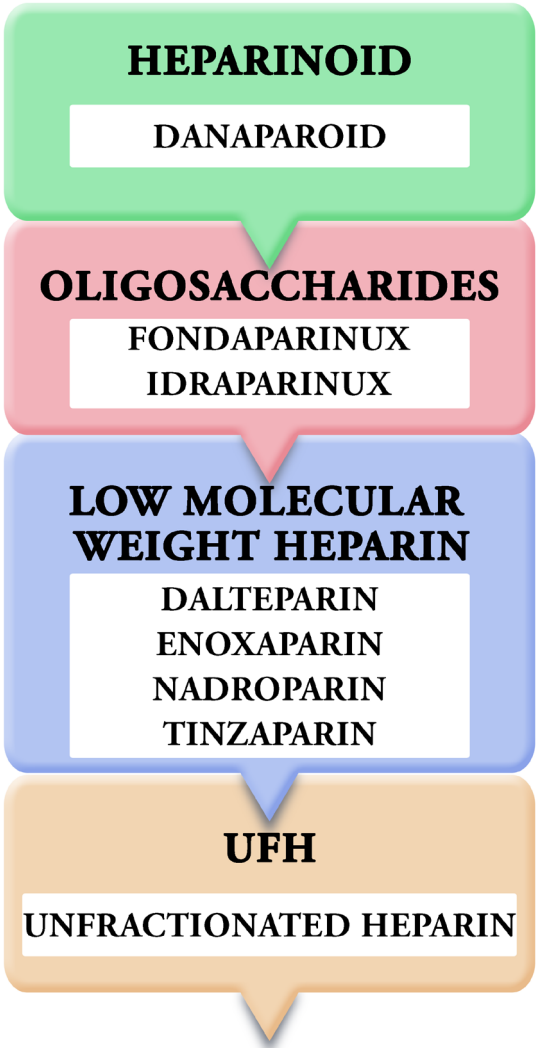



Figure 2: Heparins and Heparinoids

## Types of Anticoagulants

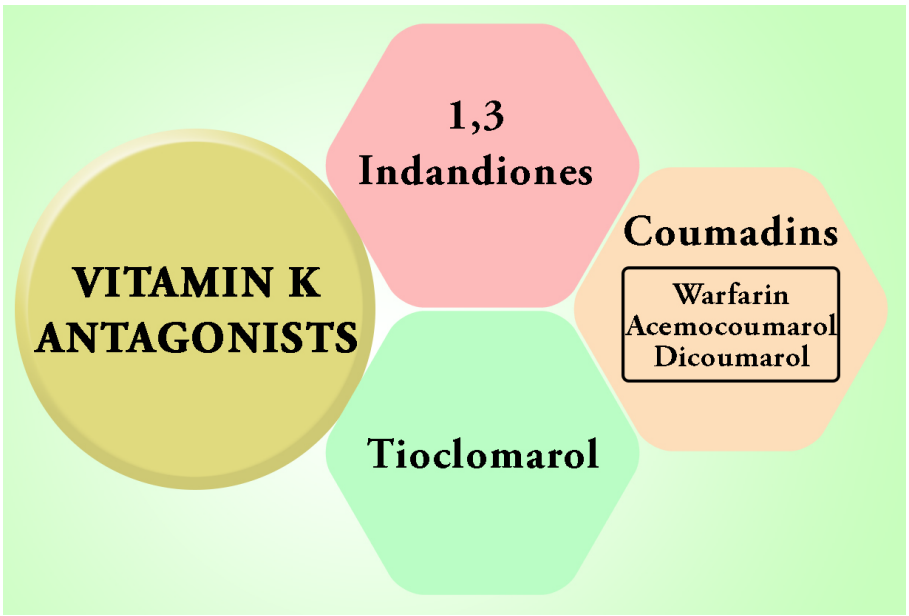



Figure 1: Vitamin K antagonists

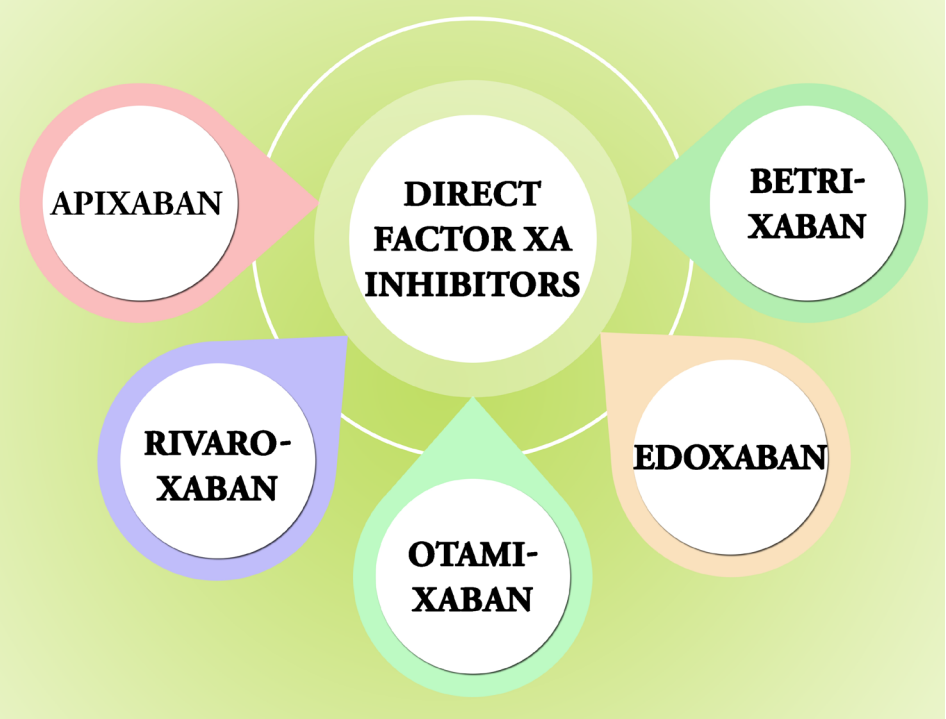



Figure 3: Factor Xa Inhibitors

## Barriers for long term Anticoagulation Therapy

The direct oral anticoagulants have been studied extensively in clinical trials and the results demonstrate they are at least as safe and effective as conventional treatment in the majority of typical venous thromboembolism (VTE) patients. However, many specific subgroups were excluded or underrepresented in these studies and the safety and efficacy of direct oral anticoagulants within these subgroups has yet to be established. ***The inclusion criteria for the VTE treatment trials included patients age ≥18 with an acute symptomatic proximal deep vein thrombosisand/or Pulmonary Embolism (PE). Exclusion criteria varied slightly among the trials, but in general, patients were excluded if they had any of the following: need for thrombolytic therapy, another indication for anticoagulation, high risk of bleeding, clinically significant liver disease*** (acute or chronic hepatitis, cirrhosis, or alanine aminotransferase level greater than three times the upper limit of normal), creatinine clearance (CrCl) <30 mL/min (for apixaban the threshold was 25 mL/min), life expectancy of <3–6 months, aspirin use >100 mg/day, using interacting medications, uncontrolled hypertension, breastfeeding or pregnant or of childbearing potential without appropriate contraceptive measures. [2, Rank 3]

## Lack of awareness of Stroke risk and the risks and benefits of Oral Anticoagulation

At least one third of patients diagnosed with atrial fibrillation are unaware of the associated stroke risk. Although awareness of stroke risk is increasing among physicians, oral anticoagulants use varies considerably according to specialty, with primary care physicians prescribing oral anticoagulants less commonly than cardiologists. Unfortunately, time during outpatient clinical encounters is often limited, and atrial fibrillation may be only one of several comorbidities to be addressed in any given office visit, particularly by general practitioners. The decision to initiate an oral anticoagulants and the associated education of patients and family members around the use of oral anticoagulants takes considerable time and resources. Further, there may be differential knowledge of the relative risks and benefits of different anticoagulation therapies, particularly with the recent approvals of novel oral anticoagulants (NOACs). These factors may partially explain the observed difference in oral anticoagulants prescription rates among specialties.

Having been in use for more than sixty years, vitamin K antagonists nonetheless remains the dominant treatment for stroke prevention in atrial fibrillation. In the modern therapeutic era, patient selection factors for warfarin therapy compared with novel oral anticoagulants may not be immediately apparent. Moreover, concern over use of vitamin K antagonists – and often over issues specific to vitamin K antagonists therapy such as the need for close INR (The international normalised ratio) monitoring – is a common reason for not using oral anticoagulants of any type. Historically, a variety of reasons not to use oral anticoagulants have been put forward. The misperception that aspirin is sufficiently effective for stroke prevention and substantially safer than the novel drugs appears to be a significant contributor to the problem of oral anticoagulants under treatment.

> **"NOACs have several advantages over vitamin K antagonists, the most salient of which is lower risk of intracranial hemorrhage and hemorrhagic stroke found for all of the NOACs. Others include lack of need for therapeutic monitoring and a modest but worthwhile reduction in mortality found in several clinical trials."**

**Reasons for Use of Vitamin K Antagonists rather than NOACs**

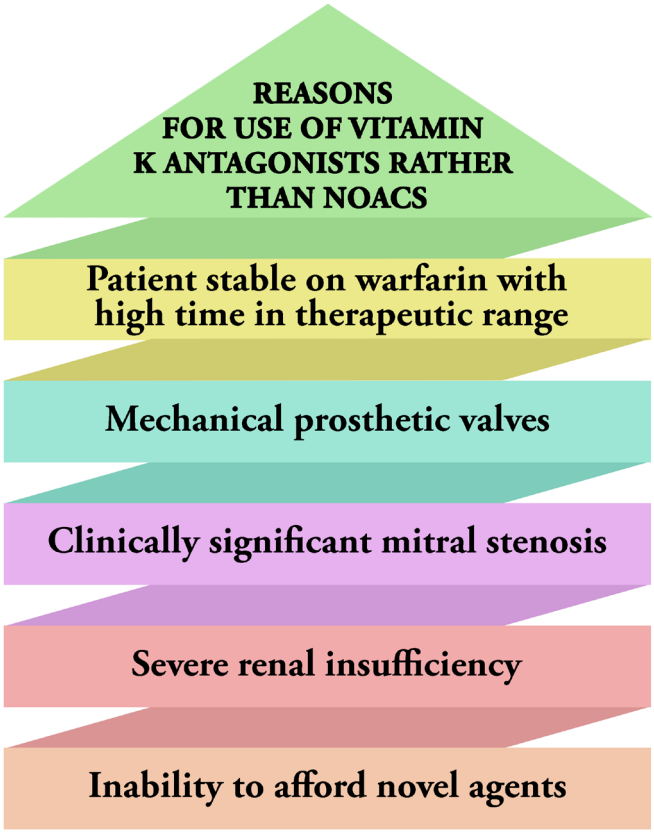



Figure 4: Reasons for Use of Vitamin K antagonists

Patients who have been on warfarin for a significant period of time, are on a stable dose with stable INRs, and can comply with frequent monitoring, may prefer to stay on warfarin despite a higher risk of intracranial hemorrhage. Similarly, novel oral anticoagulants may not be suitable for patients with advanced renal disease, e.g. creatinine clearance < 25 to 30 ml/min. Rare patients may develop intolerance to novel oral anticoagulants but can tolerate vitamin K antagonists. Novel oral anticoagulants are approved for use in "non-valvular" AF.

## Lack of Reversal Agents

Clinicians are uncomfortable with the absence of good anticoagulation reversal strategies for the novel oral anticoagulants. Concerns exist regarding life-threatening hemorrhage on oral anticoagulants, particularly in patients requiring invasive procedures and especially when those are needed emergently. Monitoring of novel oral anticoagulants treatment effect may be desirable in these situations, ***in the event of an overdose, and in advance of planned procedures such as cardioversion when there are questions about drug compliance and concern with the thrombosis risk associated with inconsistent anticoagulation.*** Unfortunately, reversal options and monitoring strategies and how they may inform care are not well-defined. [32, Rank 3]

## Lack of Reversal Agents

Much of the available data on direct oral anticoagulants and gastrointestinal (GI) bleeding is from atrial fibrillation trials, which generally consisted of older patients with more comorbidities than the venous thromboembolism (VTE) treatment populations.

In a real- world study of data among new users of dabigatran or warfarin for

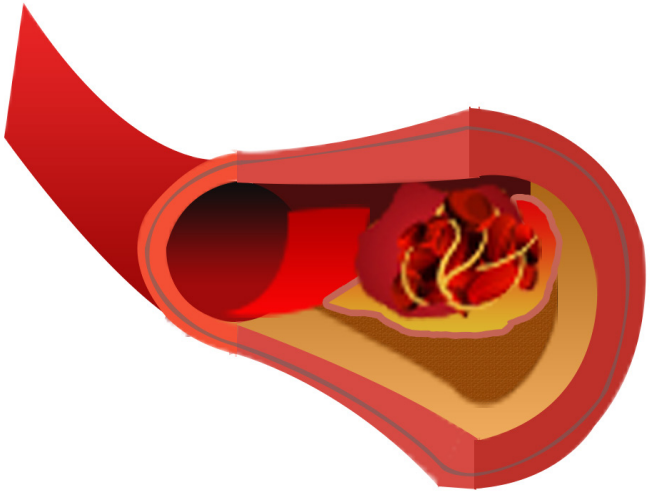


Figure 5: Venous Thromboembolism

non-valvular atrial fibrillation, there was a 28 % overall increased risk for gastrointestinal bleeding among dabigatran patients compared to warfarin patients. This was most pronounced in women ≥75 years of age (HR 1.5; 95 % CI 1.2–1.88), men ≥85 years of age (HR 1.55; 95 % CI 1.04–2.32) and in patients receiving the higher dose of 150 mg twice daily (HR 1.51; 95 % CI 1.32–1.73). A meta-analysis of 4 dabigatran trials of both NVAF (Non-valvular atrial fibrillation) and VTE (venous thromboembolism) treatment reported a 41 % increase in the risk of gastro intestinal bleeding with dabigatran. In the individual DOAC - VTE treatment trials, GI bleeding event rates were too low to draw definite conclusions (dabigatran and rivaroxaban numerically higher rates of GI bleeding, apixaban and edoxaban numerically lower rate of GI bleeding) compared to conventional anticoagulation therapy.

Intracranial hemorrhage (ICH) is the most feared complication of anticoagulant therapy. A significant advance with direct oral anticoagulants therapy over warfarin has been a reduction in the rates of intracranial hemorrhage in atrial fibrillation. Numerically lower rates of both intracranial hemorrhage and fatal bleeding were seen in all direct oral anticoagulants arms of the venous thromboembolism trials, with the exception of intracranial hemorrhage in the EINSTEIN-DVT trial (2 events in the rivaroxaban arm vs. none in the warfarin arm). A systematic review and meta-analysis of 12 randomized controlled trials including over 100,000 patients with either Non-valvular atrial fibrillation or venous thromboembolism showed that Direct oral anticoagulants are associated with less major bleeding, fatal bleeding, intracranial bleeding, clinically relevant non-major bleeding, and total bleeding compared to warfarin. This provides a compelling argument to favor these agents over conventional therapy for venous thromboembolism treatment whenever possible. [7, Rank 2]

Following the approval of dabigatran in October 2010, a substantial number of reports of serious and fatal bleeding events were submitted to the US Food and Drug Administration's Adverse Event Reporting System. ***The number of reports of bleeding associated with dabigatran was***

***considerably higher than the number of reports with warfarin.*** These findings contrasted with those of a large controlled trial, Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), which showed that ***bleeding rates with dabigatran 150 mg twice a day and warfarin were similar, and bleeding was less with dabigatran at the 110 mg twice a day dose.*** The adverse drug effects that were not detected in clinical trials can appear when a drug is broadly used. Detailed review of the spontaneous reports did not identify any unknown risk factors for bleeding, and dabigatran was generally used in accordance with its FDA label. A clearly defined denominator of patients on dabigatran and on warfarin as well as a systematic report of all observed, clinically significant bleeding events associated with each drug. Dabigatran-associated bleeding rates were clearly not increased compared with warfarin, and in fact bleeding on dabigatran appeared similar to if not lower than bleeding on warfarin.

## Reasons for Use of Vitamin K Antagonists rather than NOACs

In both venous thromboembolism treatment trials and atrial fibrillation trials, rates of major bleeding were shown to be comparable or lower with direct oral anticoagulants than with conventional approaches using LMWH and warfarin. Despite early concerns regarding excessive bleeding with dabigatran, post-marketing surveillance data from the FDA supports a favorable risk–benefit profile.

Nevertheless, direct oral anticoagulants -treated patients may experience a hemorrhagic episode and require intervention. Hospitals should develop evidence-based antithrombotic bleeding and reversal protocols that contain clinical decision support for providers and are easy to access and use in high-stress urgent or emergent situations. The general approach to a bleeding patient, regardless of anticoagulant, includes withholding the anticoagulant, hemodynamic monitoring, and resuscitation with fluid and blood products, mechanical compression if possible, and definitive procedural intervention to identify and treat the source of bleed if indicated. In addition to supporting blood pressure, assertive fluid resuscitation will promote renal elimination of direct oral anticoagulants, particularly dabigatran. Hemodialysis may be considered for dabigatran patients, particularly if they have impaired renal function and will have prolonged exposure to dabigatran without the aid of extracorporeal removal. Hemodialysis is not an effective option for removal of direct Xa

inhibitors due to their extensive protein binding. [18, Rank 4]

If a patient is refractory to general approaches, clinicians may consider non-specific reversal strategies. Several studies of clotting factor concentrates, such as activated and non-activated prothrombin complex concentrates (PCCs) or recombinant Factor VIIa, for Direct oral anticoagulants reversal have been reported. Most of these studies evaluated surrogate outcomes, such as normalization of global coagulation assays, instead of relevant clinical outcomes of in vivo hemostasis and mortality. Overall, results suggest that either inactive 4-Factor PCC 50 U/kg or active PCC 80 U/kg are reasonable options for reversal of direct Xa inhibitors and direct thrombin inhibitors, respectively. These agents contain procoagulant factors II, VII, IX and X. Activated PCC may pose a greater risk of thrombosis, but may be considered if inactive 4-Factor PCC is not available. Recombinant Factor VIIa is not recommended as a first-line reversal agent. Unlike the PCCs, rFVIIa is not formulated with marginal amounts of anticoagulants (e.g. Protein C, Protein S, Antithrombin, heparin) to mitigate thrombotic risk. Meta-analyses suggest that use of rFVIIa results in higher rates of thrombosis than prothrombin complex concentrates. Additionally, because both inactive and active prothrombin complex concentrates already contain FVII, there is no rationale to employ rFVIIa as a first-line agent for Direct oral anticoagulants reversal. Therefore, they suggest rFVIIa only be used in event prothrombin complex concentrates have failed to restore hemostasis in a patient with life-threatening bleeding. Clinicians should carefully weigh risk versus benefit of factor concentrate administration as there is no evidence that these agents improve outcomes and the risk of thrombosis is quite significant. [19, Rank 3]

Fresh frozen plasma should not be used for direct oral anticoagulants reversal, as the volume that would be required to overwhelm the inhibition of thrombin or Factor Xa precludes use in urgent or emergent situations and would likely lead to adverse events, such as fluid overload. Desmospressin or platelet transfusion may be considered in direct oral anticoagulants patients recently on concomitant antiplatelet therapy. Antifibrinolytics agents (tranexamic acid, aminocaproic acid) may be considered as adjunctive therapies if the patient is failing to respond.

Several clinical trials of specific antidotes for both DTIs and Xa inhibitors have been completed or are underway. Phase II studies and preliminary data from Phase III

studies show these agents to be safe and effective in providing complete and sustained direct oral anticoagulants reversal. [20, Rank 4]

## Dual antiplatelet therapy

Dual antiplatelets therapy and oral anticoagulants are indicated for acute coronary syndromes and atrial fibrillation, respectively. The combination of disease processes poses a therapeutic dilemma, as bleeding risk is significantly elevated when antiplatelet and antithrombotic therapies are used simultaneously. ***Compared with aspirin alone, triple therapy with aspirin, vitamin K antagonists and clopidogrel increases bleeding fourfold.*** When prasugrel rather than clopidogrel is used, bleeding rates may be even higher. There is a similar increase in risk when adding novel oral anticoagulants to aspirin and clopidogrel, with a 3-to 4-fold increased risk in major bleeding events. The use of ticagrelor or prasugrel rather than clopidogrel might be expected to further elevate bleeding risk in this setting, although empiric data are lacking. More data on these issues are needed to inform clinical decision making.

## Lack of Reversal Agents

Currently, the majority of available direct oral anticoagulants drug interaction data only illustrate changes in drug exposure conducted in pharmacokinetic studies of healthy volunteers. Available pharmacokinetic drug interaction data in actual patients are limited to subsets of the larger atrial fibrillation population clinical trials. It is unknown if these pharmacokinetic changes translate to pharmacodynamic effect resulting in excess bleeding or thrombotic events.

***Each of the direct oral anticoagulants is a substrate of permeability-glycoprotein (p-gp), an efflux transporter located in the membranes of the small intestine, blood–brain barrier, liver, and kidneys that regulates absorption of drugs into the bloodstream and tissues. Hepatic enzyme Cytochrome 3A4 (CYP 3A4) metabolizes rivaroxaban and apixaban to varying degrees (33 and 25 %, respectively). Dabigatran is not a CYP3A4 substrate, and less than 4 % of edoxaban is metabolized via CYP3A4.*** [8, Rank 5]

Given that each of the direct oral anticoagulants has some proportion of renal elimination (dabigatran 80 %, rivaroxaban 33 %, apixaban 25 %, edoxaban 50 %), patients with renal impairment or over age 75 years taking direct oral anticoagulants may be at a higher risk of bleeding complications, especially if they also have potential concomitant drug interactions

> **"Drugs that induce (increase the function of) p-gp and/ or CYP3A4 may decrease direct oral anticoagulants plasma concentrations and increase the risk for thromboembolic events, while drugs that inhibit (decrease the function of) p-gp and/ or CYP3A4 may increase direct oral anticoagulants concentrations and increase bleeding risk."**

(e.g. taking a p-gp and/or CYP3A4 inhibitor). It is important to note that these same patient characteristics (increasing age, impaired renal function and drug interactions) have been shown to convey an increased bleeding risk with warfarin as well. [9, Rank 3]

In venous thromboembolism treatment trials, dyspepsia and gastrointestinal (GI) bleeding were more common in patients taking dabigatran as compared to warfarin or placebo. Patients with these adverse effects may be frequently prescribed proton-pump inhibitors (PPIs). Even though dabigatran requires an acidic gastric environment for absorption, pharmacokinetic studies have not shown a clinically significant reduction in dabigatran exposure with concomitant proton-pump inhibitors. Therefore, proton-pump inhibitors may be safely co-administered with dabigatran without need for dose adjustment. Additionally, the product labeling for each of the direct oral anticoagulants contains detailed dosing information and necessary adjustments that consider route of metabolism and elimination and degree of renal impairment. [10, Rank 5]

## Anticoagulants and NSAIDs

When each of the direct oral anticoagulants was studied in combination with dual antiplatelet therapy (aspirin and clopidogrel) for acute coronary syndromes, investigators observed a clinically significant increase in major bleeding in patients taking triple therapy. The direct oral anticoagulants venous thromboembolism treatment trials permitted low-dose concomitant aspirin, and dual antiplatelet therapy was permitted in the dabigatran and rivaroxaban trials. The rate of low-dose aspirin use in the study populations for dabigatran, rivaroxaban, and apixaban ranged from 8 to 14 % and was not reported in the edoxaban trial. In a sub-analysis of the rivaroxaban venous thromboembolism treatment trial, patients taking rivaroxaban and low-dose aspirin had a significantly higher risk of clinically relevant bleeding (hazard ratio (HR) 1.81, 95 % CI (confidence interval) 1.36–2.41) and a non-significant increase

in major bleeding (HR 1.50, 95 % CI 0.63–3.61) compared to rivaroxaban-only patients. Patients taking rivaroxaban and NSAIDs had a 2.5-fold higher rate of major bleeding (HR 2.56, 95 % CI 1.21–5.39) and a 2-fold higher rate of clinically relevant bleeding (HR 1.9, 95 % CI 1.45–2.49) compared to those not taking NSAIDs. In this study, 14 % of the clinically relevant bleeding events were gastrointestinal. [11, Rank 3]

Potential drug interactions should be assessed to determine if an alternative non-interacting medication is available to treat the patient's condition. The duration of interaction exposure should be evaluated, as well as the patient's risk for a recurrent venous thromboembolism or major bleeding. Patients at high risk of recurrent venous thromboembolism (VTE event in the last 3 months or with ongoing venous thromboembolism risk factors) or at a high risk of bleeding may be particularly vulnerable to direct oral anticoagulants drug interactions. Conversely, patients at a lower risk of recurrent venous thromboembolism or bleeding may be able to tolerate a moderate drug–drug interaction combination without substantially increasing their risk of adverse events. [12, Rank 5]

## Switching Between Anticoagulants

In general, the need to switch between agents exposes the patient to periods of increased thromboembolic and bleeding risks. In the ROCKET AF and ARISTOTLE trials of rivaroxaban and apixaban, respectively, ***a 4-fold increase risk of stroke or bleeding was seen at the end of the study period, attributable to lack of a structured approach to ensuring study patients did not have a gap in therapeutic levels of anticoagulation while transitioning to warfarin.*** This underscores the importance of having a carefully constructed and thoughtful approach for anticoagulant transitions, especially for transition to warfarin. [13, Rank 3]

A recent study from a large outpatient anticoagulation clinic showed approximately 4–6 % of their warfarin patients are being switched to direct oral anticoagulants annually. However, these studies collectively suggest that switches between anticoagulants are not infrequent and may be expected to increase. [14, Rank 4]

There are a variety of reasons patients may switch between anticoagulants. Patients may require a switch from parenteral anticoagulants to direct oral anticoagulants for longer-term outpatient

management. Patients may also be switched from warfarin to direct oral anticoagulants, or Direct oral anticoagulants to Direct oral anticoagulants, if they experience a therapeutic failure, have drug intolerance (e.g. rash, dyspepsia, etc.) or if they express a preference for direct oral anticoagulants therapy and are deemed to be an appropriate candidate based on criteria previously discussed. [15, Rank 5]

In addition, there may be times when a patient needs to be switched from direct oral anticoagulants to warfarin, for many of the same reasons, such as drug intolerance, failure or preference. ***Patients may also acquire a new condition or comorbidity that is a contraindication to DOAC therapy, such as pregnancy, severe renal impairment, placement of a mechanical valve or need for dual antiplatelet therapy that necessitates a switch.*** [16, Rank 2]

Other situations that might warrant a switch include gastric bypass surgery where gastric absorption may be significantly altered or the need for new medication, such as protease inhibitor, that poses a major drug interaction with direct oral anticoagulants. In these instances it may be best to maintain the patient on warfarin therapy so levels of anticoagulation can be readily monitored. Patients may also not be able to tolerate oral medications during the perioperative period (e.g. bowel resection or NPO status) and thus may need to be transitioned from a parenteral back to direct oral anticoagulants or from prophylactic-dose direct oral anticoagulants to treatment-dose direct oral anticoagulants.

If a venous thromboembolism patient requires a switch between anticoagulants, clinicians should employ a carefully constructed approach that takes into consideration the patient's anticoagulation status at the time of the switch, their renal function and the pharmacokinetics of the individual direct oral anticoagulants to avoid significant under- or over anticoagulation of their patient. [17, Rank 3]

## Physiological Conditions

### Pregnancy and Breastfeeding

***Animal studies of dabigatran and rivaroxaban demonstrated pregnancy loss and fetal harm,*** and one study demonstrated that dabigatran does cross the human placenta. A case report of maternal rivaroxaban use during weeks 1–19 of pregnancy (when pregnancy discovered at week 19, the patient was switched to enoxaparin) resulted in a full-term, low growth percentile, otherwise healthy infant. ***Apixaban***

***has no human data in pregnancy, but showed no maternal or fetal harm in animal studies. Edoxaban animal studies demonstrated no fetal harm. The edoxaban VTE treatment trial reported 10 pregnancies, with edoxaban exposure during the first 6 weeks of gestation (4 full-term births, 2 pre-term births, 1 first-trimester spontaneous abortion, and 3 elective pregnancy terminations.*** It is unknown whether any of the direct oral anticoagulants are excreted in breast milk. Because of the potential for infant harm, a decision should be made to either avoid breastfeeding or use an alternative anticoagulant, such as warfarin, in these women. [3, Rank 4]

## Body Weight Extremes

Patients at extremes of weight represented a very small proportion of subjects in direct oral anticoagulants venous thromboembolism treatment trials. The mean weight was around 84 kg, with the majority of patients weighing between 60 and 100 kg. Underweight patients (<50–60 kg) comprised 2–13 % of the study populations and roughly 14–19 % of patients were >100 kg. Approximately 30 % of patients in the EINSTEIN, AMPLIFY and RE-COVER studies had a BMI ≥ 30 kg/m2, and in the AMPLIFY and RE-COVER studies, only 12 % of subjects had a BMI ≥ 35 kg/m2. Based on very limited data, extremes of weight do not appear to affect peak concentrations or bioavailability of dabigatran. ***The pharmacokinetics and pharmacodynamics of factor Xa inhibitors may be affected by weight,*** but the clinical impact of these effects remains unknown. Pending further evidence in patients at extremes of weight (e.g., <50 kg, >120 kg or BMI ≥ 35 kg/m2) it is advisable to limit DOAC use to situations where vitamin K antagonists cannot be used. [4, Rank 4]

## Thrombophilia

Patients with thrombophilias represented 2–18 % of direct oral anticoagulants venous thromboembolism clinical trial populations. A posthoc subgroup analysis of thrombophilia patients within the RE-MEDY trial was recently presented. Results showed that the frequencies of venous thromboembolism related death and PE did not differ between dabigatran and warfarin patients. The authors concluded that dabigatran's efficacy in preventing recurrent venous thromboembolism is not influenced by the presence of thrombophilia. Conversely, six cases citing

possible failure of rivaroxaban or dabigatran to prevent thrombosis in patients with antiphospholipid antibody syndrome were recently published. While it is possible the direct oral anticoagulants may be a viable option for venous thromboembolism treatment in patients with weaker underlying thrombophilias (e.g., heterozygous Factor V Leiden), caution or avoidance, especially in highly pro-thrombotic states such as antiphospholipid antibody syndrome or heparin-induced thrombocytopenia, is suggested until further evidence becomes available. [5, Rank 5]

## Cancer

***Four meta-analyses of Direct oral anticoagulants VTE clinical trials including approximately 1000 cancer patients (patients with a history of cancer or some with active cancer) demonstrated similar efficacy and safety for the DOACs compared to conventional therapy of a vitamin*** K antagonist overlapped with LMWH. Previous trials, which included approximately 2000 patients with active cancer (many in advanced stages), indicate that vitamin K antagonists are inferior to long-term LMWH monotherapy for treatment of cancer-related venous thromboembolism. While most evidence to date is with dalteparin, ***the recent CATCH study showing a trend (p = 0.07) towards superiority of tinzaparin over warfarin for prevention of recurrent symptomatic DVT and reduction in clinically relevant non-major bleeding suggests this may be a class effect of the LMWHs. Whether DOACs convey similar benefit as LMWH monotherapy for VTE treatment in cancer patients remains unknown.*** Data from head-to-head randomized controlled trials or robust comparative effectiveness studies is needed and future research in this area is encouraged. Until then, ***among patients with cancer-associated VTE, long-term LMWH is the preferred first-line therapy for anticoagulant treatment. However, for those patients who cannot (or will not) use long term LMWH, either a DOAC or VKA could be prescribed as a second-line option.*** Given their improved safety profile compared to warfarin, direct oral anticoagulants may well be preferred in these instances, particularly among patients with a perceived increased risk for bleeding. However, it is important to emphasize the lack of experience with direct oral anticoagulants compared to warfarin in cancer patients who may have profound thrombocytopenia and other clinical challenges pertaining to anticoagulation. The lack of readily available measurement assays for direct oral

anticoagulants may be particularly problematic in the setting of drug interactions, nephrotoxic chemotherapy, and potential disruption in absorption due to short gut or malnutrition, common issues in a cancer population. [6, Rank 3]

## Patient and Physician Related Barriers

Registries can also provide useful information on the reasons for non-adherence to guidelines and identify barriers to their adoption. GARFIELD-AF highlighted that nearly half of patients with a CHADS2 score ≥2 were not receiving vitamin K antagonists therapy because of physician choice, specifically because of concerns over bleeding risk, patient compliance, and uncertainty regarding guideline recommendations, fall risk or low risk of stroke. Patient factors, such as alcohol misuse, medication refusal, unsuitable co-medication use, or previous bleeding events, were the reasons for not initiating vitamin K antagonists therapy in <16% of cases. Similar reasons were given for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Similarly, in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE), a trial, which enrolled patients who were considered unsuitable for vitamin K antagonists therapy, the primary reason for enrolment in the trial (accounting for 50% of patients) was physician judgement that a vitamin K antagonists was inappropriate. Patient preference accounted for 26% of patients enrolled and specific risk of bleeding for 23% of patients. In the Apixaban vs. Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study, the most frequent reasons for not prescribing vitamin K antagonists were physician judgement that INR monitoring could not be achieved at the requisite frequency (43%) and patient preference (37%). [21, Rank 3]

The Stroke and Atrial Fibrillation Ensemble (SAFE) II study found that having a younger general practitioner and being followed up by a cardiologist were independently associated with the prescription of oral anticoagulants. ***The presence of potential contraindications, lack of an indication, low compliance, and fear of bleeding were reasons given for non-prescription.*** These findings highlight that the lack of physician awareness about oral anticoagulation and how to manage complications is a key barrier to adoption

of guideline-recommended therapies.

Another barrier to the adoption of guidelines arises when they are not considered applicable at a country level, possibly because of regional heterogeneity in patient baseline characteristics (e.g. a high proportion of patients not meeting the criteria for recommended treatments or a perception that the studies underpinning recommendations are based on non-representative populations), differences in current standards of care or cultural perceptions of risk vs. benefit of the intervention. For example, in some Asian countries, the recommended target INR (The international normalised ratio) in patients with AF ≥70 years of age is lower (1.6–2.6) than the recommended target of 2.0–3.0, which is used more widely. Similarly, a lower 15 mg once-daily dose of rivaroxaban (or 10 mg once-daily in patients with creatinine clearance 30–49 mL/min) was specifically tested in patients. [22, Rank 5]

## Access to Guideline Recommended Therapies

In some countries, prescribing of the novel oral anticoagulants is restricted at a national, regional, or local level. However, even though the oral anticoagulants are recommended as a therapeutic option by NICE, many clinical commissioning groups or regional prescribing groups in the UK interpret this 'option' as second line, with warfarin compulsory as first-line therapy. In the UK and Ireland, patients who are closer to the hospital and can attend clinics regularly for coagulation monitoring and dose adjustments are also more likely to receive VKAs than those who live further away. In Eastern European countries (e.g. Hungary), the National Health Service limits the prescription of oral anticoagulants to patients who have had a previous stroke or patients with poor INR control on coumarin therapy. This restriction is in place because the first-line use of the oral anticoagulants is considered financially prohibitive. [23, Rank 3]

Restricted access can also be a result of administrative barriers. For example, in Italy and Hungary, a limited number of specialists are allowed to prescribe the oral anticoagulants; to finalize the prescription, these specialists are required to fill out an electronic case report form, contributing to a compulsory national survey. This is a time-consuming process and, as such, the national Regulatory Authorities have indirectly discouraged routine implementation of the ESC guidelines for antithrombotic treatment. The bureaucratic situation in Italy is mirrored in other countries: in Ireland and some parts of England,

justification forms must be completed to allow physicians to prescribe the oral anticoagulants and, in Spain, patients must have an INR that is recorded to be out of range three times in a row before a patient can be prescribed any of these drugs, and this may take weeks. [24, Rank 4]

Access issues can also arise when updates to guidelines are delayed. For example, the European Stroke Organisation (ESO) has not updated its guidelines on secondary stroke prevention since 2008, and so the novel oral anticoagulants are not included. This influences the daily practice of stroke specialists: in some Eastern European countries, for instance, physicians face financial penalties or even imprisonment if they are not compliant with the guidelines recommended for their specialty, even if the guidelines are outdated and do not reflect the latest clinical advances in the field. In cases such as these, pre-existing guidelines, though relevant when they were published, are themselves a barrier to adopting new approaches or therapies. An update to the European Stroke Organisation (ESO) guidelines is anticipated. [26, Rank 3]

Even if guidelines are up to date, it does not necessarily guarantee access to recommended therapies. However, access to novel oral anticoagulants is still often restricted by local authorities because warfarin is considered to be as effective as the novel oral anticoagulants and is a low-cost drug, albeit with high monitoring costs. Therefore, the newer drugs are often limited to patients who are unstable on warfarin or who have had an ischaemic stroke and are at high risk of intra cerebral haemorrhage. [27, Rank 4]

## Financial Barriers

One of the major reasons for restricted access to new guideline-recommended therapies is perceived cost. Restrictions tend to be made based on a consideration of short-term budget impact, such as the lower acquisition costs of vitamin K antagonists compared with the novel oral anticoagulants, rather than the potential longer term economic impact of events that might have been prevented. Non-vitamin K antagonist oral anticoagulants do not require routine coagulation monitoring, which, in one US study, was shown to cost between $291 and $943 annually per patient. The National Institute for Health and Care Excellence has estimated the annual cost of INR monitoring, including transport costs, at £656 in the first year and £540 thereafter. Longer term cost savings relate to the direct costs of managing the consequences of anticoagulation. For example, considering that novel oral

anticoagulants reduce the risk of intra-cerebral haemorrhage by at least half compared with warfarin, their use could contribute substantially to long-term cost savings. More recently, a study in the USA analysing medicine and pharmacy claims for patients with atrial fibrillation estimated the mean unadjusted all-cause health costs in the year after a warfarin claim to be $41 903 for patients with at least one intra cranial haemorrhage. Despite this, it is often difficult in practical terms to implement a scheme in which a more expensive therapy is paid for from one budget (in this case, drug costs) to provide cost savings that relate to a separate budget (blood tests and monitoring). [28, Rank 3]

The lack of monitoring of the novel oral anticoagulants may also represent a financial barrier to their implementation. In some countries, primary care practices and anticoagulation clinics receive a financial incentive for providing vitamin K antagonists monitoring services, which could be considered under threat with the introduction of the novel oral anticoagulants. However, with appropriate training of personnel, these facilities could be repurposed to take on a role in the initiation and management of the novel oral anticoagulants and management of co-morbidities and to provide valuable guidance and reassurance to patients about their anticoagulation care. Indeed, overall risk factor control, not limited to the use of novel oral anticoagulants, is the most important therapeutic intervention for patients with AF.]

Financial barriers to appropriate vitamin K antagonists management specific to individual countries or regions also exist. In many Eastern and Central European countries, both INR monitoring and travel costs (for blood sampling) are covered by the healthcare system. However, blood sampling takes place in large centralized laboratories that are often a long distance from where the patient lives, meaning that substantial work time is lost through travelling to and from appointments; this can also have a negative impact on patient compliance. [29, Rank 5]

In cost-effectiveness analyses, the novel oral anticoagulants have been shown to be cost-effective compared with warfarin. Robust and well-designed cost-effectiveness analyses can be important when arguing the case for consideration of new therapeutic options with policy makers. However, these analyses are not without limitations. Their general applicability can be limited because of differences in healthcare systems between countries. Furthermore, cost-effectiveness analyses may be inadequate because they do not take into

consideration all factors, particularly indirect costs including loss of work for patients or carers due to INR clinic visits and associated travel costs. Additionally, even demonstrating the cost-effectiveness of a drug within the parameters defined in the analysis may not provide a comparison of cost-effectiveness relative to other established treatments.

In addition to their cost-effectiveness, the relative effectiveness and safety of the novel oral anticoagulants compared with the vitamin K antagonists is an important benefit. The convenience to patients in terms of lack of monitoring and dietary restrictions, which is likely to improve persistence and adherence and therefore clinical outcomes, should also not be underestimated. [30, Rank 2]

## Lack of Recognition of Expanded Eligibility for Oral Anticoagulation

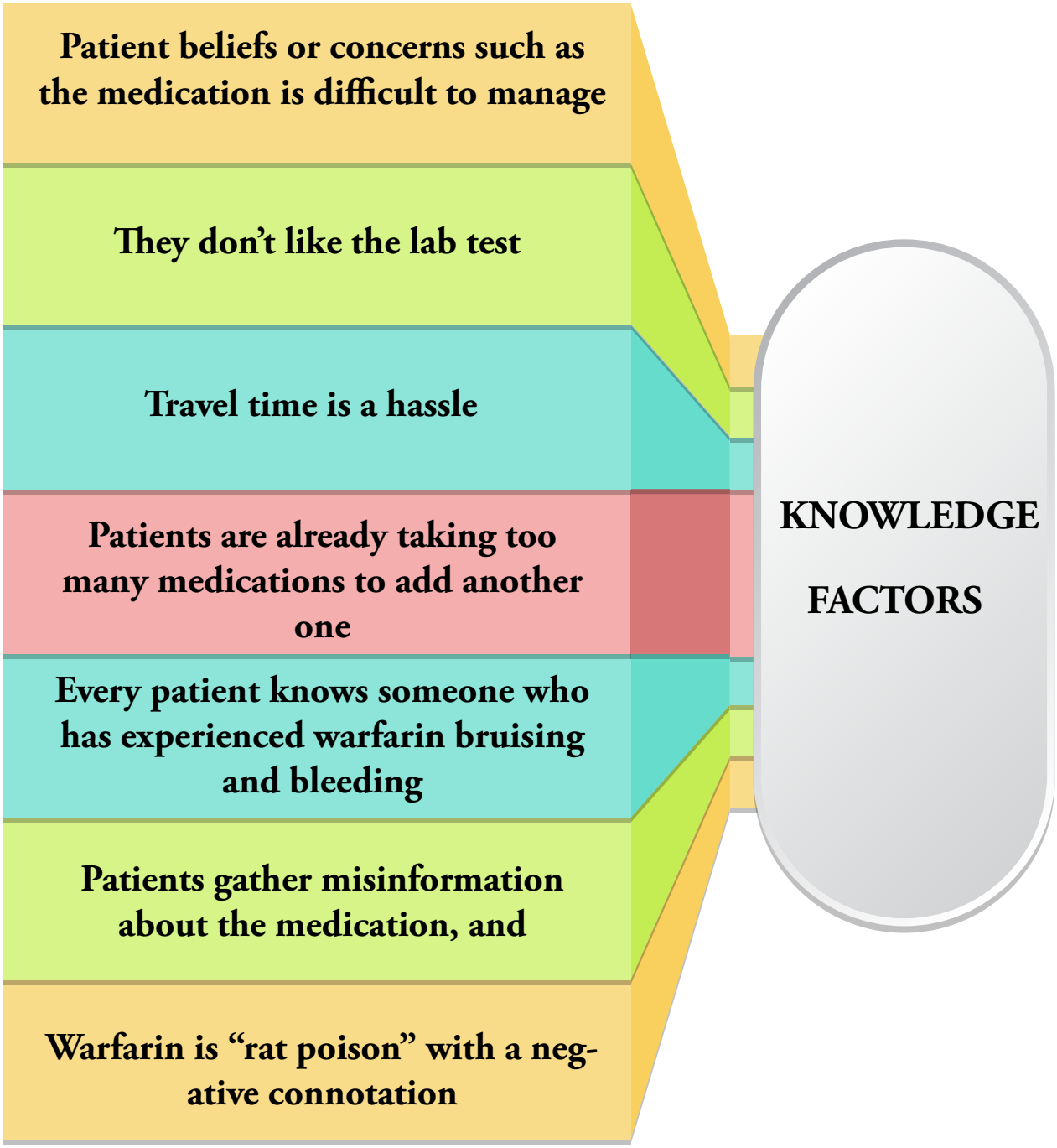
The improved side effect profile of novel oral anticoagulants over vitamin K antagonists may alter oral anticoagulants eligibility. In fact, guidelines have evolved to recommend oral anticoagulants for patients with at least 2 CHA2DS2-VASc risk factors, and to be preferred or considered for patients with at least one CHA2DS2-VASc risk factor. Further, patients not commonly thought to be at high risk for stroke may nonetheless derive benefit from the novel oral anticoagulants, which have lower risk of hemorrhagic stroke and intracranial hemorrhage.

The threshold for oral anticoagulants initiation is determined by the benefit of treatment balanced against the risk of adverse events, notably serious bleeding. The most recent study comparing warfarin to antiplatelet therapy, ACTIVE-W, found that warfarin had a favorable risk-benefit balance among patients with a CHADS2score of 1. Newer data strongly indicate that even relatively low-risk patients with AF benefit substantially from anticoagulant therapy, best shown to date with apixaban. Patients at lower risk of stroke with a CHADS2 score of 1 made up as much as one third of the population in several of the novel oral anticoagulants clinical trials. In the AVERROES trial, patients with CHADS2 score of 0 or 1 had significant relative and absolute reductions in stroke with apixaban versus aspirin (6/1004 (0.54%/year) versus 16/1022 (1.41%/-year), hazard ratio (HR) 0.38, 95% confidence interval (CI 0.14–0.93) but a comparable risk of major bleeding (6/1004 (0.54%/year) versus 6/1022 (0.53%/year), HR 1.02, 95% CI –0.32–3.26). However, neither professional guidelines nor the

Food and Drug Administration (FDA)-approved labeling support initiating OAC among AF patients with a CHADS2 score of 0, and the most recent European and American College of Cardiology/ American Heart Association guidelines recommend no antithrombotic therapy for patients with CHA2DS2-VASc score of 0. [27, Rank 3]

## Patient knowledge

The key to ensuring successful anti-coagulation for atrial fibrillation and related stroke is getting the patient to understand the importance of the medication at the very beginning. Once the patient has actually started taking the medication,



they felt the patient rarely stopped and noncompliance more typically involved patients that may never really began taking the medication. A variety of factors that may indicate a decision to stop treatment. (as shown in Figure 5) [31, Rank 4]

## Recommendations

A series of recommendations was developed around the need to better define why atrial fibrillation and stroke patients are not being treated with anticoagulants especially novel oral anticoagulants to develop methods to measure performance and provide feedback, to improve education with practical guidance for safe and effective use of the novel oral anticoagulants, to leverage coverage and health policy opportunities, and to test and implement interventions at a health system level. They are provided below.

- Define reasons for oral anticoagulant underuse classified in ways that can guide intervention to improve use.
- Increase the awareness of stroke risk and the value of oral anticoagulant use via impactful educational initiatives.
- Collect data and feedback performance regarding oral anticoagulant use among eligible patients to providers.
- Define who should receive vitamin K antagonists rather than novel oral anticoagulants.
- Identify novel oral anticoagulants reversal agents and monitoring strategies.
- Minimize the duration of dual antiplatelet therapy and concomitant oral anticoagulants use.
- Improve time in therapeutic range for patients on warfarin.
- Understand mechanism of oral anticoagulant use and outcomes (effectiveness and safety) in general practice.
- Better align health system incentives.
- Define other indications for oral anticoagulants [32, Rank 3]

## Conclusion

As clinicians gain experience using these new anticoagulation options to reduce the risk of stroke in patients with nonvalvular AF, they should remind themselves that they are not trying to hit the ball out of the park by first using these therapies for their most challenging patients. Instead, they should start these treatments in

patients who have nonvalvular AF and several stroke risk factors but for whom treatment is expected to be uncomplicated; for example, patients with normal renal function, average body weight, no history of gastrointestinal bleeding, and no concomitant medications associated with drug interactions. Once clinicians have established a comfort level in using novel oral anticoagulants to treat these patients, they can expand to treat a wider patient population with more complex risks. [25, Rank 5]

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

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