

New Oral Anticoagulants: An Update

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Summary:

One of the most common and useful forms of medical intervention is anticoagulant therapy and it is the mainstay of treatment and prevention of thrombosis in different clinical settings, like atrial fibrillation (AF), acute coronary syndrome (ACS), acute venous thromboembolism (VTE), and in patients undergoing invasive cardiac procedures. More than 6 million patients in the United States receive long-term anticoagulation therapy for the prevention of thromboembolism due to AF, placement of a mechanical heart-valve prosthesis, or VTE.¹ For more than 60 years, until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants (OAC) available.

Introduction:

One of the most common and useful forms of medical intervention is anticoagulant therapy. It is the mainstay of treatment and prevention of thrombosis in different clinical settings, like atrial fibrillation (AF), acute coronary syndrome (ACS), acute venous thromboembolism (VTE), and in patients undergoing invasive cardiac procedures.^{2,3,4,5} More than 6 million patients in the United States receive long-term

Although these drugs are highly effective in prevention of TE, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments. This results in substantial risk and inconvenience, leading to inadequate anticoagulant prophylaxis. Recently some new OAC have been marketed which are effective, easier to use and has less side effects. Dabigatran is a new oral thrombin inhibitor and Rivaroxaban, Apixaban and Edoxaban are oral factor Xa inhibitors. This review outlines why these new OACs were essential and describes in detail about these new drugs.

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anticoagulation therapy for the prevention of TE due to AF, placement of a mechanical heart-valve prosthesis, or VTE.⁶ Omission of appropriate anticoagulant prophylaxis is a widely recognized medical error.⁷ Bleeding is the primary complication of anticoagulant therapy, and is a risk of all anticoagulants,⁸ even when maintained within usual therapeutic ranges.

For more than 60 years, until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants (OAC) available. Although these drugs are highly effective in prevention of thromboembolism, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. The therapeutic range of anticoagulation for Warfarin is measured via the international normalized ratio (INR). The range is normally 2.0 to 3.0 for AF,⁹ and an INR < 2.0 increases the risk of thromboembolism.^{10,11} An INR > 4.0 increases the risk of major bleeding,^{12,13} though some studies have shown increased risk of hemorrhage with an INR > 3.0 also.¹⁴ This limitation has translated into poor patient adherence and probably contributes to the systematic underuse of vitamin K antagonists for stroke prevention.^{15,16} Owing to the high-risk profile of warfarin and difficulty of management, only approximately half of those patients with nonvalvular atrial fibrillation who should be

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anticoagulated are anticoagulated.¹⁷ To compound this under treatment, of those patients' eligible and anticoagulated with warfarin, analysis shows that such patients are only in the therapeutic range approximately 50% of the time. Keeping the INR in the therapeutic range is difficult due to its variable pharmacodynamics and interactions with other medications and diet and other factors. The percent of time that the INR is within the therapeutic range predicts the risk of adverse events, and in order to obtain maximum benefit, patients must have a minimum threshold of time in the therapeutic range of at least 60%.¹⁸ Time in therapeutic range is 60% to 65% in controlled clinical trials but may be lower in the true population.¹⁹ Indeed, time in therapeutic range < 40% may completely offset the benefit of vitamin K antagonists.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia responsible for one third of the hospitalizations because of cardiac rhythm disturbances. There is a 25% lifetime risk in adults for the occurrence of AF,²⁰ with rising prevalence and incidence with age,²¹ and future increases predicted.^{22,23} AF increases the risk of ischemic stroke 5-fold and accounts for 15% of stroke, with a 23.5% attributable risk of stroke at age 80–89 years,²⁴ rising with age.²⁵ Numbers of AF-related ischaemic strokes at age >80 years are projected to triple by 2050, along with numbers of systemic emboli, unless rates of anticoagulation in older patients increase.²⁶

The main focus of managing AF is on alleviating symptoms, by either rate control or rhythm control. The other focus is on preventing stroke—a devastating outcome—with anticoagulation therapy. The increased stroke risk with AF is heterogeneous and dependent on cumulative risk of various risk factors.²⁷ Table I shows the traditional stroke risk scores which stratify

patients into low, moderate, and high-risk groups, although the risk of stroke is a continuum and such an artificial categorization is only of modest predictive value for thromboembolism. In older guidelines, OAC is recommended for high-risk patients, whereas OAC or aspirin is recommended for moderate-risk patients and aspirin is recommended for low-risk patients.²⁸ OACs increase the risk of bleeding manifestations so risk factors for bleeding should be assessed before initiation of OAC therapy.²⁹ The HAS-BLED score (Table II) is a simple score which predicts the risk of bleeding. It incorporates risk factors which are present in community patients and improves predictive value among Warfarin naïve patients.³⁰ A large Danish study³¹ proved the effectiveness of this score and the HAS-BLED score has been incorporated into international guidelines.³² The details of the CHADS₂ score and CHA₂DS₂-VASc score and the HAS-BLED score is provided in Table II. The most commonly used CHADS₂ score has only modest predictive value for stroke and many common stroke risk factors are excluded.^{33,34} The novel CHA₂DS₂-VASc score is consistently better at identifying “truly low-risk” subjects, performs at least as well as the CHADS₂ score^{35,36} (or possibly better^{37,38}) when predicting “high-risk” subjects, and is included in recent European guidelines.³⁹ One recent analysis examining the net clinical benefit (risk of ischemic stroke versus intracranial hemorrhage) found a non-negative (i.e., neutral or positive) net clinical benefit with OAC in patients with a CHADS₂ score of < 0 and CHA₂DS₂-VASc score of ≥ 1 and a negative net clinical benefit only with a CHA₂DS₂-VASc score = 0 (given the “truly low risk” for these patients).⁴⁰ Of interest, the net clinical benefit was even greater at HAS-BLED scores of ≥ 3, given that higher risk individuals would have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events.

Table-I

Approach to Thromboprophylaxis in Patients with Atrial Fibrillation

Risk Category	CHA ₂ DS ₂ -VASc Score	Recommended
One “major” or ≥ 2 “clinically relevant nonmajor” risk factors	≥ 2	OAC, given as well-controlled VKA (INR 2.0 – 3.0) or Dabigatran
One “clinically relevant nonmajor” risk factor	1	OAC or Aspirin 75 – 325 mg daily; preferred: OAC
No risk factors	0	Either Aspirin 75 – 325 mg daily or No antithrombotic therapy; Preferred: no antithrombotic therapy

OAC such as a Vitamin K Antagonist (VKA) adjusted to an intensity range of INR of 2. – 3.0 (target 2.5) in patients with 1 “clinically relevant nonmajor” stroke risk factor (i.e. CHA₂DS₂-VASc score = 1), Dabigatran at 110 mg twice a day may be considered in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial hemorrhage and major bleeding compared with the VKA and (probably) aspirin.

AF indicates arterial fibrillation CHA₂DS₂-VASc, cardiac failure, hypertension, age ≥ 75 y (doubled), diabetes, stroke (doubled) – vascular disease, age 65 - 74 y, and sex category (female) INR, international normalized ratio, OAC, oral anticoagulation such as a

vitamin K antagonist (VKA) adjusted to an intensity range of INR of 2.0 – 3.0 (target 2.5).

*Adapted from European Society of Cardiology 2010 guidelines. The guidelines clearly state that antithrombotic therapy is necessary in patients with AF, unless they are age < 65 and truly low risk, and thus, female AF patients (a CHA₂DS₂-VASc score = 1) would not need anticoagulation, if they fulfil the criteria of “age <65 and lone AF”.

Dabigatran at 150 mg twice a day if a patient is at low risk of bleeding (eg, HAS-BLED score of 0-2) or Dabigatran at 110 mg twice a day considered if a patient has a measurable risk of bleeding (eg, HAS-BLED score of ≥3)

Table-II

*The CHADS₂, CHA₂DS₂-VASc, and HAS - BLED Scores for Assessing Stroke and Bleeding Risk**

CHADS ₂	Score
I. Congestive cardiac failure†	1
II. Hypertension (blood pressure consistently >140/90 mm Hg or treated hypertension on medication)	1
III. Age ≥75 y	1
IV. Diabetes mellitus	1
V. Stroke/transient ischemic attack/thromboembolism	2
Maximum score	6
CHA ₂ DS ₂ -VASc	
I. Congestive cardiac failure†	1
II. Hypertension(blood pressure consistently >140/90 mm Hg or treated hypertension on medication)	1
III. Age ≥75 y	2
IV. Diabetes mellitus	1
V. Stroke / transient ischemic attack / thromboembolism	2
VI. Vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque)	1
VII. Age 65 – 74 y	1
VIII. Sex category (ie, female)	1
Maximum score	9
HAS-BLED	
I. Hypertension (systolic ≥160 mmHg)	1
II. Abnormal renal and liver function (1 point each)	1 or 2
III. Stroke	1
IV. Bleeding tendency or predisposition	1
V. Labile international normalized ratio (if on warfarin)	1
VI. Elderly (age ≥65 y)	1
VII. Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

CHADS₂ score and risk of stroke and TE: 0, low risk; 1, moderate risk; ≥2, high risk; CHA₂DS₂-VASc score and risk of stroke and TE: 0, low risk; 1, moderate risk; ≥2, high risk; HAS-BLED score and risk of major bleeding: 0–2, low risk; 3, high risk. TE – thromboembolism

*Adapted from European Society of Cardiology guidelines 2010.³⁹

†Congestive cardiac failure is moderate to severe systolic left ventricular dysfunction, defined arbitrarily as left ventricular ejection fraction <40%.

Oral anticoagulation with vitamin K antagonists (warfarin, phenprocoumon) is successful in both primary and secondary stroke prevention in patients with atrial fibrillation, yielding a 60-70% relative reduction in stroke risk compared with placebo, as well as a mortality reduction of 26%. In contrast, antiplatelet therapy results in a stroke reduction of 22%, although when the meta-analysis is confined to aspirin only trials, this reduction was a nonsignificant 19%. Compared with antiplatelet therapy, OAC reduces stroke by 37%.⁴¹ Acetylsalicylic acid (ASA) reduces the relative risk of stroke by a nonsignificant 19% compared with placebo, and increased bleeding risk offsets any therapeutic gain from the combination of ASA with clopidogrel.

Antiplatelet therapies

Aspirin

Aspirin irreversibly inhibits cyclooxygenase, which, in platelets, prevents the production of the platelet agonist TxA₂,⁴² thereby attenuating TxA₂-mediated platelet activation. However, because aspirin only blocks the TxA₂ pathway, platelet activation and subsequent formation of platelet-rich thrombi/emboli via other pathways may still occur.

P2Y₁₂ ADP receptor antagonists

P2Y₁₂ ADP receptor antagonists inhibit ADP-induced platelet activation by irreversibly binding to the platelet P2Y₁₂ ADP receptor.⁴³ The P2Y₁₂ ADP receptor

inhibitors include ticlopidine, clopidogrel, and prasugrel, which are pro-drugs that are converted to active metabolite(s), as well as AZD 6140 and cangrelor, which are active drugs that do not require metabolism and are reversible. Properties of these drugs are provided in Table III. Similar to aspirin, ADP antagonists are limited by their inability to block platelet activation and subsequent thrombosis in response to agonists other than ADP. Thus, the most effective therapy for stroke prevention in AF is OAC. As age increases, stroke risk rises, and absolute benefit of OAC increases, whereas absolute benefit of antiplatelet therapy markedly diminishes. Major bleeding risk increases with age, but to a lesser extent than absolute benefit of OAC on stroke.⁴⁴

Venous Thromboembolism

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is also a major cause of morbidity and mortality. In the United States, it is estimated that 2 million people develop DVT each year. DVT progresses to PE in 600,000 of these patients, and the PE is fatal in 200,000.^{45,46} In addition to PE, DVT can lead to debilitating postphlebotic syndrome in up to one-third of patients.⁴⁷

Anticoagulant therapy remains the cornerstone of VTE treatment. Such treatment is usually divided into 2 stages. Rapid initial anticoagulation is given to minimize the risk of thrombus extension and

Table-III

<i>Properties of P2Y₁₂ ADP receptor antagonists</i>						
Agent	Class	Administration	Metabolism	Time to peak platelet inhibition	Rever-sibility	Half-life
Ticlopidine	Thienopyridine	Oral	CYP450-mediated conversion of pro-drug	4 days ^a	Irrever-sible	N/A
Clopidogrel	Thienopyridine	Oral	CYP450-mediated conversion of pro-drug	2 – 6 hrs ^b	Irrever-sible	N/A
Prasugrel	Thienopyridine	Oral	CYP450-mediated conversion of pro-drug	1 hr ^c	Irrever-sible	N/A
Cangrelor	ATP analogue	IV	Not a pro-drug	30 min	Rever-sible	3-5 min
Ticabrelor	Cyclopentytria-zolopyrimidine	Oral	Not a pro-drug	2 hr	Rever-sible	12 hr

CYP450 – Cytochrome P450

^a With 500 mg dose ^b With 600 mg loading dose. ^c With 60 mg loading dose

subsequent fatal PE, whereas extended anticoagulation is administered to prevent recurrent VTE, thereby reducing the risk of postphlebotic syndrome. With currently available drugs, immediate anticoagulation can only be effected with parenteral anticoagulants, such as heparin, low-molecular-weight heparin (LMWH), or fondaparinux. Extended therapy usually involves the administration of an oral anticoagulant. Till recently, the only orally available anticoagulants were the vitamin K antagonists, such as warfarin. Warfarin also is problematic in the setting of VTE. Its slow onset of action necessitates overlap with a parenteral anticoagulant for at least 5 days.⁴⁸ In recent years with emerging evidence, patients with unprovoked VTE now require anticoagulation therapy for at least 6 months after their index event, and possibly longer.⁴⁹

New Oral Anti Coagulants

Due to the various limitations of the vitamin K antagonists (Table IV), search has been on to find new oral anticoagulants. Two major classes of novel oral

agents have been marketed, with more predictable pharmacodynamics than vitamin K antagonists.⁵⁰ These are:

- a) the direct thrombin inhibitors (eg, dabigatran), and
- b) factor Xa inhibitors (eg, apixaban, rivaroxaban and edoxaban).

Direct factor Xa inhibition may cause more coagulation-specific effects, whereas direct thrombin inhibition may have beneficial effects outside the coagulation cascade.

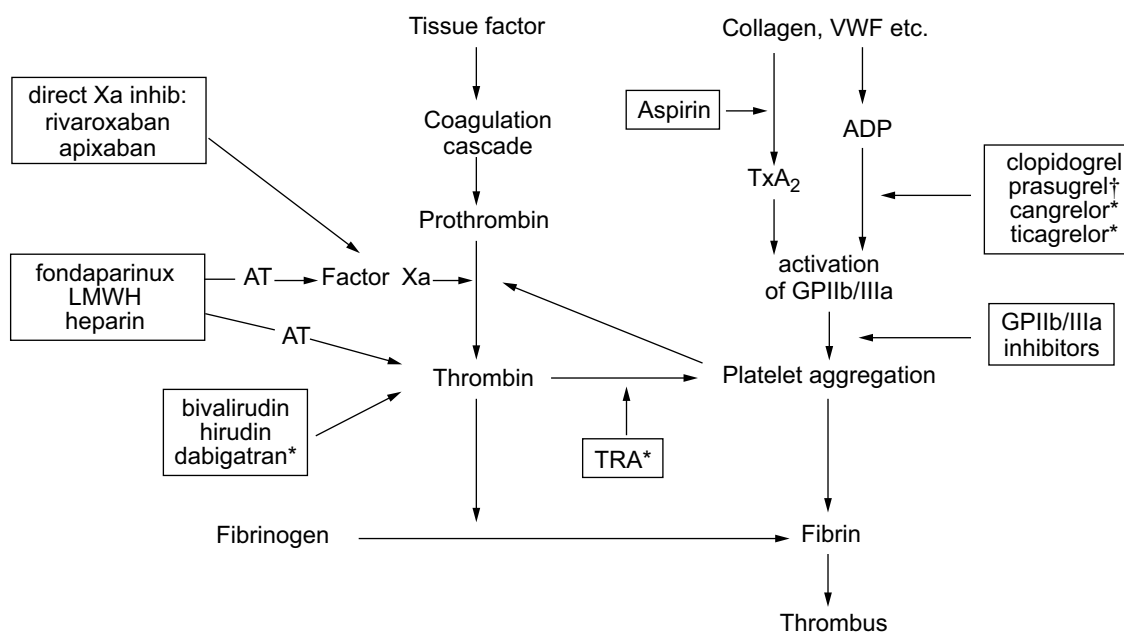
Direct thrombin inhibitors (DTIs)

Thrombin occupies a central role in the control of haemostasis making it an obvious target for antithrombotic therapy. In addition to blocking the direct generation of fibrin, thrombin inhibitors also inhibit the amplification of the coagulation cascade by blocking the thrombin mediated activation of factors V, VIII and XI, and inhibit thrombin mediated platelet activation.

Table-IV

Main limitation of current widely used antithrombotics⁵¹

Warfarin	Unfractionated Heparin	Low molecular weight heparin
Narrow therapeutic window: high bleeding risk from overdosing and high re-thrombosis risk from underdosing	Lack of effect via the oral route	Lack of effect via the oral route
Slow onset of anticoagulant action	Poor availability from subcutaneous injections and short circulation half-life: need for administration by intravenous infusion	Unclear dose requirements in obese and underweight adults and in infants and children. Lack of a routinely available assay.
Wide inter-individual dose requirements, in part genetically determined	Wide inter-individual dose requirements, in part determined by binding to acute phase proteins	Accumulation in renal impairment
Metabolism by the cytochrome P450 pathway giving rise to a high risk of interaction with co-medications	Essential requirement for monitoring of anticoagulant effect	Role of HITT lower than with unfractionated heparin, but present
Sensitivity to dietary vitamin K leading to day-to-day variation in anticoagulant effect	Risk of heparin-induced thrombocytopenia (HIT), often complicated by thrombosis (heparin-induced thrombocytopenia with thrombosis – HITT)	



The coagulation cascade, platelet activation pathways, and targets of antithrombotic agents. Simplified presentation of the coagulation cascade and platelet activation pathways together with antithrombotic agents. AT, antithrombin; LMWH, low-molecular-weight heparin; TRA, thrombin receptor antagonist; TA2, thromboxane A2; VWF: Von Willebrandt factor; *agents recently approved, †recently approved.

Fig-1: *The coagulation cascade and targets of antithrombotic agents*

Anticoagulation through inhibition of thrombin is not a novel approach. Unfractionated heparin and to a lesser extent LMWH act by inhibiting thrombin and other activated serine proteases. Heparins achieve this indirectly by binding to and enhancing the activity of the natural anticoagulant antithrombin III. Antithrombin III is a large molecule which cannot permeate fibrin clot. The thrombin inhibitors which directly bind to thrombin, blocking its interactions with its natural substrates are being advocated as the new anticoagulants. Likely advantages of these agents are that they bind to both clot-bound and free thrombin and that unlike heparin they do not bind to neutralising plasma proteins including some acute phase reactants, thus producing more predictable anticoagulation.

Inhibitors of factor Xa block thrombin generation, whereas thrombin inhibitors block the activity of thrombin, the enzyme that catalyzes the conversion of fibrinogen to fibrin. Whether thrombin generation is attenuated or thrombin action is suppressed, the net effect is a reduction in thrombin activity and fibrin formation, events that result in inhibition of

coagulation. Limiting thrombin generation or activity is critical because, in addition to its role in fibrin formation, thrombin serves as a potent platelet agonist and amplifies its own generation by feedback activation of factors VIII and V, key cofactors involved in factor Xa and thrombin generation, respectively.

Two groups of DTIs have emerged. The first includes three products approved by the FDA: argatroban (GlaxoSmithKline), bivalirudin (Angiomax, The Medicines Company), and desirudin (Iprivask, Canyon). They have been developed for intravenous use and have found their main roles in the management of heparin-induced thrombocytopenia (HIT) and in percutaneous coronary intervention.

The second, potentially of broader clinical use, includes oral prodrugs that are rapidly biotransformed into their active forms. They are targeted for use as longer-term antithrombotics, especially in venous thromboembolism and atrial fibrillation. The first oral direct thrombin inhibitor to be marketed, ximelagatran, was withdrawn in 2004 due to severe hepatotoxicity.⁵⁰ Dabigatran is now available in the market.

Dabigatran Etxilate

Dabigatran etexilate, a prodrug of dabigatran, which reversibly inhibits the active site of thrombin, has an oral bioavailability of 6%.⁵² After oral administration, dabigatran etexilate

is rapidly and completely converted to dabigatran by esterases. Plasma levels of dabigatran peak 2 hours after drug administration. Dabigatran has a half-life of 14 to 17 hours, which permits once- or twice-daily administration, and 80% of the drug is excreted unchanged by the kidneys. Dabigatran etexilate is a substrate of the P-glycoprotein (P-gp) transporter. This efflux transporter is highly expressed in the intestine and kidneys, and co-administration of potent

P-gp inhibitors, such as quinidine, can increase plasma levels of dabigatran by reducing its clearance.⁵³ Consequently, quinidine is contraindicated in patients taking dabigatran etexilate. Co-administration of dabigatran etexilate and amiodarone, a weak P-gp inhibitor, increases dabigatran levels by 50% without significantly affecting those of amiodarone. The dosage is 150 mg twice a day, or 75 mg twice a day if renal function is impaired. For a patient who needs surgery that poses a low risk of bleeding, the general recommendation is to stop dabigatran

the night before the surgical procedure. For operations with a greater risk of bleeding, many surgeons recommend stopping the drug 3 or 4 days before. Advantages of dabigatran include that it is not influenced by diet and that the onset of therapeutic benefit is within 1 hour. Although some drugs affect dabigatran, drug interactions are more troublesome with warfarin. A serious concern about dabigatran and the other new agents is that if a bleeding problem arises, the effects of these drugs are not reversible by administration of fresh frozen plasma. Dabigatran is reversible by dialysis; however, if a patient is also hypotensive, dialysis is not an option, and simply waiting for the drug to clear is the only choice.

Another drawback is that therapeutic levels cannot be monitored. If a patient taking warfarin requires cardioversion, the INR is carefully monitored for several weeks beforehand to reduce the risk of stroke. With dabigatran, there is no way to know if a patient is actually taking the drug as prescribed.

Factor Xa Inhibitors

Factor Xa can be inhibited indirectly through antithrombin or by direct inactivation per se, blocking conversion of prothrombin to thrombin. The oral fXa inhibitors are small molecules that bind reversibly to the active site of fXa. Rivaroxaban, and Apixaban are now available in the market.

Rivaroxaban

An oxazolidinone derivative with a molecular weight of 436, rivaroxaban is a potent and selective inhibitor of factor Xa.⁵⁴ It binds to the active site of factor Xa and inhibits the enzyme in a reversible and competitive fashion regardless of whether factor Xa is free in solution or bound within the prothrombinase complex.⁵⁵ Rivaroxaban is well absorbed from the gastrointestinal tract with a bioavailability more than 80%, and food has no major effect on its absorption. Rivaroxaban should be taken with food. Plasma levels of the drug peak in about 3 h. The terminal half-life is 5 to 9 hours in young individuals, and 11 to 13 hours in the elderly.⁵⁶

Rivaroxaban has a dual mode of elimination; one third is cleared as unchanged drug via the kidneys, one third is metabolized by the liver via CYP3A4-dependent and -independent pathways with the metabolites then excreted in the feces, and one third is metabolized in the liver with the inactive metabolites then eliminated via the kidneys. Of that found in the urine, 30% to 40% reflects unchanged drug that is excreted via a combination of glomerular filtration and tubular secretion, whereas the remainder reflects metabolites. Because of its renal clearance, rivaroxaban must be used with caution in patients with renal insufficiency. Rivaroxaban is a substrate for P-gp, and concomitant administration of potent inhibitors or both P-gp and CYP3A4, such as ketoconazole or ritonavir, is contraindicated because they increase plasma drug levels. Rivaroxaban is metabolized in the liver via CYP3A4, CYP2J2, and CYP-independent mechanisms. The drug is contraindicated in patients with severe liver disease because metabolic inactivation may be impaired. Caution must also be exercised in patients receiving treatment with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole or ritonavir. Reduced fecal and renal clearance of rivaroxaban by these drugs can cause an exaggerated anticoagulant effect.

The licensed dose of rivaroxaban is 20mg once a day. In patients with moderate or severe renal impairment (defined as a creatinine clearance of 15–49mL/minute) the recommended dose of rivaroxaban is 15mg once a day. Rivaroxaban should be taken with food. Like other direct factor Xa inhibitors, rivaroxaban prolongs the prothrombin time (PT) and activated partial thromboplastin time (aPTT), with the PT being more sensitive than the aPTT depending on the reagents used for testing.⁵⁷ However, the effect of the drug on these tests is short-lived, with prolongation only seen at peak drug levels. Factor Xa inhibition is the best test to monitor drug concentrations in plasma.

Apixaban

An active drug, apixaban is absorbed rapidly, and maximal plasma concentrations are achieved 3 hours after oral administration. The drug is cleared with a terminal half-life of 8 to 14 hours. Apixaban is eliminated via multiple pathways, including hepatic metabolism via CYP3A4 and renal and intestinal excretion. Concomitant treatment with potent inhibitors of CYP3A4 is contraindicated in apixaban-treated patients. The licensed dose of apixaban is 5mg twice daily. A dose of 2.5mg twice daily is recommended when patients meet at least two of the following criteria: age \leq 80 years, body weight \geq 60kg, or serum creatinine \leq 133 μ mol/L (1.5mg/dL). The lower dose should also be used for patients with severe renal impairment (defined in the Summary of Product Characteristics as a creatinine clearance of 15–29mL/minute).

Edoxaban

Edoxaban is an oral, reversible, direct factor Xa inhibitor with a linear and predictable pharmacokinetic profile and 62% oral bioavailability.⁵⁸ It achieves maximum concentrations within 1 to 2 hours, and 50% is excreted by the kidney.⁵⁹ An active drug that is rapidly absorbed, edoxaban has a half-life of 9 to 11 hours. Edoxaban has a dual mechanism of elimination; approximately one third is eliminated via the kidney, and the remainder is excreted in the feces. The dose of edoxaban is 60 mg once daily, or 30 mg once daily in case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg.

Trials for examining the efficacy of the new drugs:

In the RE-LY trial,⁶⁰ 18,113 patients who had atrial fibrillation and a risk of stroke were randomly assigned in a blinded fashion, to receive fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The authors concluded that in patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. An accompanying editorial⁶¹ also advocated the usefulness of dabigatran, “In summary, although there are qualifications, we can rely on RE-LY.”

The AVERROES trial⁶² was a double blind study in which 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable, were randomly assigned to receive apixaban (at a dose of 5 mg twice daily) or aspirin (81 to 324 mg per day), to determine whether apixaban was superior. The authors concluded that in patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.

In the ROCKET-AF trial,⁶³ 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke were randomly assigned in a double blind fashion to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The authors concluded that in patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

In the ARISTOTLE trial,⁶⁴ 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke, were randomly assigned to apixaban (at a dose of 5 mg twice daily) or warfarin (target international normalized ratio, 2.0 to 3.0) in a double-blind fashion.

The authors concluded that in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

The ENGAGEAF-TIMI 48⁶⁵ was a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban (30 or 60 mg once daily) with warfarin in 21,105 patients with moderate to high-risk atrial fibrillation (median follow-up, 2.8 years). The authors concluded that both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

The RECOVER⁶⁶ study was a double blind randomized trial in which it was tested whether direct oral thrombin inhibitor dabigatran has a predictable anticoagulant effect and may be an alternative therapy to warfarin for patients who have acute venous thromboembolism. The authors concluded that for the treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has a safety profile that is similar to that of warfarin, and does not require laboratory monitoring.

The Hokusai-VTE study⁶⁷ was a randomized, double-blind, noninferiority study, in which patients with acute venous thromboembolism, who had initially received heparin, received edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or received warfarin. The authors concluded that edoxaban administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism.

The EINSTEIN-PE Investigators trial,⁶⁸ was a randomized, open-label, event-driven, non-inferiority trial involving 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, in which rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) was compared with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The authors concluded that a fixed-

dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit-risk profile.

Potential drawbacks of new anticoagulants

The major complication of all anticoagulants is bleeding. When a patient receiving anticoagulant therapy presents with a major bleed, it is desirable to have a safe rapidly-acting antidote to reverse the anticoagulant effects. An antidote also is useful when anticoagulant-treated patients require urgent surgery or suffer from major blunt trauma. The short half-life of these new anticoagulants relative to warfarin is beneficial when discontinuation of anticoagulation is needed. Emergency reversibility, however, is a limitation. Apart from SSR 126517, none of the new agents has a specific antidote. Currently, no medication or transfusion is capable of completely neutralizing or specifically reversing the anticoagulant activity of the direct thrombin or (direct or indirect) factor Xa inhibitors. Thus patients currently using these drugs who suffer from an intracranial haemorrhage are at great risk for continued hemorrhage, hematoma expansion, intraventricular extension, and added morbidity and mortality. In addition to possibly administering oral charcoal to any patient recently ingesting oral anticoagulants, empiric transfusion of plasma coagulation products or recombinant coagulation factors may be considered to neutralize the effects of these new anticoagulants.⁶⁹ Given the more reliable composition of Prothrombin complex concentrates (PCCs), and greater concentration of thrombin and factor X, PCCs may be preferred over Fresh Frozen Plasma (FFP) or recombinant Factor VIIa (rF-VIIa).⁷⁰

Since heparinoids, hirudin-like agents and dabigatran possess relatively low or no protein binding, as opposed to other direct or indirect thrombin and factor Xa inhibitors, hemorrhage in conjunction with these agents may theoretically be more likely to respond to serologic extraction by dialysis.⁷¹ Although not well studied, dialysis may also clear the direct factor Xa or thrombin inhibitors, all of which are small molecules. Unfortunately, the time required to place central access and administer hemodialysis may prove to be a costly limitation.

For the new direct thrombin or factor X inhibitors, research to produce reversing agents is urgently needed given the increasing use of these anticoagulants and the inevitable cerebral and systemic hemorrhages that will ensue.

Contraindications and cautions⁷²

The risk of serious haemorrhage makes certain contraindications applicable to all the new anticoagulants for all indications and doses. These include lesions or conditions considered to be a significant risk factor for major bleeding, e.g. presence of gastrointestinal ulceration; malignant neoplasm at high risk of bleeding; recent brain or spinal injury; recent brain, spinal or ophthalmic surgery; oesophageal varices; arteriovenous malformations; vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Contraindications also include concomitant treatment with any other anticoagulant agent (e.g. unfractionated heparin, low molecular weight heparin, heparin derivatives, oral anticoagulant). Exceptions are switching of therapy to or from the medicine, or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter. Special care should be taken when deciding to prescribe these drugs to patients with other conditions, undergoing procedures, or taking concomitant treatments (e.g. non-steroidal anti-inflammatory drugs, antiplatelet drugs) which may increase the risk of major bleeding. Annually, 10% of patients taking antithrombotic agents undergo surgical or other invasive procedures that require temporary discontinuation of therapy.⁷³ Pregnancy is a contraindication for rivaroxaban, whereas apixaban use is not recommended during pregnancy. The use of apixaban and rivaroxaban are not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both cytochrome P450 enzyme CYP3A4 and P-glycoprotein (P-gp), such as azole-antimycotics (e.g. itraconazole) or HIV protease inhibitors (e.g. ritonavir). These medicines can more than double the plasma concentration of apixaban and rivaroxaban. In the presence of additional factors that increase drug exposure (e.g. severe renal impairment) this may lead to an increased bleeding risk. The concomitant use of apixaban or rivaroxaban with strong CYP3A4 and P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital) may lead to an

approximately 50% reduction in apixaban or rivaroxaban exposure and should be co-administered with caution.

Unwanted effects

In the RE-LY study,⁶⁰ the only unwanted effect that occurred more commonly with dabigatran than with warfarin was dyspepsia (11.3% with dabigatran 150mg twice daily vs. 11.8% with dabigatran 110mg twice daily vs. 5.8% with warfarin). More patients discontinued dabigatran than warfarin (around 15% vs. 10% with warfarin at 1 year, and around 21% vs. 17% at 2 years).

Follow-up of the RE-LY cohort continued for only 2 years, and so information on the long-term safety of dabigatran is limited. The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran ($P = 0.003$) and 3.11% per year in the group receiving 150 mg of dabigatran ($P = 0.31$). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran ($P < 0.001$) and 0.10% per year with 150 mg of dabigatran ($P < 0.001$). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran ($P = 0.13$) and 3.64% per year with 150 mg of dabigatran ($P = 0.051$).

In the RE-COVER study,⁶⁶ major bleeding episodes occurred in 1.6% (20) patients assigned to dabigatran and in 1.9% (24) patients assigned to warfarin, and episodes of any bleeding were observed in 16.1% (205) patients assigned to dabigatran and 21.9% (277) patients assigned to warfarin. The numbers of deaths, acute coronary syndromes, and abnormal liver-function tests were similar in the two groups. Adverse events leading to discontinuation of the study drug occurred in 9.0% of patients assigned to dabigatran and in 6.8% of patients assigned to warfarin ($P = 0.05$). There have been two published case reports of serious bleeding associated with dabigatran used at lower doses (75mg twice daily and 110mg twice daily) in women aged 84 and 89 years.⁷⁴

The safety of apixaban has been assessed in 11,886 patients with non-valvular AF in studies for an average of 1.7 years. In ARISTOTLE⁶⁴ and AVERROES,⁶² 35.0% and 22.2% of patients taking apixaban experienced serious adverse reactions compared with

36.5% and 27.2% of warfarin and aspirin patients respectively. Major, minor and clinically relevant non-major bleeding events occurred in 11.7% of apixaban patients compared with 9.9% of aspirin patients. In ARISTOTLE, 18.1% of apixaban patients had a bleeding event compared with 25.8% of warfarin patients ($p < 0.001$). Common adverse reactions were epistaxis, confusion, haematuria, haematoma, eye haemorrhage (including conjunctival haemorrhage) and gastrointestinal haemorrhage. In ARISTOTLE the annual event rate for gastrointestinal bleeding was 0.76% with apixaban vs. 0.86% with warfarin.

In the ROCKET-AF trial,⁶³ rates of major and clinically relevant non-major bleeding were similar with rivaroxaban and warfarin (14.9% vs. 14.5%) as were rates of major bleeding (3.6% and 3.4%, $p = 0.58$). The annual event rate for gastrointestinal bleeding was 3.2% with rivaroxaban vs. 2.2% with warfarin. A meta-analysis of five randomised controlled trials that reviewed the bleeding risk with rivaroxaban showed that compared with warfarin, rivaroxaban was not associated with an increased risk of a composite endpoint of major or clinically relevant non-major bleeding. Rivaroxaban was associated with a significant decrease in fatal bleeding and a decreased risk of intracranial bleeding compared with warfarin but it was not associated with a decreased risk in all-cause mortality.⁷⁵ A rebound effect has been reported when rivaroxaban is discontinued. There is a potential for inadequate anticoagulation during the transition to vitamin K antagonists (e.g. warfarin).

The safety profile of edoxaban has also been favourable. In the ENGAGE AF- TIMI 48 trial,⁶⁵ the annualized rate of major bleeding events was 3.43% with warfarin, as compared with 2.75%

with high-dose edoxaban and 1.61% with low dose edoxaban. The rates of life-threatening bleeding, intracranial bleeding, and major bleeding plus clinically relevant nonmajor bleeding were 0.78%, 0.85%, and 13.02%, respectively, with warfarin, as compared with 0.40%, 0.39%, and 11.10%, respectively, with high-dose edoxaban and 0.25%, 0.26%, and 7.97%, respectively, with low-dose edoxaban ($P < 0.001$ for the comparison of warfarin with each dose of edoxaban). The annualized rate of major gastrointestinal bleeding was higher with high-dose edoxaban than with warfarin (1.51% vs. 1.23%), but the rate was lowest with low-dose edoxaban (0.82%).

Finally, the cost of new anticoagulants will impact on their uptake, particularly if these drugs prove only to be as safe and effective as existing agents. Although regulatory agencies may approve the new agents on the basis of noninferiority compared with warfarin, payers are unlikely to embrace the higher cost of new anticoagulants in the absence of superior efficacy or safety over warfarin. Warfarin may be difficult to administer in an effective fashion, but it is inexpensive, even with the added expense of coagulation monitoring.⁷⁶ Unless the cost of the new anticoagulants is relatively low, these drugs are likely to be reserved for patients who cannot be adequately controlled on warfarin, or for those without ready access to a laboratory.

Meta-analyses⁷²

There are no head to head trials comparing any of the four new oral anticoagulant drugs. Several systematic reviews and meta-analyses have used the trial data from the studies of the individual drugs to make comparisons between them.

Table-V

<i>Drug Dose Annual Treatment Cost⁷²</i>		
Drug	Dose	Annual treatment cost
Apixaban	5 mg or 2.5 mg twice daily	£ 802
Dabigatran	150 mg or 110 mg twice daily	£ 802
Rivaroxaban	20 mg or 15 mg once daily	£ 767
Warfarin*	Variable	£ 45 + £ 241 for INR monitoring

Drug costs based on prices in *Chemist and Druggist* and the *Drug Tariff*.

*Costs for warfarin based on NICE Technology Appraisal 249 costing template.

In the evidence submission for the technology appraisal for apixaban, the National Institute for Health and Care Excellence (NICE) reviewed two network analyses undertaken by the company.⁷⁷ The first analysis included data from ARISTOTLE, ROCKET-AF and RE-LY and the second analysis also included data from AVERROES. However, the results were not sufficiently robust to reliably differentiate between apixaban, rivaroxaban and dabigatran. A network meta-analysis (50,578 patients) of three studies (RE-LY, ROCKET-AF and ARISTOTLE) reviewed the composite outcome of ischaemic stroke and systemic embolism, major bleeding, intracerebral bleeding, mortality and myocardial infarction. The authors suggested that apixaban or dabigatran 110mg twice daily may offer the best benefit-risk balance for stroke prevention and that dabigatran 150mg twice daily may be preferred for patients at higher risk of embolism.⁷⁸ However, an adjusted indirect meta-analysis (50,578 patients) of the same studies concluded that the overall superiority of the newer oral anticoagulants over warfarin is largely influenced by the reduction of haemorrhagic stroke and that dabigatran 150mg twice daily may have the best risk/benefit profile.⁷⁹ A meta-analysis (44,733 patients) and indirect comparison of four trials (PETRO [dabigatran with or without aspirin versus warfarin; 502 patients], RE-LY, ROCKET-AF and ARISTOTLE) concluded that dabigatran lowers the composite of stroke and systemic embolism and ischaemic stroke in comparison to rivaroxaban.⁸⁰ However, the authors only included data for the dose of dabigatran that had been approved by the US Food and Drug Administration. Most analyses showed no difference between the drugs, and no difference between all strokes and mortality was seen. However, the authors concluded that apixaban lowers the risk of major and gastrointestinal bleeding compared with dabigatran and rivaroxaban, and that dabigatran lowers the composite of stroke or systemic emboli, and ischaemic stroke compared with rivaroxaban.

The authors of another systematic review (50,578 patients) concluded that the treatment benefit compared with warfarin was small and varied depending on the level of control achieved with warfarin treatment.⁸¹ An analysis of seven studies (52,701 patients) prompted a more optimistic conclusion with the authors recommending that given the superiority of the newer

drugs (in terms of efficacy, safety and ease of use) “warfarin should not remain first choice of anticoagulation in patients with non-valvular atrial fibrillation and at least moderate thromboembolic risk”.⁸² The largest review (21 studies, 80,906 patients) suggested that the three agents are therapeutically comparable when warfarin is inappropriate.⁸³ Two other reviews (44,563 patients and 51,895 patients) concluded that the newer agents are more efficacious than warfarin for prevention of stroke and systemic embolism, largely as a result of the reduction in haemorrhagic strokes.^{84,85}

The latest meta-analysis published in March 2014,⁸⁶ compared new oral anticoagulants with warfarin and included data from the ENGAGE AF-TIMI 48, RE-LY, ROCKET-AF, and ARISTOTLE trials amounting to 42411 participants who received a NOAC and 29272 who received warfarin. The authors concluded that patients receiving high-dose NOACs had fewer stroke and systemic embolic events than patients on warfarin, a result mainly driven by substantial protection against haemorrhagic stroke. The NOACs had an overall favourable safety profile as compared with warfarin, although they were associated with an increase in gastro-intestinal bleeding. A reduced all-cause mortality was observed with NOACs in comparison with warfarin. But an accompanying editorial⁸⁷ commented, “*Such a meta-analysis assumes that all the novel oral anticoagulant drugs are the same (which they are not) and work on the basis of a class effect or are broadly equivalent; and that the randomised trials are homogeneous, which again they are not*”.

Conclusion:

Warfarin has been the standard for oral anticoagulation for over 50 years. The newer oral anticoagulant agents (apixaban, dabigatran and rivaroxaban) produce predictable anticoagulation and have been shown to result in similar or better mortality and vascular outcomes compared with warfarin. Systematic reviews and meta-analyses have made indirect comparisons but the results have not been sufficiently robust to reliably differentiate between apixaban, dabigatran or rivaroxaban. Dabigatran was the first of the new oral anticoagulants licensed to prevent stroke in patients with non-valvular atrial fibrillation. It was approved by

Table-VI*Indications and doses for FDA approved oral anticoagulants⁹¹*

	Atrial Fibrillation	VTE Prevention	VTE Treatment
Dabigatran	150 mg bid; 75 mg bid. ^a	-	-
Rivaroxaban	20 mg daily; 15 mg daily ^b	10 mg daily ^{d,e}	15 mg bid x 21 days, then 20 mg daily ^c
Apixaban	5 mg daily; 2.5 mg daily ^c	-	-

^aFor patients with a CrCl of 15 to 30 mL/min or a CrCl of 30 to 50 ml/min and concomitantly receiving a strong P-glycoprotein inhibitor.

^bFor patients with a CrCl of 15 to 50 mL/min.

^cIf the patient is taking a strong dual inhibitor of CYP3A4 and a permeability glycoprotein (P-gp) inhibitor, or has two or more of these characteristics: 80 years of age or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL or greater.

^dPostoperative thromboprophylaxis following hip or knee replacement surgery.

^eAvoid use in patients with a CrCl of 30 mL/min or lower.

bid=twice daily, CrCl=creatinine clearance; CYP=cytochrome P450; VTE=venous thromboembolism.

the US Food and Drug Administration in 2010 and by the European Medicines Agency for this use a year later. Once on the market, dabigatran proved a rapid financial success, with global turnover exceeding \$1bn by April 2012. But, as sales soared, concerns grew about the reports of fatal bleeds that were beginning to emerge.⁸⁸ A QuarterWatch report analysed all the adverse events submitted to the FDA's reporting system in 2011. It found the most commonly identified drugs reported to the FDA were the anticoagulants dabigatran and warfarin. For dabigatran alone, this included 542 patient deaths and 2367 reports of haemorrhage. Warfarin accounted for 72 deaths in the same period.⁸⁹ As of December 2011, the company summary cited 9049 reported bleeding events in its global experience, including 368 deaths.⁹⁰ The company found that if the plasma levels of the drug were measured and the dose was adjusted accordingly major bleeds could be reduced by 30-40% compared with well controlled warfarin. The adjustment would have little or no effect on the risk of ischaemic stroke. It has also identified the plasma levels at which the dose adjustment should occur to reduce the risk of a major bleed.⁸⁹ Experts are urging that the regulators should recommend plasma level testing of dabigatran in all new patients, and eliminate the recommendation dabigatran "does not in general require routine anticoagulant monitoring."⁹¹

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