LONG TERM ANTICOAGULATION INDICATIONS, CHOICES & CONSIDERATIONS

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Long Term Anticoagulation Indications, Choices & Considerations

ANCC Accredited NCPD Hours: 2.3 hrs

Target Audience: RN/APRN

Need Assessment

Anticoagulation medications are high-risk drugs. In 2008, The Joint Commission published a new National Patient Safety Goal (NPSG) to address high-risk anticoagulation drugs used for treatment. This Goal, with an implementation date of January 2009, required organizations to develop and implement standardized practices in order to reduce harm. The pharmacokinetic characteristics of anticoagulants make prescribing complex. Provider choices and considerations act as a barrier against long term anticoagulation therapy. Thus it is imperative that Practitioners/ Nurses are aware of specific treatments, indications and choices so as to maximise their benefits and minimise their pitfalls.

Objectives

- Identify two new oral anticoagulants
- Describe the role of direct FXa inhibitors in anticoagulation therapy
- Discuss the choices of direct thrombin inhibitors in anticoagulation therapy
- Describe the pharmacology of NOACs when compared with Warfarin
- Discuss the clinical considerations applied in the management of new oral anticoagulants

Goal

The goal of this article is to evaluate the indications, choices and considerations in clinical management of patients in high-risk subgroups and issues that may be faced by clinicians prescribing long term anticoagulants

Introduction

Immediately acting unfractionated heparins (UFHs), low molecular weight heparins (LMWHs), hirudins or argatroban, and slowly acting vitamin K antagonists (VKAs) reduce the morbidity and mortality of patients at risk of recurrent venous thromboembolism (VTE), cerebral and non-cerebral embolism, and coronary occlusion or reocclusion. The use of these anticoagulants is limited by several drawbacks. Heparins, LMWHs, hirudins and argatroban have to be administered intravenously or subcutaneously and require dose adjustment guided by monitoring of the anticoagulant effect. LMWHs have to be administered subcutaneously, with the dose being adjusted in older patients and in renal impairment. Severe side effects such as heparin-induced thrombocytopenia or the generation of antibodies to hirudins and other drug-related side effects limit their administration. The main downsides of VKAs are the requirement

of regular dose adjustments by monitoring the anticoagulant effect, the low prevalence of international normalized ratio (INR) values within the therapeutic range (2–3), the interactions with food and many drugs, severe intracranial and extracranial bleeding complications, and other severe side effects such as coumarin-induced hepatitis. The slow onset and offset of action of VKAs necessitate simultaneous administration of heparins and LMWHs during the induction of anticoagulation as well as during surgical interventions. [1, Rank 5]

Indications for Anticoagulant Therapy

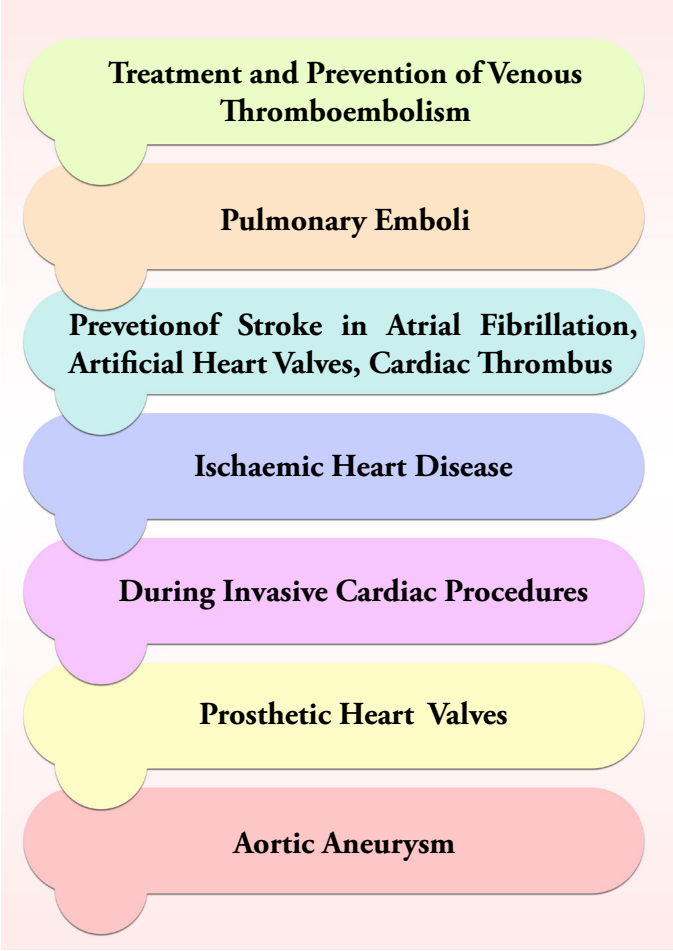

Figure 1: Anticoagulant therapy - Indications

Vitamin K antagonists such as warfarin, phenprocoumon, and acenocoumarol reduce the rate of atrial fibrillation related

stroke by approximately 40 % relative to acetylsalicylic acid (ASA). However, owing to the narrow therapeutic range, large intra-individual variation in response, unpredictable pharmacology, and numerous drug interactions associated with Vitamin K antagonists use, routine coagulation (international normalized ratio) monitoring is required to avoid an excess risk of cerebrovascular events.

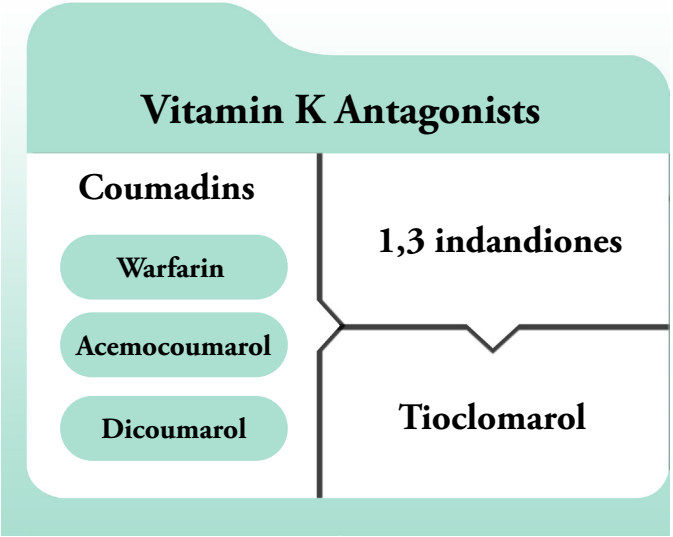

Figure 2: Vitamin K antagonists

Types of Anticoagulants

Figure 3: Factor Xa Inhibitors

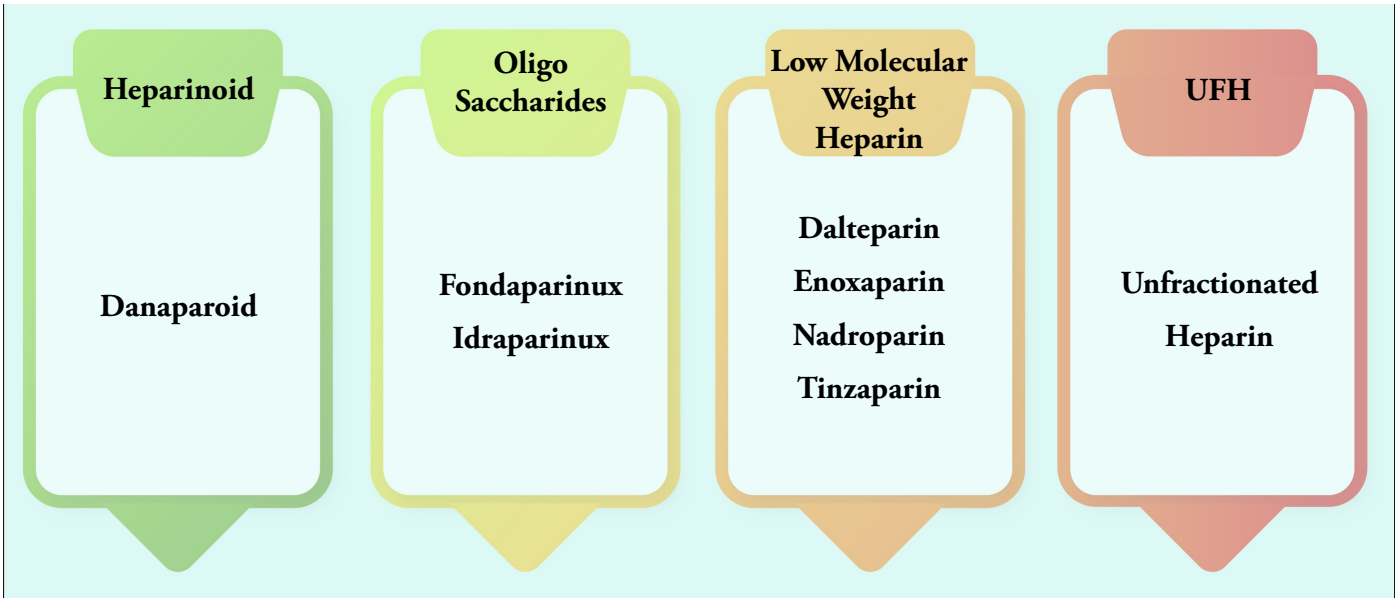

Figure 4: Heparins and Heparinoids

Together with diet and lifestyle restrictions, this negatively impacts on patients' quality of life, contributes to under-prescribing, and is responsible for poor compliance in some patients. Real-world evidence from patients with newly diagnosed non-valvular atrial fibrillation enrolled in cohort one of GARFIELD-AF (between 2009 and 2011, before widespread approval of the new oral anticoagulants) indicates that under-prescribing of oral anticoagulants and over-reliance on antiplatelet agents is commonplace; approximately 40 % of patients did not receive oral anticoagulants (against guideline recommendations), and the majority of these patients (around two-thirds) received antiplatelet agents alone. [13, Rank 4]

The choice of any antithrombotic agent is based on achieving a balance between the patient's risks of thromboembolism and bleeding. Current international guidelines in atrial fibrillation advocate use of the CHADS2 and the CHA2DS2-VASc scores for assessing stroke risk. In general, oral anticoagulation is recommended for all patients with atrial fibrillation, except for low-risk patients with a CHADS2 or CHA2DS2-VASc score of 0 (including women aged <65 years with no other risk factors), who do not need any antithrombotic therapy.

The updated ESC 2012 guidelines no longer recommend the use of antiplatelet agents for stroke prophylaxis (except in patients refusing oral anticoagulants therapy), and the 2014 American Heart Association (AHA) guidelines reserve it as an

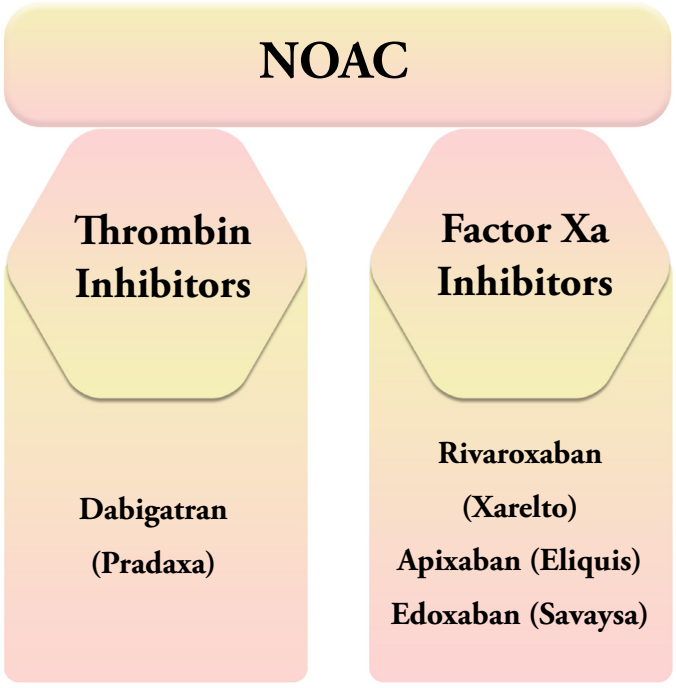

Figure 5: Classification of New Oral Anticoagulants

> "CHADS2 - 1 point each for Congestive heart failure, Hypertension, Age ≥75 years, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack.
> CHA2DS2-VASc - as CHADS2, but 2 points for Age ≥75 years and 1 point each for vascular disease, Age 65–74 years, and Sex category female."

alternative to oral anticoagulation or to no therapy in patients with a CHA2DS2-VASc score of 1. The balance between anticipated benefit and potential risk of bleeding with oral anticoagulants therapy should be considered on an individual basis. However, according to the guidelines, bleeding risk alone should not be used to exclude patients for anticoagulation, but should draw attention to modifiable risk factors affecting the risk of bleeding. [14, Rank 2]

Clinical Trial Data in Licensed Indications

Prevention of venous thromboembolism after elective hip or knee replacement in adults

Patients are at high risk of venous thromboembolism after major elective orthopaedic surgery. Without thrombo-prophylaxis, the estimated incidence of deep vein thrombosis (DVT) is 40–60%. Apixaban, dabigatran and rivaroxaban are all approved in the EU for the prevention of venous thromboembolism after elective hip or knee replacement surgery. The approvals are based on the results of phase III trials in which each drug was compared with standard thromboprophylaxis with subcutaneous enoxaparin. Edoxaban has not undergone a European phase III study in this indication. [15, Rank 3]

The ADVANCE trials compared apixaban with enoxaparin 30 mg twice daily started 12–24 h after surgery (used in North America; ADVANCE-1) or 40 mg

once daily started 12 h before surgery (used in Europe) after elective total hip (THR; ADVANCE-3) or total knee (TKR; ADVANCE-2) replacement surgery in a total of 11 659 patients. Apixaban was shown to be superior to enoxaparin 40 mg once daily for the reduction of the incidence of venous thromboembolism - reduction in occurrences: 64% total hip replacement (THR); 38% total knee replacement (TKR), with no significant differences in the incidence of major bleeding events. However, apixaban did not meet non-inferiority criteria compared with enoxaparin 30 mg twice daily.

Dabigatran has also obtained mixed results from phase III trials for the prevention of venous thromboembolism after total hip replacement and total knee replacement, which involved 10265 patients. Dabigatran, at both doses tested -150 mg once daily and 220 mg once daily, starting with a half-dose 1–4 h post-surgery , was non-inferior to enoxaparin 40 mg once daily - started the evening before surgery, with no statistical difference in the incidence of major bleeding; however, dabigatran - starting with a half-dose 6–12 h post-surgery failed to meet non-inferiority criteria against enoxaparin 30 mg twice daily, started 12–24 h after surgery. [16, Rank 4]

Rivaroxaban has been studied in four prospective phase III studies: RECORD1 and RECORD2 involved patients undergoing THR surgery, and RECORD3 and RECORD4 involved patients undergoing TKR surgery. Unlike apixaban and dabigatran, rivaroxaban (started 6–8 h after surgery) demonstrated superior efficacy for the prevention of total VTE versus all enoxaparin regimens (40 mg once daily started 12 h before surgery, RECORD1–3; 30 mg twice daily started 12–24 h after surgery, RECORD4), with no significant differences in major bleeding events. A pooled analysis of all four studies, involving 729 patients, demonstrated a 50% reduction (p=0.001) in the composite of symptomatic venous thromboembolism and all-cause mortality with rivaroxaban compared with enoxaparin. The incidence of bleeding was similar (6.6% vs 6.2%) during active treatment. Rivaroxaban has also been studied in a phase IV, non-interventional open-label study (XAMOS), in which the attending physician determined which type and regimen of drug was used. Overall, these results are somewhat mixed, which may partly be explained by variations in the dosing approach of the direct oral anticoagulants and comparator regimen arms. [17, Rank 4]

Venous Thromboembolism – Treatment and Secondary Prevention

Venous Thromboembolism (DVT and pulmonary embolism (PE)) is associated with significant morbidity and mortality, and its incidence increases with age. Rivaroxaban has been approved in the EU and the USA for the treatment of deep vein thrombosis and pulmonary embolism and for the prevention of recurrent Venous Thromboembolism. Apixaban, dabigatran and edoxaban have also completed phase III trials for both acute and secondary prevention of Venous Thromboembolism; they are not yet licensed in this indication in the EU, but dabigatran has recently been approved for Venous Thromboembolism treatment in the USA. [18, Rank 3]

It is important to note the different approaches of the phase III studies of direct OACs for Venous Thromboembolism treatment. For acute treatment, rivaroxaban and apixaban, given as single-drug treatments, were compared with standard parenteral anticoagulation overlapping with and transitioning to a vitamin K antagonists; in contrast, dabigatran and edoxaban were compared with standard therapy after induction by a parenteral agent. Only rivaroxaban was tested in separate studies in patients with Deep Vein Thrombosis - without pulmonary embolism or PE (with or without DVT). All four direct oral anticoagulants were non-inferior to standard therapy for prevention of recurrent venous thrombo embolism. Compared with standard therapy, apixaban (in AMPLIFY) and rivaroxaban (in EINSTEIN PE) led to significantly less major bleeding, whereas rivaroxaban (in EINSTEIN DVT), dabigatran (in RE-COVER and RE-COVER II) and edoxaban (in Hokusai-VTE) led to significant reductions in clinically relevant bleeding. Pooled analyses of the EINSTEIN DVT and EINSTEIN PE studies, and the RE-COVER studies, have supported the overall efficacy and safety of rivaroxaban and dabigatran, including in high-risk subgroups such as the elderly, patients with low body weight and those with unprovoked initial Venous Thromboembolism.

Because it is not standard practice to give long term anticoagulation for the prevention of recurrent Venous Thromboembolism in the extended treatment studies, apixaban (AMPLIFY-EXT), rivaroxaban (EINSTEIN EXT) and dabigatran (RE-SONATE) were all compared with placebo. All three direct oral anticoagulants were associated with significant reductions in the incidence of recurrent Venous Thromboembolism with a low incidence of

major bleeding. However, long-term or even lifelong anticoagulation is recommended for some patients who have suffered a Venous Thromboembolism. Uniquely, dabigatran was directly compared with warfarin for long-term secondary prevention of Venous Thromboembolism and was shown to have non-inferior efficacy, with 50% fewer major bleeding events but a significant increase in the incidence of ACS (0.9% vs 0.2%; p=0.02). [19, Rank 2]

Stroke Prevention in Atrial Fibrillation

More than six million people suffer from atrial fibrillation in the EU, and the prevalence of from atrial fibrillation increases 0 age. Patients with from atrial fibrillation have an increased risk of stroke, and stroke-associated deaths in the EU total more than one million annually. Vitamin K antagonists such as warfarin have proved remarkably effective in reducing this risk of stroke. Despite this, patients with from atrial fibrillation at high risk of stroke are often undertreated, and Vitamin K antagonists are associated with limitations.

The phase III trials for apixaban (ARISTOTLE), dabigatran (RE-LY), rivaroxaban (ROCKET AF) and edoxaban (ENGAGE-AF) involved large numbers ofpatients with non-valvular from atrial fibrillation (between 14 000 and 18 000) and evaluated the agents' efficacy in the prevention of stroke or systemic embolism compared with that of dose-adjusted warfarin (target international normalised ratio (INR) 2.0–3.0). Dabigatran is approved at the 150 mg twice-daily dose, with 110 mg twice daily approved for at-risk groups in whom dose adjustment may be required. These groups include patients aged ≥80 years and those taking concomitant verapamil, but dose reduction can also be considered, based on assessment of thromboembolic and bleeding risk, for individuals aged 75–80 years, those with moderate renal impairment, patients with gastritis, oesophagitis or gastro-esophageal reflux, and any other patients at increased risk of bleeding.

In these phase III trials, dabigatran 150 mg twice daily and apixaban 5 mg twice daily demonstrated superiority to warfarin in the reduction of stroke and systemic embolism (34% risk reduction for dabigatran; 21% risk reduction for apixaban; p<0.001 for both). Edoxaban 60 mg once daily was superior (p=0.02) to warfarin, whereas edoxaban 30 mg once daily was non-inferior (p<0.005 for non-inferiority) to warfarin. Dabigatran 110 mg twice daily and rivaroxaban 20 mg once daily were non-inferior to warfarin (p<0.001 for non-inferiority). In subsequent subgroup

analyses, the relative safety and efficacy of these agents was similar regardless of patients' history of stroke or transient ischaemic attack. Dabigatran (150 mg twice daily) is the only agent to have achieved significant reductions in both ischaemic stroke (p=0.03) and haemorrhagic stroke (p<0.001), whereas apixaban, for example, reduced the rate of haemorrhagic stroke only. [20, Rank 4]

A concern with anticoagulants is the increased risk of bleeding at critical sites or bleeding that proves fatal. Rivaroxaban and dabigatran (150 mg twice daily) resulted in similar incidences of major bleeding compared with warfarin (p=0.58 and p=0.31, respectively), whereas apixaban reduced the risk of major bleeding by 31% (p<0.001); however, the definitions of major bleeding varied by trial. Rivaroxaban and dabigatran were associated with more gastrointestinal bleeding events compared with warfarin in patients with Atrial Fibrillation, and the dabigatran 150 mg dose led to a slight but significant increase in the rate of myocardial infarction.

In the absence of true direct (head-to-head) clinical trials, comparisons of results across different trials remain inadvisable due to different study populations and trial designs. For example, RE-LY included patients at lower risk of stroke than the other studies. ROCKET from atrial fibrillation included a higher-risk population with a mean CHADS2 score of 3.5 compared with 2.1 in both RE-LY and ARISTOTLE; in ENGAGE-AF, 77% of patients had a CHADS2 score ≤3.

Apixaban has also been evaluated in a smaller trial (AVERROES), in which patients for whom Vitamin K antagonists therapy was not suitable were assigned to receive either apixaban or acetylsalicylic acid (ASA). Apixaban reduced the risk of stroke by >50% (p<0.001) compared with acetylsalicylic acid, without significantly increasing the risk of major bleeding or intracranial haemorrhage. Acetylsalicylic acid is no longer recommended for the prevention of stroke, given that the results of numerous trials have demonstrated its low efficacy in stroke prevention compared with warfarin and its increased bleeding risk compared with placebo. [21, Rank 5]

Choices of New Oral Anticoagulants

Indirect, Antithrombin Dependent Anticoagulants

Idraparinux and Idrabiotaparinux

The antithrombin-dependent indirect inhibitors in development are idraparinux, idrabiotaparinux and semu-

loparin. Idraparinux and idrabiotaparinux are polymethylated derivatives of fondaparinux. Their elimination half-life increases from 7 days after single administration up to 60 days after a 6–12 month treatment period. The development of idraparinux was terminated due to the very long elimination half-life and due to increased bleeding after treatment for longer than 6 months. Biotinylated Idraparinux, named idrabiotaparinux, is structurally similar to idraparinux, with the addition of a biotin segment. It has the same anticoagulant activity as idraparinux. Avidin exposes a strong affinity to biotin and can be given intravenously to rapidly bind, neutralize and eliminate idrabiotaparinux. [22, Rank 4]

Idrabiotaparinux was investigated in a randomized double blind trial in 757 patients with symptomatic deep venous thrombosis, comparing equimolar doses of idrabiotaparinux (3 mg) with idraparinux (2.5 mg) subcutaneously once weekly for 6 months. Inhibition of Factor Xa was similar in the two treatment groups. Recurrent Venous Thromboembolism occurred in 2.3% of patients randomized to idrabiotaparinux and in 3.2% of patients randomized to idraparinux (not different). The incidence of clinically relevant bleeding was 5.2% in the idrabiotaparinux group and 7.3% in the idraparinux group. Deaths were not different between the groups.

The concentration of the two idraparinux and idrabiotaparinux did not differ in the study. They did not reach steady state conditions after 6 months of therapy. During a 3 month post-study observation period, the decline of the concentration of the anticoagulants was not determined. An increase of the elimination half-life of idraparinux up to 60 days was described during 6 to 12 months' treatment with idraparinux. This long half-life may be related to the observed bleeding complications. Such information was not generated during administration of idrabiotaparinux. Idrabiotaparinux (3.0 mg) once weekly subcutaneously compared with INR-adjusted warfarin for 6–12 months was investigated for the prevention of embolic events in patients with atrial fibrillation. [23, Rank 3]

Semuloparin

Semuloparin, previously named AVE5026, is an ultra-low molecular weight heparin with a mean molecular weight of 2500 Da (range of conventional LMWH 2000–10 000 Da) and an anti-FXa/antithrombin ratio of >30. The following studies using 20 mg semuloparin once daily (OD) subcutaneously have been

completed: prophylaxis of post-operative thromboembolism following elective knee or hip surgery or hip fracture, extended prophylaxis of venous thromboembolism in patients having undergone hip fracture surgery (SAVE-HIP3), prevention of venous thromboembolism in acutely ill medical patients with restricted mobility (SAVE-VEMED), prevention of venous thromboembolism in patients undergoing major abdominal surgery (SAVE-ABDO), prevention of venous thromboembolism in cancer patients undergoing chemotherapy (SAVE-ONCO). [24, Rank 5]

SR123781

SR123781 is a short-acting synthetic hexadecasaccharide for OD injection, which is an indirect antithrombin-dependent inhibitor of Xa coagulation factor. The DRIVE phase IIb study evaluating the hexadecasaccharide in the prevention of venous thromboembolic events in patients undergoing total hip replacement demonstrated a correlation between dose and clinical response, with a positive efficacy/safety ratio. The SHINE phase IIb study evaluated SR123781 in patients with non-ST elevated acute coronary syndrome. The study demonstrated good safety, with a bleeding rate similar to UFHs with or without abciximab. [25, Rank 5]

Direct Factor Xa (FXa) Inhibitors

Intravenous Direct FXa Inhibitor

Otamixaban is a direct potent and selective inhibitor of FXa for intravenous administration. Its half-life is 0.5–1.5 h and it is renally excreted by up to 30%. A phase IIb dose-finding study showed similar TIMI bleeding (major or minor) for all dose groups of otamixaban as compared with intravenous laboratory-adjusted UFH (two to threefold prolongation of the activated partial thromboplastin time). Ongoing studies investigate the influence of renal and hepatic impairment on the metabolism of otamixaban, and the efficacy compared with UFH plus eptifibatide in patients with unstable angina. [26, Rank 3]

Oral Direct Factor Xa Inhibitors

The largest group of anticoagulants consists of direct FXa and direct thrombin inhibitors (DTIs). Direct FXa inhibitors are given intravenously as otamixaban or orally such as rivaroxaban, apixaban, edoxaban, betrixaban. All compounds directly and selectively bind to free FXa and to FXa bound to phospholipids.

Rivaroxaban is a competitive, reversible, direct FXa inhibitor with a Ki of 0.4

nM for purified human FXa and a molecular mass of Mr = 435.89. After oral administration in man, 60 to 80% are absorbed. Peak plasma levels are achieved in 3 h, and the drug circulates with a half-life of 9 h. Rivaroxaban is excreted by the kidney (66%) and the liver (28%) mainly as unchanged drug. Co-administration of rivaroxaban with food increased the peak plasma concentrations slightly. No additive effects on platelet aggregation were observed during intake of aspirin or the non-steroidal anti-inflammatory drug naproxen, antazid drugs or digoxin. The half-life of rivaroxaban is prolonged in the elderly and in patients with renal impairment. [27, Rank 1]

Rivaroxaban was investigated in two independent dose-finding studies for the treatment of acute deep vein thrombosis. It was decided to treat patients with 15 mg twice daily (BID) rivaroxaban for 3 weeks followed by 20 mg OD rivaroxaban over 3–12 months in a large phase III clinical trial. This intervention was compared with body-weight adjusted enoxaparin (1 mg/kg body weight bid) followed by warfarin adjusted to an INR of 2–3. The trial was open, prospective and randomized in patients with acute deep vein thrombosis. During 3–12 months' therapy, 2.1% of patients initially randomized to rivaroxaban developed recurrent VTE (deep vein thrombosis or pulmonary embolism) as compared with 3.0% of patients initially randomized to enoxaparin/warfarin (P < 0.001 for non-inferiority). Major and clinically relevant bleeding complications occurred in 8.1% of patients in both treatment groups. [28, Rank 2]

After termination of prophylaxis of recurrent VTE after initial acute deep vein thrombosis or pulmonary embolism, thromboembolic events re-occur in up to 10 patients within 1 year. Therefore, the benefit of a prolonged prophylaxis of VTE was investigated in patients following a 6 months' anticoagulation of acute deep vein thrombosis using 20 mg OD rivaroxaban compared with placebo over 12 months for prevention of recurrent VTE in a double-blind study. Patients (7.1%) initially randomized to placebo (n = 594) developed a recurrent VTE during 12 months compared with 1.3% of patients initially randomized to rivaroxaban (n = 602, P = 0.001 for superiority). Severe bleeding complications occurred in 0.7% of patients on rivaroxaban, but in no patient receiving placebo (P= 0.05). [29, Rank 3]

The benefit of an oral anticoagulation with rivaroxaban has been demonstrated for the treatment of acute deep vein thrombosis and recurrent events over a period of 3–12 months as well as the prolonged prophylaxis of recurrent VTE

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The benefit of an oral anticoagulation with rivaroxaban has been demonstrated for the treatment of acute deep vein thrombosis and recurrent events over a period of 3–12 months as well as the prolonged prophylaxis of recurrent VTE for additional 12 months. The safety of rivaroxaban is comparable with that of warfarin. The benefit on mortality remains to be investigated. Rivaroxaban is currently investigated for the treatment of acute symptomatic pulmonary embolism and the prevention of recurrent events. [30, Rank 5]

Patients with atrial fibrillation and a CHADS2 score above 2 were randomly assigned to 20 mg OD rivaroxaban or warfarin adjusted to an INR of 2–3 in a prospective randomized double-blind study. The mean follow-up was 706 days for rivaroxaban and 708 days for warfarin. The mean CHADS2 score was 3.5 in both treatment groups. Cerebral and non-cerebral embolism occurred in 1.71% per year in patients initially randomized to rivaroxaban and in 2.16% per year in patients initially randomized to warfarin (non-inferiority, P < 0.001, hazard ratio 0.79, 95% confidence interval 0.66–0.96). The superiority of overall safety in the treatment population (total n = 14 143) was significant (P = 0.015). Based on the intention to treat analysis (n = 14 171), cerebral and non-cerebral embolic events occurred in 2.12% per year in patients initially randomized to rivaroxaban and in 2.42% per year in patients initially randomized to warfarin (P = 0.117). Haemorrhagic strokes occurred at rates of 0.26% per year under rivaroxaban

and 0.44% per year under warfarin (hazard ratio 0.59, 95% confidence interval, 0.37–0.93 P = 0.024). Mortality was similar in both treatment groups, with 1.87% per year during treatment with rivaroxaban and 2.21% per year for patients treated with warfarin (P = 0.073). Severe bleeding complications were observed in 3.6% on treatment with rivaroxaban and in 3.45% of patients on treatment with warfarin (P = 0.576). Other bleeding complications were also similar in both treatment groups: 11.8% per 100 years for patients on rivaroxaban and 11.37% per 100 years for patients on warfarin (P = 0.345).

The reduction of embolic events by rivaroxaban was less frequently accompanied by bleeding complications compared with warfarin on the basis of the safety analysis. However, using the intention to treat analysis, the incidence of cerebral and non-cerebral embolic events was not different for rivaroxaban compared with warfarin. Intracerebral haemorrhagic bleeding occurred less frequently during treatment with rivaroxaban. This is comparable with the results of the randomized evaluation of long-term anticoagulant therapy (RE-LY) study. Other relevant side effects were not different between the two treatment groups. [27, Rank 5]

Prevention of ischaemic events in patients with unstable angina with rivaroxaban was investigated in a phase IIb study and is currently investigated in a phase III trial. Apixaban is a selective and potent (Ki = 0.08 nM) inhibitor of both free and prothrombinase-bound FXa in human plasma. Following oral administration in human, the compound is absorbed to 80% within 3.5 h and is eliminated with a half-life ranging from 8 to 15 h. It is eliminated to about 25% by urinary excretion. Apixaban is not a significant inhibitor of CYP enzymes or P-glycoprotein and, therefore, is unlikely to be a significant perpetrator of drug–drug interactions. Apixaban is investigated for the treatment of acute deep vein thrombosis or pulmonary embolism, and for the extended prophylaxis of recurrent events. [22, Rank 3]

Apixaban was compared with aspirin for the prevention of cerebral and non-cerebral embolism in 5600 patients with atrial fibrillation in whom vitamin K antagonists were not indicated according to the case history or the decision of the patient or the treating physician. Apixaban (5 mg BID) (n = 2808) was compared with acetylsalicylic acid (81–324 mg) OD (n = 2791) in a double-blind prospective and randomized trial. A subgroup of patients at an age >80 years, a creatinine clearance <50 mL•min−1 or a risk factor for bleeding, received 2.5 mg BID apixaban. The reasons for unsuitability of vitamin K antagonists therapy were not

different between the groups; main reasons were assessment that INR was unlikely to be measured at requested intervals, patients' refusal to take vitamin K antagonists and multiple reasons for unsuitability of vitamin K antagonists therapy (multiple reasons possible). Patients had a mean CHADS score of 2.0 (apixaban group) or 2.1 (aspirin group). Cerebral and non-cerebral embolism occurred in 1.6% of patients per year during treatment with apixaban and in 3.7% of patients per year under aspirin (hazard ratio 0.45, 95% confidence interval, 0.32–0.62, P < 0.001 for superiority). Death rates were 3.5% per year for patients treated with apixaban and 4.4% per year for patients treated with aspirin not significant. Major bleeding complications were not different and occurred in 1.4% of patients per year under apixaban and in 1.2% under aspirin (hazard ratio 1.13, 95% confidence interval, 0.74–1.75, P = 0.57). Haemorrhagic stroke, myocardial infarction and death were not different in the treatment groups. Hospitalization for a cardiovascular cause occurred more frequently in patients treated with aspirin (15.9% per year) as compared with apixaban (12.6% per year) (P < 0.001). Minor bleeding complications were higher in patients treated with apixaban (5.0% per year) compared with aspirin (3.6% per year, P = 0.05). Apixaban was shown to be superior to aspirin for the prevention of cerebral and non-cerebral embolism in patients with atrial fibrillation. [20, Rank 3]

Direct Thrombin Inhibitors

The most relevant synthetic, small molecule DTIs are argatroban, ximelagatran and dabigatran etexilate, and AZD 0837. They bind specifically to the active centre of thrombin and inactivate free and fibrin-bound thrombin. After inactivation of thrombin, the inhibitors reverse from their binding site, thereby leaving a small amount of free and active thrombin available to control haemostasis. The vascular binding differs from that of the irreversible, non-covalent binding of the DTIs hirudin and hirologs. AZD 0837 is a prodrug of the direct inhibitor AR-H067637, with a concentration that dependently inhibits tissue factor-induced generation of free thrombin. The inhibition constant is in the same concentration range as reported for melagatran and dabigatran. [19, Rank 4]

Oral Direct Thrombin Inhibitors

Dabigatran, an oral direct thrombin inhibitor, has been investigated for the treatment of acute deep vein thrombosis and pulmonary embolism and the prevention of recurrent events over 6 months

compared with warfarin in a double-blind prospective randomized trial. Patients were initially treated with 150 mg BID dabigatran or body weight adjusted enoxaparin (1 mg•kg–1 body weight BID) or with warfarin adjusted to an INR of 2–3. 2.4% of patients initially randomized to dabigatran (n = 1274) and 2.1% of patients initially randomized to warfarin (n = 1265) developed recurrent thromboembolic events. The study hypothesis of non-inferiority was fulfilled (P = 0.001, relative risk 1.1, 95% confidence interval 0.65–1.86).

Dabigatran has been proven to be effective and safe for the treatment of acute VTE and prevention of recurrent events. The advantage of this study over the analogous study on rivaroxaban is its double-blind study design. A minor limitation in the study is the occurrence of dyspepsia. [17, Rank 2]

In a phase III trial, RE-LY compares the efficacy and safety of two blinded doses of dabigatran etexilate with open-label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It was a prospective, multicentre, randomized, open-label, controlled parallel group, non-inferiority trial. Systemic embolic events occurred in 1.69% per year in patients randomized to warfarin, 1.53% per year in patients randomized to 110 mg dabigatran BID and 1.11% per year in patients randomized to 150 mg dabigatran BID [relative risk (RR) 0.91, CI 0.74 to 1.11, P < 0.001 for non-inferiority with 110 mg dabigatran BID; and RR 0.66, CI 0.53 to 0.82, P < 0.001 for superiority with 150 mg dabigatran BID]. Major bleeding occurred in 3.36% of patients per year on warfarin, in 2.71% of patients per year on 110 mg dabigatran BID (P = 0.003),and 3.11% of patients per year on 150 mg dabigatran BID [not significant (NS)]. The mortality rates were 4.13, 3.75 and 3.64% per year in the warfarin, 110 and 150 mg dabigatran groups (NS and P = 0.051 vs. warfarin), respectively. Dyspepsia occurred in 348 patients (5.8%) in the warfarin group and in 707 patients (11.8%) and 688 patients (11.3%) in the 110 and 150 mg dabigatran groups, respectively (P < 0.001 each). The rates of myocardial infarction were 0.53% per year with warfarin, 0.72% per year with 110 mg BID dabigatran (RR 1.35, 95% CI 0.98 to 1.87; P = 0.07) and 0.74% per year with 150 mg BID dabigatran (RR 1.38, 95% CI 1.00 to 1.91; P = 0.048). [25, Rank 1]

The dabigatran treatment in patients with atrial fibrillation who completed RE-LY trial (RE-LY-ABLE) is an extension trial of dabigatran treatment in patients who successfully completed the RE-LY study. The trial will provide an opportunity

for about 8000 patients to remain on blinded 110 mg BID and 150 mg BID dabigatran for 12–36 months without switching to vitamin K antagonists. The data will provide additional safety information on patients with long-term exposure to dabigatran. [15, Rank 5]

The RE-LY study compares two doses of dabigatran with warfarin. For the first time, an anticoagulant regimen of 150 mg BID dabigatran was proven to be more effective in reducing embolic events in patients with atrial fibrillation compared with warfarin. In addition, cerebral haemorrhage occurred significantly less with both doses of dabigatran compared with INR-adjusted warfarin. The higher incidence of myocardial infarction was outweighed by the benefits of dabigatran on the other endpoints. The continuation of patients in the RE-LY-ABLE study will generate additional safety data for dabigatran. The Food and Drug Administration has approved the 150 mg BID dabigatran dose for the prevention of embolism in patients with atrial fibrillation as well as a dose of 75 mg BID dabigatran for patients with impaired renal function (creatinine clearance 20–50 mL•min–1).

Currently, the costs of the drug dabigatran for the prevention of stroke in patients with atrial fibrillation currently exceed that of warfarin by about 7000-fold. Therefore, the quality-adjusted survival, costs and cost-effectiveness of dabigatran were compared with those for warfarin adjusted to an INR of 2–3 using the data of the patients included into the RE-LY study. The Markov decision model was used for this analysis. Warfarin targeted at an INR of 2–3, dabigatran 110 mg BID and dabigatran 150 mg BID was compared. Outcome measures were quality-adjusted life years, costs in US$ (year 2008) and incremental cost-effectiveness ratios. The model was sensitive to the costs of dabigatran but was relatively insensitive to other model inputs. According to this model, high-dose dabigatran was more cost-effective than low-dose dabigatran. The analysis showed that treatment with dabigatran could be cost-effective compared with warfarin for the prevention of cerebral and non-cerebral embolism in patients above 65 years and with an increased risk of stroke. The main limitation of this investigation was the assumption of no change of the costs for dabigatran.

The prevention of ischaemic events in patients with acute coronary syndromes was investigated in a phase II b study using dabigatran in addition to aspirin and clopidogrel. Dabigatran, in addition to dual antiplatelet therapy, was associated with a dose-dependent increase in bleeding events and significantly reduced coagulation

activity in patients with a recent myocardial infarction. [10, Rank 4]

Pharmacology of Novel Oral Anticoagulants versus Warfarin

enzymes involved in its metabolism, all of which can affect INR.

In order to assure that a therapeutic international normalised ratio is maintained, frequent patient monitoring is

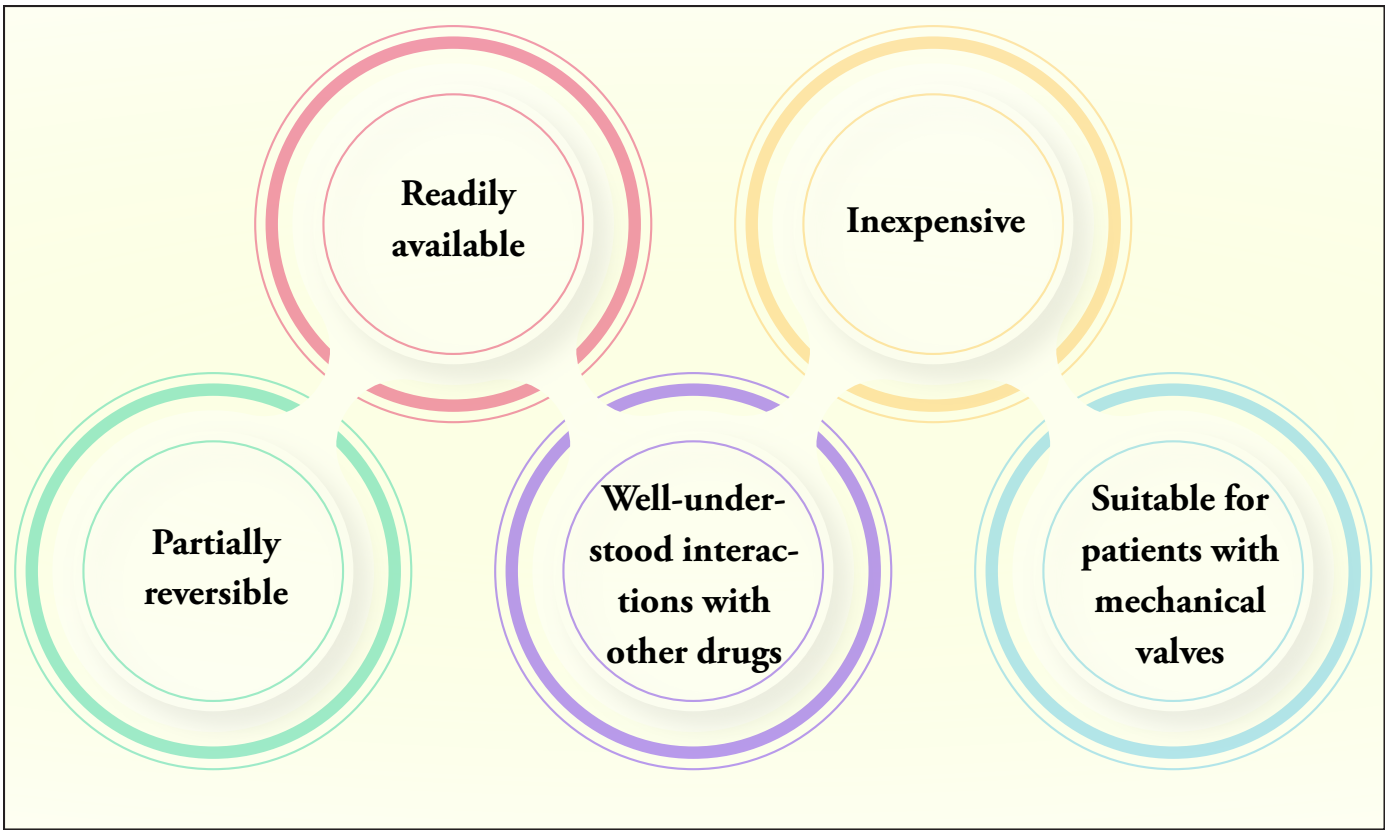

Figure 6: Basic advantages of Warfarin

Warfarin is relatively inexpensive and readily available, is partially reversible, and has well-understood interactions with other drugs. Warfarin is broadly indicated, and is suitable for patients with mechanical valves. Despite its proven effectiveness, there are several recognized disadvantages of warfarin, including a narrow therapeutic range, drug–drug interactions that can be delayed, food–drug interactions, slow dose-adjustment time, and genetic variability in the required, which some patients may find burdensome. Novel oral anticoagulants which directly inhibit factor Xa (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran), were developed to address some of the disadvantages of warfarin. Novel oral anticoagulants have a predictable anticoagulant response, making regular laboratory monitoring unnecessary. Anticoagulation with Novel oral anticoagulants is achieved quickly, reaching peak plasma

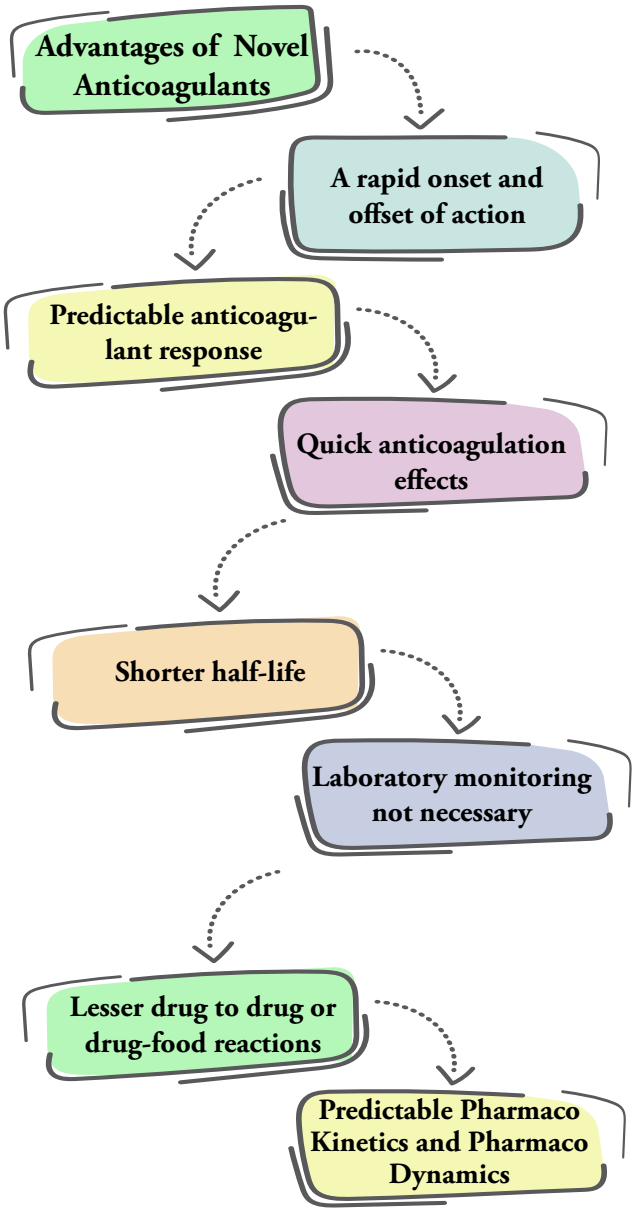

Figure 7: Advantages of NOAC

concentrations 1–4 h following oral administration, in comparison with the delayed onset of warfarin. Half-lives of Novel oral anticoagulants are shorter than that of warfarin, and range from 5 to 15 h. Novel oral anticoagulants have fewer drug–drug and drug–food interactions than warfarin. Although rivaroxaban should be administered with food, the other Novel oral anticoagulants can be administered without regard to food. [16, Rank 3]

There are disadvantages associated with Novel oral anticoagulants. Bleeding risks increase when Novel oral anticoagulants are administered with other anticoagulants, platelet inhibitors, or non-steroidal anti-inflammatory drugs. Novel oral anticoagulants are substrates of the P-glycoprotein (P-gp) transporter, and many rate-controlling and anti-arrhythmic drugs interact with P-gp. In addition, the Novel oral anticoagulants, to varying degrees, are substrates of cytochrome P450 (CYP) isoenzyme 3A4. As such, co-administration of Novel oral anticoagulants with P-gp inducers or inhibitors and/or CYP3A4 inducers or inhibitors may impact exposure to the Novel oral anticoagulants. This is related to the degree to which the Novel oral anticoagulants depend on P-gp for transport or on CYP3A4 for metabolism. Thus, verapamil, diltiazem, quinidine, amiodarone, and dronedarone are associated with increased Novel oral anticoagulants exposure, and use of these agents may require Novel oral anticoagulants dose reduction or may be contraindicated in patients taking Novel oral anticoagulants. The lack of laboratory monitoring for Novel oral anticoagulants may also be a negative as it is difficult to determine the level of anticoagulation, and

compliance can be assessed only by patient feedback and refill frequency. [15, Rank 2]

Clinical Considerations in the Management of New Oral Anticoagulants

Hemostasis is a cautiously balanced process that teeters between thrombus formation and degradation and that consists of a series of enzyme-mediated reactions in which thrombin plays a central role. A basic understanding of the physiology of the hemostatic system might help when considering the selection of a reversal agent. It is theoretically possible that an agent such as activated prothrombinase complex concentrate (aPCC) is a better option when treating bleeding in patients who are receiving dabigatran, because it might provide a more efficient activation of the coagulation cascade, although it is also possible that if dabigatran is still present in plasma, it could neutralize the newly generated thrombin. In the case of rivaroxaban, it is also conceivable that PCC or aPCC might be effective since they would bypass the effect of Factor Xa inhibition. However, it should be underscored that these considerations remain theoretical and are clinically unproven. It is also possible that pro-hemostatic agents lessen Novel oral anticoagulants related bleeding by overcoming the inhibitory effect of these drugs by means of providing massive amounts of factors II and X, either active or inactive. [3, Rank 4]

In general, it should be recognized that pro-hemostatic agents are not antidotes to Novel oral anticoagulants and do not affect the ongoing inhibitory effect of these drugs on factors II a and X a. Furthermore, it should be noted that previous studies in patients with intracerebral hemorrhage have suggested that, although pro-hemostatic agents can limit the extent of bleeding, their effect on mortality and disability appears minimal. It should also be recognized that there is a small but clinically important risk when administering these agents as their use has been associated with an increased risk for venous and arterial thrombosis.

Blood products such as cryoprecipitate and fresh frozen plasma are unlikely to result in a clinically significant reversal. We were unable to find evidence supporting the use of anti-fibrinolytic agents such as aminocaproic and tranexamic acid. A number of new agents are currently in different phases of development. They include monoclonal antibodies and small molecules with specific affinity for the novel oral anticoagulants. [4, Rank 3]

A number of practical considerations must be made when managing bleeding in

patients on anticoagulants. It is necessary to understand the two different types of bleeding events often reported in the literature evaluating anticoagulants for different indications. A major bleed is usually defined as a fatal or symptomatic event that involves a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intra muscular with compartment syndrome) or causes a hemoglobin level decrease of 20 g/L or more within 24 hours or results in transfusion of more than two units of packed red blood cells. The most common sites of major bleeding are gastrointestinal (approximately 80% of all bleeds), genitourinary, intracranial (including subdural, intra-cerebral (worst prognosis: 45% to 50% case fatality), and subarachnoid), and soft tissue and intra-articular, which are typically traumatic. In contrast, minor bleedings are those that may require medical attention but, in general, do not require transfusion or hospitalization, are usually self-limiting, and do not require interruption of anticoagulant medication, although this could be necessary in cases of non-self-limiting events. [5, Rank 4]

In the case of patients requiring an invasive procedure, temporary interruption of Novel oral anticoagulants might be considered, but this should be individualized according to the type of procedure required. It should be remembered that Novel oral anticoagulants have much shorter half-lives than warfarin (38 to 42 hours): dabigatran (11 to 17 hours), rivaroxaban (5 to 9 hours), and apixaban (9 to 12 hours). Thus, their anticoagulant effects may be reduced by over 75% within 24 to 36 hours of the last novel anticoagulants dose, after two half-lives have elapsed. Thus, even if coagulation tests are normal, elective procedures should not be performed until at least 24 to 36 hours (or longer in renal dysfunction) after discontinuation. Paradoxically, however, their short half-lives might put the patients at a higher risk of thrombosis in the case of interruptions, as was suggested by the slight increase in thrombotic events in patients enrolled in the ROCKET AF trial when transitioning from rivaroxaban to warfarin at the end of the study, although this remains largely a theoretical concern. [6, Rank 3]

In the case of patients with kidney disease, dose reductions are required in patients with a creatinine clearance (CrCl) of 30 to 50 mL/min because renal impairment prolongs the half-lives of NOACs, especially dabigatran. The use of NOACs is contraindicated in patients with a CrCl of less than 30 mL /min in the case of dabigatran or a CrCl of less than 15 mL/ min

for rivaroxaban and apixaban. For patients with a CrCl of between 15 and 30 mL/min, no clear dosing recommendations exist. In bleeding patients receiving dabigatran, hemodialysis may be considered in cases of acute renal failure and laboratory evidence of an excessive anticoagulant effect since 80% of dabigatran is not plasma-bound. There is no available information for rivaroxaban or apixaban in this regard, although owing to their high protein binding, dialysis is unlikely to be very effective. One study showed that hemodialysis removes 62% to 68% of drug after a single 50 mg dabigatran dose in patients with end-stage renal disease [19]. Another study suggests that dabigatran could be removed with the use of dialysis and charcoal hemo perfusion columns. However, it is not known whether the removal of dabigatran by dialysis results in better bleeding control clinically. Finally, Novel oral anticoagulants should be avoided in patients with moderate-to-severe liver dysfunction because of the lack of data in such patients.

Concomitant use of P-glycoprotein and CYP3A4 inhibitors (for example, azole antifungals such as ketoconazole) or inducers for example, rifampicin and anti-epileptics may increase or decrease both drugs' anticoagulant effect, and their concurrent use is contra-indicated. [7, Rank 5]

Caution should be exerted when interpreting coagulation tests since all Novel oral anticoagulants may alter common coagulation laboratory tests. Although routine coagulation tests generally are not useful in evaluating the degree of anticoagulation in patients receiving Novel oral anticoagulants, there is some evidence that, in a bleeding patient, the activated partial thromboplastin time (aPTT) may be useful in determining anticoagulant activity. A prolonged aPTT of greater than 90 seconds and a prolonged quick prothrombin time (PT) may indicate overdosing or accumulation of dabigatran. However, it is very important to note that a normal aPTT or international normalized ratio result may not exclude the presence of clinically relevant levels of dabigatran and other novel anticoagulants In addition, fibrinogen concentration can be falsely low in patients receiving dabigatran and this may lead to the unnecessary use of blood products such as cryoprecipitate. Although it has been noted that a normal thrombin time may indicate a lack of dabigatran activity, this test is extremely sensitive to very small amounts of the drug, rendering it unsuitable for clinical use. Owing to their predictable pharmacokinetic and pharmacodynamic profiles, novel anticoagulants do not require routine laboratory monitoring, but

this does not preclude the need to monitor specific coagulation-related conditions related to bleeding complications or changes in bleeding risk factors such as renal function. [8, Rank 2]

Practical Management

Interactions with Rhythm Controlling Drugs

Patients with atrial fibrillation frequently receive antiarrhythmic drugs such as amiodarone, verapamil, and dronedarone. These agents are inhibitors of P-glycoprotein and cytochrome P450 3A4, and because Novel oral anticoagulants are substrates of one or both of these enzymes, interactions are expected. Caution is advised with the co-administration of antiarrhythmic agents, and some are contraindicated in patients prescribed Novel oral anticoagulants. There is a lack of data regarding the use of dronedarone in patients taking rivaroxaban, so co-administration should be avoided. In ROCKET AF no significant interaction was observed between treatment effects in patients receiving amiodarone (8 % of enrolled patients) versus no antiarrhythmic drugs. Dronedarone is contraindicated in patients taking dabigatran because it has been shown to increase plasma levels of dabigatran. Increases in dabigatran plasma concentration were also reported in patients co-administered amiodarone, quinidine, and verapamil. Close clinical surveillance is recommended in patients receiving amiodarone or quinidine in combination with dabigatran, especially in patients with mild-to-moderate renal impairment. Patients receiving concomitant treatment with dabigatran and verapamil should receive the lower approved dose of dabigatran (110 mg bid). Amiodarone and verapamil have fewer significant interactions with apixaban, and in the ARISTOTLE trial there was no evidence of heterogeneity of outcomes between treatment groups in patients receiving amiodarone (11.4 % of enrolled patients) or not at randomization. In ENGAGE AF, the concomitant use of dronedarone,verapamil, or quinidine required the edoxaban dose to be halved for each dose group. However, the edoxaban Summary of Product Characteristics only recommends an edoxaban dose reduction in patients receiving dronedarone, who should receive the lower approved dose (30 mg od); by contrast, no dose reduction is required for concomitant use of quinidine or verapamil. In ENGAGE AF no dose reduction was required for patients receiving amiodarone (11.8 % of enrolled

patients), and the relative efficacy and safety outcomes between patients receiving warfarin or the higher dose of edoxaban tested (60 mg od) were similar for patients with and without amiodarone use. [9, Rank 4]

Reversal and Anticoagulation Monitoring with New Oral

The predictable pharmaco-kinetic/pharmaco-dynamic characteristics of the Novel oral anticoagulants including short half-lives and a wide therapeutic window obviate the need for routine coagulation monitoring. However, there is a need to measure drug levels under certain circumstances; for example, possible overdose or drug accumulation, trauma, or suspected poor compliance. The Hemoclot Thrombin Inhibitor assay, ecarin clotting time, and thrombin generation time assay are the most sensitive tests for measuring dabigatran anticoagulant effects; however, the activated partial thromboplastin time could also be used, because it has adequate sensitivity and is widely available. Normal values of the activated partial thromboplastin time can exclude substantial overdosing of dabigatran. Anti-Factor Xa chromogenic assays such as Rotachrom are recommended for the assessment of rivaroxaban, apixaban, and edoxaban. Such assays will use agent-specific calibrators and controls to measure plasma concentrations for the different Factor Xa inhibitors. [10, Rank 4]

For reversal of anticoagulation, fresh–frozen plasma and prothrombin complex concentrates have been recommended as general strategies, but the former is poorly effective in the presence of substantial plasma concentrations of the active compounds. Other non-specific reversal agents include recombinant activated Factor VIIa (NovoSeven) and activated prothrombin complex concentrates (FEIBA); however, these require testing in a clinical population and may be associated with a prothrombotic risk. Specific reversal agents for the Novel oral anticoagulants are now in development. Idarucizumab, a monoclonal antibody that binds dabigatran and neutralizes its activity is at the most advanced stage of development; interim results from the REVERSE-AD trial have shown that it successfully reverses the anticoagulation effects of dabigatran in patients with serious bleeding or requiring emergency surgery. Andexanet alfa (PRT064445) is a universal antidote for Factor Xa inhibitors that is currently in phase III development; results from phase III studies in elderly patients (ANNEXA-A and ANNEXA-R) show that it is capable of rapidly reversing the anticoagulant effects of apixaban and rivaroxaban. A third phase III study, recruiting patients

receiving a Factor Xa inhibitor and experiencing acute major bleeding, is currently ongoing. [11, Rank 3]

Although the very limited availability of specific reversal agents may be perceived as a current drawback of Novel oral anticoagulants therapy, it should be remembered that reversing the effects of vitamin K antagonists with vitamin K is slow and takes at least 24 h, which means that it is not clinically effective for serious bleeding events such as intra cerebral haemorrhage. By contrast, the half-life of the Novel oral anticoagulants rapidly removes their anticoagulation effect, which is likely to reduce the need for a specific reversal agent. Real-world evidence on the management of bleeding complications during rivaroxaban therapy from the Dresden Novel oral anticoagulants Registry demonstrated that most cases of major bleeding events could be managed conservatively. The use of non-specific reversal agents was rare: out of the 66 major bleeding events (6.1 % of all bleeding events) reported in patients receiving rivaroxaban, prothrombin complex concentrate was used in six (9.1 %) of these patient. [12, Rank 5]

Recommendations for Novel oral anticoagulants

Defining Reasons

Although numerous studies have documented that only about half of atrial fibrillation patients with risk factors for stroke are treated with an oral anticoagulants in various health care settings, the specific reasons are less well known. There was consensus in the working group that better understanding of why so many patients are not being treated is a high priority. Multiple reasons are often reported in individual patients. Patient and/ or physician preference for antiplatelet therapy is a frequently cited reason, but this presumably reflects a lack of understanding of how inferior anti-platelet therapy is compared to oral anticoagulants. Concern with potential bleeding is an important factor, and the lack of reversal agents for the Novel oral anticoagulants is a widely expressed concern among physicians even though this may be less of a problem due to their relatively short half-lives. Reasons to withhold oral anticoagulants therapy could be categorized in two domains: according to whether it is a patient, a provider, or a system level reason; and according to

whether it is appropriate, inappropriate, or of uncertain appropriateness. [9, Rank 4]

Increase Awareness

Patient educational efforts should focus on the threat of preventable stroke despite atrial fibrillation often asymptomatic nature. Educational initiatives should target a broad array of physician groups involved in the management of atrial fibrillation patients. To maximize the yield of patient-provider interactions, the development of decision aids for shared decision-making, multifaceted educational materials, and point-of-care decision support is needed. Although it is logical to focus on educating cardiologists, education of primary care physicians, hospitalists, emergency physicians, and advanced practice providers will be essential to guide improved care. Case based studies, interactive teaching methods, education embedded into patient care environments, and assessment of education effectiveness are important elements of improvement efforts. Identifying barriers to use and opportunities to guide optimal use of oral anticoagulants at a health system level is an important priority. [8, Rank 4]

Feedback Collection

Although the CHADS2 risk factors are easy to measure, they may not be easy to assess in an electronic medical record without specifically collecting information on whether or not they are present. A crucial question, as yet unanswered, is, "How much atrial fibrillation is enough to warrant treatment?" The trials studying anticoagulants have generally included patients with a clinical diagnosis of atrial fibrillation who were either in atrial fibrillation at the time of enrolment or who had two documented episodes two weeks apart. Six minute episodes of silent atrial fibrillation in older patients with cardiac devices are associated with a 2.5 fold risk of subsequent stroke, but more studies are needed to determine if oral anticoagulants is beneficial for these patients.

To measure performance in clinical care, patients with atrial fibrillation must be identified, the presence of stroke risk factors must be assessed, and the use of oral anticoagulants and presence of contraindications should be determined. Traditional registries, while helpful in assessing how populations are being treated, are not well suited to providing measurement and feedback in real time to improve care for individual patients. A data warehouse in a health

system could be used to identify candidates for oral anticoagulants treatment and follow-up on a system level rather than solely relying on individual physicians to make appropriate decisions in real-time. The increasing availability of electronic health records represents a rich opportunity for broad, real-time assessment and feedback of therapeutic decisions and clinical outcomes. Improvement in standardized electronic decision support tools may enhance the point of care use of oral anticoagulants. Oral anticoagulants adherence may be enhanced electronically by providing reminders to patients on their mobile devices that their prescription refill time has lapsed. These strategies, in conjunction with data analytics of the health system data warehouse, may provide a true "safety net" for select patients. [22, Rank 3]

Identify the Patients

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 anti- coagulants 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 anticoagulants but can tolerate vitamin K antagonists. Novel anticoagulants are approved for use in "non-valvular" atrial fibrillation. The term "non-valvular atrial fibrillation," however, needs further definition, since more than one quarter of patients in some of the trials of novel anticoagulants had moderate or severe valvular abnormalities, with consistent treatment effects in that subgroup. The novel agents should not be used in patients with significant mitral stenosis (who were excluded from the trials) or with mechanical prosthetic valves (for which the novel agent tested was neither safe nor effective). Finally, out-of-pocket expenses may be substantially less with warfarin compared with novel anticoagulants, and higher cost will continue to be an important barrier for many patients. [7, Rank 3]

Identify Novel Oral Anti-Coagulants Reversal Agents

It is important to recognize that while vitamin K, fresh frozen plasma, and prothrombin complex concentrates reverse the coagulation test effects of vitamin K antagonists their effectiveness on reducing bleeding and its consequences is much less well established. Furthermore, data

regarding risk of Novel Oral Anti-Coagulants associated periprocedural bleeding are reassuring, including data from the RE-LY trial showing similar or lower serious bleeding with dabigatran than with warfarin, even among patients undergoing emergent procedures. This may be due, in part, to their shorter half-life in comparison with vitamin K antagonists such that the effect is largely gone 1 to 2 days after the last dose. Nonetheless, research to identify ways to quickly reverse the effect of Novel Oral Anti-Coagulants and monitor their anticoagulant effect is needed and is underway. Andexanet alpha, for example, is a recombinant protein that functions as a factor X a decoy, and it has shown promise with regard to reversing effects of oral factor X a inhibitors. A monoclonal antibody fragment antidote for dabitatran is under development. As more data become available, there will be a value in making Novel Oral Anti-Coagulants reversal strategies widely interpretable and accessible, perhaps analogous to the poison control model. Along these lines, reviews providing practical guidance are currently available. Helping providers deal with every-day practical issues in the use of the novel drugs is important in enhancing their safe and effective use. [5, Rank 4]

Minimize Duration

Among atrial fibrillation patients undergoing percutaneous coronary interventions, a bare metal stent is preferable to a drug-eluting stent in the absence of a clear need for the latter. Among patients with a significant bleeding diathesis and acceptably low stroke risk, consideration can be given to temporarily suspending Oral anti-coagulants and resuming it when an antiplatelet agent is no longer required. Guidelines have encouraged avoiding aspirin when using vitamin K antagonists, unless there is a clear indication, i.e. within a year of a myocardial infarction. Such advice is likely to be applicable to the novel agents as well. Avoiding aspirin may result in important reductions in bleeding. [24, Rank 4]

Time Improvement in Therapeutic Range

Organized anticoagulation services have been shown to improve care and outcomes for patients on vitamin K antagonists. Scheduling and ensuring appropriate follow-up is part of this systematic approach. International normalised ratio checks should generally occur at least monthly among those on a stable dose and

more often among those requiring dosing adjustments. Automated telephone or electronic appointment reminders may aid in the process. Alternatively, use of point-of-care international normalised ratio devices may also improve TTR. In a randomized clinical trial, international normalised ratio self-testing was comparable to in-office venous blood draws with regard to bleeding and stroke rates. The safety of self-monitoring has been demonstrated in several other clinical trials. [12, Rank 4]

Better Alignment of Health System Incentives

The full set of patient outcomes over the care cycle should be weighed against total costs for the patient's condition, rather than the costs borne by a single payor. Educational programs should be designed that include systems improvement to measure, provide feedback on, provide tools for, and establish incentives to guide optimal oral anticoagulants for atrial fibrillation. An important step is to be able to identify the atrial fibrillation population with electronic health records. A system is needed to categorize patients not being treated in a way that assesses their risks and can lead to specific interventions that will improve their care. The goal is to enhance value for patients, rather than simply focusing on cost containment. Patients with AF should be fully educated regarding risk of stroke and its consequences. Further, out-of-pocket expenses of oral anticoagulants in various formularies should be made clear. With therapeutic benefit and costs in mind, patients will be better equipped to make appropriate, informed decisions regarding whether to use oral anticoagulants and what insurance coverage best suits them. An important opportunity will be to advocate for use of oral anticoagulants performance measures with feedback to providers and health systems as appropriate. [5, Rank 5]

Future Perspectives

At present, several studies have been published recently for the treatment of deep vein thrombosis and the prevention of embolic events in patients with atrial fibrillation. Both are the main new indications for new oral anticoagulants to overcome the drawbacks of conventional anticoagulation. The major drawbacks of the new oral anticoagulants will become visible only after market approval. They comprise high daily treatment costs; fear of unforeseen and unknown side effects, and – in patients comfortably performing therapy with Vitamin K antagonists– fear of switching to an oral anticoagulant with less experience.

The current underuse of Vitamin K antagonists will be reduced by the availability of new oral anticoagulants. Younger patients will be more prone to be treated with the new anticoagulants due to the simplicity of the treatment. The availability of several new oral anticoagulants should help to competitively reduce the daily price for the drugs. Additional information including meta-analyses will improve the knowledge about the added values of the new oral anticoagulants compared with conventional ones. [10, Rank 4]

New Oral Anticoagulants and Neuraxial Anesthesia

Like other anticoagulants, regional anaesthesia in patients receiving full therapeutic doses of new oral anticoagulants is contraindicated. Catheter manipulation and removal carry similar risks to insertion and should be timed to take place at the nadir of the concentration of the anticoagulant. Based on the fact that only 25% of the active drug remains after two half-lives have elapsed, researchers recommend delaying removal of a neuraxial catheter until at least after this period of time. As the formation of a stable clot takes 8 h the authors propose restarting anticoagulation to be left until 8 h minus the time to reach maximum activity (tmax). The approach appears to be a reasonable compromise between the risk of bleeding and venous thrombo- embolism. [6, Rank 3]

Management of Bleeding Associated with New Oral Coagulants

General principles should be observed for managing bleeding, including resuscitation, bleeding source control, drug cessation, and appropriate use of blood products. Activated charcoal can be considered if the offending drug was taken within two hours. In the case of life-threatening or intracranial bleeding, the use of pro-hemostatic agents should be considered. The best evidence so far comes from four studies in healthy volunteers who were receiving NOACs. The first study included healthy volunteers to whom rivaroxaban (20 mg twice a day) or dabigatran (150 mg twice a day) was administered for 2.5 days, after which they received a single dose of 50 IU/kg of four-factor (II, VII, IX, X) PCC, and its effects on PT, aPTT, thrombin time (TT), ecarin clotting time (ECT), and endogenous thrombin potential (ETP) were evaluated. The study used Cofact, an agent available in Europe, but other similar four-factor PCCs (such as Octaplex or Beriplex) are available. The study showed that in subjects receiving rivaroxaban, both the

prothrombin time and the Endogenous Thrombin Potential corrected to normal levels after administration of the PCC. In contrast, in patients receiving dabigatran, there were no corrections in the aPTT, ECT, ETP, or TT. In three other studies including healthy volunteers, participants received one or two doses of rivaroxaban (20 mg) or dabigatran (150 mg), and samples were obtained at different times after administration. To test the ex vivo effect of pro-hemostatic agents, patients' samples were incubated with different concentrations of recombinant activated factor VII (rFVIIa, Novoseven), four-factor PCC (Kanokad, available in Europe; Beriplex; and Cofact), and activated four-factor PCC (aPCC) (FEIBA; similar to four-factor PCC but with a more rapid effect because of the presence of 'activated' clotting factors). Coagulation was evaluated by measuring thrombin generation and other tests. The results of the studies showed that overall aPCC achieved the best correction of the coagulation parameters after rivaroxaban and dabigatran administration. Less efficient corrections were achieved with PCC and rFVIIa. Interestingly, one study suggested that lower doses of FEIBA might also be effective. [11, Rank 3]

Bleeding has been assessed in some studies in animal models. A study evaluating the effects of rFVIIa and PCC in a rabbit bleeding model failed to show reversal of rivaroxaban-induced bleeding in spite of improvement in laboratory parameters. However, other studies have reported reduced bleeding time in animal models of rivaroxaban-induced bleeding after administration of FEIBA. In the case of dabigatran, animal models suggest that PCC, FEIBA, and rFVIIa could reduce bleeding. There are other agents, such as three-factor (II, IX, X) PCC (currently used in the US), but evidence supporting their use in bleeding patients receiving NOACs is lacking and their use cannot be supported on the basis of currently available evidence. Researchers found that PCC at a dose of 100 IU/kg decreased the size and deterred the progression of the intra-parenchymal hematoma and resulted in a lower mortality in the treated animals. Finally, only one study has described the experience with bleeding events in trials evaluating dabigatran for different indications. The study reviewed 1,121 reports of major bleeding events and found that patients receiving dabigatran who developed major bleeding were older, had a lower creatinine clearance, and had more concurrent use of antiplatelet agents than those receiving warfarin. However, only nine patients received PCCs and two received rFVIIA, but no details were a

vailable at the time of review, and nothing can be extrapolated to the clinical scenario on the basis of the available information.

It should be re-emphasized that all information on clinical management should be considered low-quality on the basis of currently available data. When considering the use of these reversal agents, clinicians should very carefully consider the trade-off between benefits and potential risk. [14, Rank 4]

Conclusion

In spite of the emerging information, there is still a considerable lack of evidence to inform clinical practice, and most of the recommendations are based on expert opinion and interpretation of available evidence. Whereas experience today suggests that in the case of a catastrophic event such as an intracerebral bleeding the use of reversal agents is unlikely to result in major clinical benefit, such agents still have a role in the case of patients requiring urgent surgical interventions which are potentially life-saving. The overall evaluation of the limited available studies suggests that the agents most likely resulting in benefit are PCC and aPCC but evidence for rFVIIa is less consistent. However, it is essential to note that no clinical experience is available to date and that all studies have used surrogate measures such as coagulation-based assays of hemostatic function or animal models. The actual effect of these agents in patients with bleeding events remains to be determined. In addition, the existing literature suggests that correction in hemostatic parameters does not necessarily correlate with an improvement in actual bleeding, and the currently available evidence is still confusing because of the diversity of experimental models and assessments used and because of the lack of conclusive evidence relating the correction of laboratory parameters evaluating the hemostatic system with the effect on actual bleeding events.

Providing patients with a choice of therapy and allowing physicians to prescribe the most appropriate anticoagulant for their patients will only be possible if there is access to all guideline-recommended therapies. In outlining practical measures that physicians and medical health societies working in this field can instigate to improve guideline implementation, we believe that substantial benefits, in terms of improved patient outcomes and reduced healthcare burden, can be achieved. [10, Rank 5]

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