Anticoagulation in Atrial Fibrillation – Current Concepts

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Abstract

This article presents the current status of the use of anticoagulation for the treatment of AF, particularly with the use of non-vitamin K-dependent anticoagulants. Comparisons between these agents and warfarin are made and methods for assessment of anticoagulant activity and reversal are discussed.

Keywords

Atrial fibrillation, guidelines, anticoagulants, thromboprophylaxis

Disclosure: The authors have no conflicts of interest to declare

Acknowledgements: Andrew Grace, Section Editor– Arrhythmia Mechanisms/Basic Science acted as Editor for this article. This article is adapted from Chapter 52: Atrial Fibrillation. In: Katritsis D, Camm AJ, Gersh BJ. *Clinical Cardiology: Current Practice Guidelines*. Oxford, UK: Oxford University Press, with kind permission. © Oxford University Press, 2013.

Received: 11 May 2015 **Accepted:** 21 July 2015 **Citation:** *Arrhythmia & Electrophysiology Review*, 2015;4(2):100–7 **Access at:** www.AERjournal.com

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Thrombotic material in atrial fibrillation (AF) usually develops in the left atrial appendage as a result of decreased flow and stasis, possible endothelial dysfunction and a hypercoagulable state as indicated by increased fibrinogen, D-dimer, thromboglobulin and platelet factor 4 levels.¹ In the Framingham Heart Study, the percentage of strokes attributable to AF increases steeply from 1.5 % in patients aged 50–59 years to 23.5 % in those aged 80–89 years.² In patients with a history of hypertension but no prior diagnosis of clinical AF, subclinical AF predisposes them to embolic events.³ Undiagnosed silent AF is a probable cause of cryptogenic strokes,^{4,5} and subclinical episodes of AF are associated with silent cerebral infarcts, particularly in patients with diabetes.^{6,7}

The frequency of AF-related incident ischaemic strokes in patients aged ≥80 years have increased threefold over the last 25 years, despite the introduction of anticoagulants, and are projected to further increase threefold by 2050.⁸ Among patients with AF who are at moderate-to-high risk of stroke and are receiving anticoagulation, those with persistent AF have a higher risk of thromboembolic events and worse survival rates compared with those with paroxysmal AF.⁹ The risk of stroke is similar in patients with and without valvular disease.¹⁰ Serial ECGs, Holter monitoring, mobile outpatient telemetry, external loop recorders and implantable loop recorders detect post-stroke AF in 23.7 % of patients.¹¹ However, AF that occurs early after stroke can be caused by a transient neurogenic mechanism, and AF that occurs several months post-stroke can be an incidental finding; therefore, it cannot be concluded that the cause of cryptogenic stroke has been identified in all patients found to have post-stroke AF.¹¹

Anticoagulation

Adjusted-dose warfarin and antiplatelet agents reduce the risk of stroke by approximately 60 % and 20 %, respectively, in patients with AF.¹² In general, oral anticoagulation is preferred in patients with CHA₂DS₂-VASc score ≥2, and no anticoagulation in patients with a score of 0 (see *Figure*

1 and *Table 1*). In patients with CHA₂DS₂-VASc score of 1, anticoagulation should be individualised as the risk of stroke is low.¹³ However, patients aged >65 years, especially women, are at high risk of ischaemic stroke,¹⁴ and in these individuals anticoagulation reduces the rate of mortality.^{15,16} The risk of bleeding is assessed by schemes such as the HAS-BLED, ATRIA and HEMORR2HAGES scoring systems.¹⁷ A HAS-BLED score ≥3 indicates 'high risk'. New oral anticoagulants are now recommended for nonvalvular AF as a potential alternative to warfarin. Nonsteroidal anti-inflammatory drugs increase the risk of both serious bleeding and thromboembolism in anticoagulated patients with AF.¹⁸

Aspirin

The protective value of acetylsalicylic acid (aspirin) as monotherapy has come under question, and there are concerns that it may even increase risk of stroke in elderly patients (aged >75 years).^{19,20} Warfarin is superior to aspirin in patients aged >75 years, offering a 52 % reduction in yearly risk of a combined end-point of stroke, intracranial haemorrhage and peripheral embolism (1.8 % versus 3.8 %; Birmingham Atrial Fibrillation Treatment of the Aged Study [BAFTA]).¹⁵ Thus, the use of aspirin for stroke prevention in patients with AF should be limited to those who refuse any form of oral anticoagulation,²¹ or, perhaps, to those with a CHA₂DS₂-VASc score of 1.¹

Aspirin and Clopidogrel

The combination of aspirin and clopidogrel offers increased protection compared with aspirin alone, albeit at an increased risk of major bleeding,²² and is preferred when warfarin is contraindicated. However, aspirin and clopidogrel together offer less protection than warfarin alone (RR of 1.44 for stroke, peripheral embolism, MI and vascular death).²² In patients who sustain an ischaemic stroke despite international normalised ratio (INR) of 2.0–3.0, targeting a higher INR should be considered (3.0–3.5) rather than adding an antiplatelet agent, as major bleeding risk starts at INR >3.5.²³

Warfarin

Warfarin is a racemic mixture of isomers that inhibits the synthesis of vitamin K-dependent coagulation factors. The effective dose of warfarin varies significantly among individuals, as a result of genetic variations in its receptor, metabolism via the cytochrome P450 (CYP) system and interactions with other drugs, vitamins and green vegetables.¹

The risk of AF increases with INR >3.5–4.0. Recommended INR values for AF are 2–3. Pharmacogenetic testing for guiding doses, by means of genotyping for the variants CYP2C9 and VKORC1, which are associated with reduced clearance and thus a decrease in warfarin requirement, is not clinically useful.²⁴ Patients initiating warfarin may be at an increased risk of stroke during the first 30 days of treatment, probably owing to rapid deactivation of proteins S and C, two endogenous anticoagulants.²⁵ In high-risk cases, warfarin should be started with concomitant low molecular weight heparin administration for the initial 3–5 days of treatment. Increased levels of coronary calcification have been recently reported in patients on long-term therapy with vitamin K antagonists.²⁶

Non-vitamin K Oral Anticoagulants

Non-vitamin K oral anticoagulants (NOACs) are direct thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban) inhibitors. Thrombin catalyses the final step in the coagulation cascade by converting fibrinogen to fibrin. Factor Xa, in conjunction with factor Va, mediates activation of prothrombin to thrombin. In patients with non-valvular AF (ie not mechanical valves or mitral valve disease), they are associated with a relative 50% reduction in the risk of intracranial haemorrhage and haemorrhagic stroke compared with warfarin that is also maintained in elderly patients. There is no need for frequent laboratory monitoring and dose adjustments.^{27,28} The main problems associated with NOACs are the lack of antidotes and specific assays to measure anticoagulant effect, and the considerably higher cost than warfarin.²⁹ It should be also noted that all major clinical trials with warfarin have included patients without severe renal impairment (CrCl <25–30 ml/min), and renal function should always be considered, especially when treated with dabigatran (see Table 2). They are not indicated in patients on haemodialysis because they may precipitate inadvertent bleeding.³⁰ NOACs do not interact with food but with inhibitors (or inducers) of P-glycoprotein transporters and CYP3A4. Caution is required when they are coadministered with drugs such as verapamil, amiodarone and dronedarone. In patients taking warfarin, switching to a new agent is appropriate when the INR is <2. The mode of action of novel oral anticoagulants in the coagulation cascade is presented in Figure 2. A comparison of new anticoagulants is presented in Tables 3 to 5. A practical guide by EHRA on the use of NOACs in patients with AF has been published (www.NOACforAF.eu).³¹

Direct Thrombin Inhibitors

Dabigatran

Dabigatran is preferred to warfarin for nonvalvular AF as recommended by the European Society of Cardiology²¹ and the Canadian Cardiovascular Society.³² In 2010, the US Food and Drug Administration (FDA) approved dabigatran at a dose of 150 mg twice daily (CrCl >30 ml/min), or 75 mg twice daily (CrCl 15–30 ml/min) based on the results of the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.³³ However, in the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial, during 2.3 years of continued treatment with dabigatran, there was a higher rate of major bleeding with dabigatran 150 mg twice daily

Figure 1: Choice of Anticoagulant for Atrial Fibrillation

Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered. Colour: CHA₂DS₂-VASc; green = 0, blue = 1, red = ≥2. Line: solid = best option; dashed = alternative option.

NOAC = novel oral anticoagulant; OAC = oral anticoagulant; VKA = vitamin K antagonist.

³¹Includes rheumatic valvular disease and prosthetic valves.

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in comparison with 110 mg, and similar rates of stroke and death.³⁴ The European Medicines Agency (EMA) has approved both the 110 mg twice-daily and 150 mg twice-daily doses for nonvalvular AF. Elective cardioversion may be performed in patients taking dabigatran for at least 3 weeks.²¹ Dabigatran is excreted through the kidneys and no dosing recommendation is given for clearance <15 ml/min. In elderly patients a reduced dose is reasonable (75 mg twice daily),³⁵ especially for those aged >80 years. It can be used safely together with aspirin.^{33,36} A higher risk of major and gastrointestinal haemorrhage compared with warfarin has been seen in African Americans and patients with chronic kidney disease, but the risk of intracranial haemorrhage remains lower.³⁷ Main side-effects of dabigatran are dyspepsia and stomach pain (11%), and transaminase elevations 0.9–2.0%, although with a frequency similar to that caused by warfarin. There is no evidence of liver toxicity as observed with ximelagatran.

A trend in the RE-LY study towards more MIs in the dabigatran arm as compared with warfarin was not confirmed in a subsequent post-hoc analysis.³⁸ A recent meta-analysis of seven trials including the RE-LY detected a higher risk of MI (1.19 % versus 0.79 %; p=0.03),³⁹ and this was also observed in the recent Secondary Prevention of Venous Thromboembolism (RE-MEDY) trial.⁴⁰ However, in the recent Danish Registry report (4,978 patients on dabigatran and 8,936 patients on

Table 1: Prevention of Thromboembolism

ESC 2012 Guideline Update on Atrial Fibrillation: Prevention of Thromboembolism in Non-valvular Atrial Fibrillation	
General	
Antithrombotic therapy for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications)	I-A
The choice of the antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding	I-A
The CHA ₂ DS ₂ -VASc score is recommended as a means of assessing stroke risk in nonvalvular AF	I-A
In patients with a CHA ₂ DS ₂ -VASc score of 0 (i.e. aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy	I-B
In patients with a CHA ₂ DS ₂ -VASc score of ≥2, OAC therapy with: adjusted dose VKA (INR 2–3), or a direct thrombin inhibitor (dabigatran), or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) unless contraindicated	I-A
In patients with a CHA ₂ DS ₂ -VASc score of 1, OAC therapy with: adjusted dose VKA (INR 2–3), or a direct thrombin inhibitor (dabigatran), or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) based on an assessment of the risk of bleeding complications and patient preferences	IIa-A
No antithrombotic therapy for female patients who are aged <65 and have lone AF (but still have a CHA ₂ DS ₂ -VASc score of 1 by virtue of their gender)	IIa-B
When patients refuse the use of any oral anticoagulation (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or – less effectively – aspirin 75–325 mg daily	IIa-B
NOACs	
When adjusted-dose VKA (INR 2–3) cannot be used due to difficulties in keeping within therapeutic anticoagulation, experiencing side-effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: a direct thrombin inhibitor (dabigatran), or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) is recommended	I-B
Where OAC is recommended, one of the NOACs, either: a direct thrombin inhibitor (dabigatran), or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) should be considered rather than adjusted-dose VKA (INR 2–3)	IIa-A
Where dabigatran is prescribed, a dosage of 150 mg twice daily is preferred to 110 mg twice daily, with the latter dosage recommended in: elderly patients, age ≥80 years concomitant use of interacting drugs (e.g. verapamil) high bleeding risk (HAS-BLED score ≥3) moderate renal impairment (CrCl 30–49 ml/min)	IIa-B
Where rivaroxaban is being considered, a dosage of 20 mg once daily is preferred to 15 mg once daily, with the latter dosage recommended in: high bleeding risk (HAS-BLED score ≥3) moderate renal impairment (CrCl 30–49 ml/min).	IIa-C
Annual baseline and subsequent regular assessment of renal function (by CrCl) in patients following initiation of any NOAC, but 2–3 times per year in those with moderate renal impairment	IIa-B
NOACs (dabigatran, rivaroxaban and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 ml/min)	III-A
Bleeding	
Assessment of the risk of bleeding when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel or aspirin)	I-A
The HAS-BLED score should be considered to assess bleeding risk. A score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy (with OAC or antiplatelet therapy)	IIa-A
Correctable risk factors for bleeding (e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs [aspirin, NSAIDs, etc.], alcohol, etc.) should be addressed	IIa-B
Use of the HAS-BLED score should be used to identify modifiable bleeding risks, but should not be used on its own to exclude patients from OAC therapy	IIa-B
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC	IIa-B
<small>OAC: oral anticoagulation with VKA (vitamin K antagonists) or NOACs; NOACs: non-vitamin K oral anticoagulants, ie dabigatran, rivaroxaban, apixaban. From: Camm et al, 2012.²¹ By permission of Oxford University Press on behalf of European Society of Cardiology. © ESC 2014. www.escardio.org</small>	
Additional Recommendations on the Prevention of Thromboembolism in Atrial Fibrillation (ESC, 2010)	
For patients with mechanical heart valves, the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of ≥2.5 in the mitral position and ≥2.0 for an aortic valve	I-B
Antithrombotic therapy for patients with atrial flutter as for those with AF	I-C
The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent or permanent)	IIa-A
Interruption of VKA (with subtherapeutic anticoagulation for up to 48 h), without substituting heparin as 'bridging' anticoagulation therapy in patients without mechanical prosthetic heart valves or not at high risk for thromboembolism, and who are undergoing surgical or diagnostic procedures that carry a risk of bleeding	IIa-C

Table 1 (cont.): Prevention of Thromboembolism

Additional Recommendations on the Prevention of Thromboembolism in Atrial Fibrillation (ESC, 2010), cont.	
'Bridging' anticoagulation with therapeutic doses of either LMWH or UFH during the temporary interruption of VKA therapy should be considered in patients with a mechanical prosthetic heart valve or at high risk for thromboembolism who are undergoing surgical or diagnostic procedures	Ila-C
Following surgical procedures, resumption of VKA therapy at the 'usual' maintenance dose (without a loading dose) on the evening of (or the next morning after) surgery, assuming there is adequate haemostasis	Ila-B
Re-evaluation at regular intervals of the benefits, risks and need for antithrombotic therapy should be considered	Ila-C
In patients with AF presenting with acute stroke or TIA, management of uncontrolled hypertension before antithrombotic treatment is started, and cerebral imaging (CT or MRI) performed to exclude haemorrhage	Ila-C
In the absence of haemorrhage, VKA should be considered ~2 weeks after stroke, but, in the presence of haemorrhage, anticoagulation should not be given	Ila-C
In the presence of a large cerebral infarction, delay the initiation of anticoagulation given the risk of haemorrhagic transformation	Ila-C
In patients with AF and an acute TIA, VKA as soon as possible in the absence of cerebral infarction or haemorrhage	Ila-C
UFH or subcutaneous LMWH when surgical procedures require interruption of VKA for longer than 48 h in high-risk patients	Ilb-C
In patients who sustain ischaemic stroke or systemic embolism during treatment with usual intensity VKA (INR 2.0–3.0), raising the intensity of the anticoagulation to a maximum target INR of 3.0–3.5, rather than adding an antiplatelet agent	Ilb-C

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AHA/ACC/HRS 2014 Guideline on Atrial Fibrillation: Prevention of Thromboembolism	
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences	I-C
Antithrombotic therapy selection based on risk of thromboembolism irrespective of paroxysmal, persistent or permanent AF	I-B
CHA ₂ DS ₂ -VASC score recommended to assess stroke risk	I-B
Warfarin recommended with mechanical heart valves. Target INR should be based on the type and location of prosthesis	I-B
With prior stroke, TIA, or CHA ₂ DS ₂ -VASC score ≥ 2, oral anticoagulants recommended. Options include:	
· Warfarin	I-A
· Dabigatran, rivaroxaban, or apixaban	I-B
With warfarin, determine INR at least weekly during initiation and monthly when stable	I-A
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR	I-C
Re-evaluate the need for anticoagulation at periodic intervals	I-C
Bridging therapy with LMWH or UFH with a mechanical heart valve if warfarin is interrupted. Decisions regarding bridging therapy should balance the risks of stroke and bleeding	I-C
Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated	I-C
Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually	I-B
For atrial flutter, antithrombotic therapy as for AF	I-C
With nonvalvular AF and CHA ₂ DS ₂ -VASC score of 0, omit antithrombotic therapy	Ila-B
With CHA ₂ DS ₂ -VASC score ≥ 2 and end-stage CKD (CrCl <15 mL/min) or on haemodialysis, prescribe warfarin for oral anticoagulation	Ila-B
With nonvalvular AF and a CHA ₂ DS ₂ -VASC score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin	Ilb-C
With moderate-to-severe CKD and CHA ₂ DS ₂ -VASC scores of ≥ 2, direct thrombin or factor Xa inhibitors at reduced doses	Ilb-C
For PCI, BMS may be considered to minimise duration of DAPT	Ilb-C
Following coronary revascularisation in patients with CHA ₂ DS ₂ -VASC score of ≥2, use clopidogrel concurrently with oral anticoagulants, but without aspirin	Ilb-B
Direct thrombin inhibitor, dabigatran, and factor Xa inhibitor rivaroxaban are not recommended with AF and end-stage CKD or on haemodialysis because of no benefit	III-C
Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve	III-B (harm)

bd = twice daily; BMS = bare-metal stent; CKD = chronic kidney disease; CrCl = creatinine clearance; DAPT = dual antiplatelet therapy; INR = international normalised ratio; LMWH = low molecular weight heparin; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; TIA = transient ischaemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist. From: January et al., 2014.¹ By permission of Elsevier on behalf of American College of Cardiology. © AHA/ACC/HRS 2014.

warfarin), rates of mortality, pulmonary embolism, and MI were lower with dabigatran compared with warfarin. Stroke/systemic embolism and major bleeding rates were similar in the two treatment groups.⁴¹ Thrombin time in diluted plasma (dilute TT using hemoclot direct thrombin inhibitor assay) and ecarin clotting time are precise methods to assess the anticoagulant effect of dabigatran. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) are prolonged by dabigatran but the correlation is not linear to guide dosage.⁴² However, in the presence of a normal aPTT dabigatran is unlikely to contribute to bleeding, and aPTT can be used in emergencies as a rough estimate.⁴³

Antidotes

For nonspecific and specific antidotes to direct thrombin inhibitors, please see the article by Rahmat and Lip, *Monitoring the Effects and Antidotes of the Non-vitamin K Oral Anticoagulants*, in this issue of the journal.

Factor Xa Inhibitors

Apixaban

Apixaban, an oral factor Xa inhibitor, is approved in Europe and Canada, and by the FDA for nonvalvular AF, and may be the most cost-effective NOAC.^{29,44} Apixaban has demonstrated reduced risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial haemorrhage in patients with nonvalvular AF for whom vitamin K antagonist therapy was unsuitable (apixaban versus aspirin; AVERROES trial).⁴⁵ In the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial, apixaban was found superior to warfarin in preventing embolic or haemorrhagic stroke, and resulted in less bleeding and lower mortality rates (11 % reduction; $p=0.047$).⁴⁶ Benefits of apixaban have been seen in both paroxysmal and persistent/permanent AF.⁴⁷ Rates of intracranial bleeding have been demonstrated to be significantly lower in patients treated with apixaban

Table 2: Oral Anticoagulants for AF

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose	Variable od	150 or 110 bd 75 mg bd if CrCl 15–30 ml/min	20 mg od 15 mg od if CrCl 15–30 ml/min	2.5–5 mg bd 2.5 mg bd if Cr $\geq$ 1.5 mg/dl, $\geq$ 80 years of age, body weight $\leq$ 60 kg	30–60 mg od (no data in renal impairment)
Target	Vitamin K- dependent factors	Thrombin (factor II)	Factor Xa	Factor Xa	Factor Xa
Half life	40 h	12–14 h	9–13 h	8–11 h	8–10 h
Renal clearance	0	80 %	60 %	25 %	40 %
Onset of action	3–5 h	2 h	2.5–4.0 h	3 h	1–5 h
inhibition					
Anticoagulation monitoring	INR 2–3	Not required	Not required	Not required	Not required
Interactions	Multiple	P-gp	P-gp; CYP3A4	P-gp; CYP3A4	P-gp; CYP3A4
Antidote	Vitamin K	3- and 4-factor prothrombin complex concentrates idarucizumab	4-factor prothrombin complex concentrates andexanet alfa, aripazine	4-factor prothrombin complex concentrates andexanet alfa, aripazine	4-factor prothrombin complex concentrates andexanet alfa, aripazine

Dabigatran is eliminated via the P-gp transporter, while the Xa inhibitors are eliminated via P-gp and cytochrome P450 (CYP)3A4 activity. Their dosage should be reduced with co-administration of P-gp or CYP3A4 inhibitors, and they should be used with caution or avoided with administration of P-gp or CYP3A4 inducers. P-gp inhibitors include verapamil, amiodarone, dronedarone, quinidine, erythromycin, clarithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, cyclosporin, grapefruit juice. P-gp inducers include rifampicin, St. John's wort, carbamazepine, phenytoin, phenobarbital, trazodone. CYP3A4 inhibitors include ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, chloramphenicol, clarithromycin, HIV protease inhibitors (e.g., ritonavir, atazanavir). CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, rifampicin, and St. John's wort (Hypericum perforatum). bd = twice daily; CrCl = creatinine clearance; CYP = cytochrome P450; od = once daily; P-gp = P-glycoprotein.

Table 3: New Anticoagulants (NOACs) vs Warfarin in Nonvalvular AF

Trial	Dose of NOAC	NOAC (%/y)	Warfarin (%/y)	P
Stroke/systemic embolism				
RE-LY	Dabigatran 110 md bd	1.53	1.69	0.34
	Dabigatran 150 mg bd	1.11	1.69	<0.001
ROCKET-AF	Rivaroxaban 15–20 mg od ^a	2.10	2.40	0.12
ARISTOTLE	Apixaban 2.5–5.0 mg bd ^b	1.27 ^c	1.60 ^c	0.01
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	1.57	1.80	0.08
	Edoxaban 30 mg od ^d	2.04	1.80	0.10
Intracranial haemorrhage				
RE-LY	Dabigatran 110 md bd	0.12	0.38	<0.001
	Dabigatran 150 mg bd	0.10	0.38	<0.001
ROCKET-AF	Rivaroxaban 15–20 mg od	0.50	0.70	0.02
ARISTOTLE	Apixaban 2.5–5.0 mg bd	0.24	0.47	<0.001
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	0.26	0.47	<0.001
	Edoxaban 30 mg od	0.16	0.47	<0.001
Major bleeding				
RE-LY	Dabigatran 110 md bd	2.71	3.36	0.003
	Dabigatran 150 mg bd	3.11	3.36	0.31
ROCKET-AF	Rivaroxaban 20 mg od	3.6	3.40	0.58
ARISTOTLE	Apixaban 2.5–5.0 mg bd	2.13	3.09	<0.001
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	2.75	3.43	<0.001
	Edoxaban 30 mg od	1.61	3.43	<0.001
Total mortality				
RE-LY	Dabigatran 110 md bd	3.75	4.13	0.13
	Dabigatran 150 mg bd	3.64	4.13	0.051
ROCKET-AF	Rivaroxaban 20 mg od	4.50	4.90	0.15
ARISTOTLE	Apixaban 2.5–5.0 mg bd	3.52	3.94	0.047
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	3.99	4.35	0.08
	Edoxaban 30 mg od	3.80	4.35	0.006

^a15 mg od if CrCl 40–49 ml/min; ^b2.5 mg bd if $\geq$ 2 of the following: age $\geq$ 80 y BW<60 kg, creatinine $\geq$ 1.5 mg/dl; ^cThis number includes both embolic and haemorrhagic strokes; ^d30 mg od if CrCl 30–50 ml/min, BW<60 kg, concomitant verapamil or quinidine. bd = twice daily; BW = body weight; CrCl = creatinine clearance; od = once daily.

than with warfarin, regardless of renal function.⁴⁸ Benefits of apixaban are irrespective of concomitant aspirin use⁴⁹ or of patients' age.⁵⁰

A substudy of the ARISTOTLE trial has also shown that cardioversion of AF can be safely performed in apixaban-treated patients.⁵¹ The

drug is metabolised in the liver via P450-dependent and -independent mechanisms and 25 % is excreted renally. It is not recommended for use in patients with severe hepatic impairment. Apixaban is also not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-glycoprotein, such as azole antimycotics

Table 4: EHRA Practical Guide on the Use of New Oral Anticoagulants – Possible Measures in Case of Bleeding

Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening bleeding	
Inquire last intake + dosing regimen	Inquire last intake + dosing regimen
Estimate normalisation of haemostasis:	Normalisation of haemostasis: 12–24 h
Normal renal function: 12–24 h	
CrCl 50–80 ml/min: 24–36 h	
CrCl 30–50 ml/min: 36–48 h	
CrCl <30 ml/min: ≥48 h	
Maintain diuresis	
Local haemostatic measures	Local haemostatic measures
Fluid replacement (colloids if needed)	Fluid replacement (colloids if needed)
RBC substitution if necessary	RBC substitution if necessary
Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9/l$ or thrombopathy)	Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9/l$ or thrombopathy)
Fresh frozen plasma as plasma expander (not as reversal agent)	Fresh frozen plasma as plasma expander (not as reversal agent)
Tranexamic acid can be considered as adjuvans	Tranexamic acid can be considered as adjuvans
Desmopressin can be considered in special cases (coagulopathy or thrombopathy)	Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Consider dialysis (preliminary evidence: -65 % after 4 h) ⁴⁸	
Charcoal haemoperfusion not recommended (no data)	
Life-threatening bleeding	
All of the above	All of the above
Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice, but no clinical evidence)	PCC 25 U/kg (may be repeated once or twice, but no clinical evidence)
Activated PCC 50 IE/kg (max. 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available	Activated PCC 50 IE/kg (max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available
Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)	Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit + expensive (only animal evidence)

CrCl = creatine clearance; RBC = red blood cell. From: Heidbuchel et al., 2013.³¹ By permission of Oxford University Press on behalf of European Heart Rhythm Association. © EHRA 2013.

Table 5: EHRA 2013: Last Intake of NOAC before Elective Surgical Intervention

No important bleeding risk and/or adequate local haemostasis possible:
Perform 12–24 h after last intake

	Dabigatran		Apixaban/Rivaroxaban	
	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24	≥48	≥24	≥48
CrCl 50–80 ml/min	≥36	≥72	≥24	≥48
CrCl 30–50 ml/min	≥48	≥96	≥24	≥48
CrCl 15–30 ml/min	not indicated		≥36	≥48

CrCl = creatine clearance. From: Heidbuchel et al., 2013.³¹ By permission of Oxford University Press on behalf of European Heart Rhythm Association. © EHRA 2013.

and HIV protease inhibitors, and should be used with caution in patients taking rifampicin, phenytoin, carbamazepine and phenobarbital. There are limited clinical data on patients with a CrCl of 15–29 ml/min, and the drug is not recommended in patients with a CrCl of <15 ml/min. Anti-factor Xa assays may be used to estimate the anticoagulant effect. APTT and PT are prolonged by apixaban but they cannot be used to guide dosage as the correlation is not linear, especially with PT.⁴² Concomitant use with diltiazem results in increased apixaban levels.

Rivaroxaban

Rivaroxaban is an oral factor Xa inhibitor that has been approved by the FDA and EMA for nonvalvular AF. In the ROCKET-AF trial (Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation), rivaroxaban was not found to be inferior to warfarin (INR 2–3) in patients with nonvalvular

AF for the prevention of stroke or systemic embolism, and offered a lower rate of intracranial bleeding, but a higher rate of gastrointestinal bleeding.⁵² In a substudy of this trial, rivaroxaban demonstrated equal safety and efficacy with warfarin in patients aged >75 years.⁵³ The half-life of rivaroxaban is 7–11 hours, but factor Xa is inhibited for up to 24 hours, allowing once-daily dosage. Its bioavailability increases with food consumption. The drug is metabolised in the liver via P450-dependent and -independent mechanisms, and is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-glycoprotein inhibitors (see the apixaban section). The drug is not recommended in patients with a CrCl of <15 ml/min. Anti-factor Xa assays are used to estimate the anticoagulant effect.²¹ APTT and PT are prolonged by rivaroxaban but they cannot be used to guide dosage as the correlation is not linear.⁴² However, prolonged PT bleeding can be attributed to rivaroxaban, and PT can be used as a rough estimate in case of emergencies.⁴³

Figure 2: Coagulation Cascade

AT = antithrombin; VKA = vitamin K antagonist.
From: January et al, 2014.¹ By permission of Elsevier on behalf of American College of Cardiology. © AHA/ACC/HRS 2014.

Edoxaban

Edoxaban has been demonstrated as noninferior to warfarin with respect to prevention of stroke or systemic embolism and shown to be associated with significantly lower rates of bleeding and death from cardiovascular causes (ENGAGE AF-TIMI 48 trial), and it is approved by the FDA.⁵⁴ Both the 30 and 60 mg doses were not inferior to warfarin, but in the intention-to-treat analysis with the 60 mg dose there was a trend favoring edoxaban.

Betrixaban

Betrixaban has also been found equivalent to warfarin.⁵⁵

Antidotes

For nonspecific and specific antidotes to factor Xa inhibitors, please see the article by Rahmat and Lip, *Monitoring the Effects and Antidotes of the Non-vitamin K Oral Anticoagulants*, in this issue of the journal. Although clinical experience is limited, antidotes for Xa inhibitors should be effective for all available agents.

Transition between NOACs/Warfarin

Transitioning from one anticoagulant to another is a period of high risk for both strokes and bleeding. A reasonable strategy is to reduce

Figure 3: Management of Bleeding in Patients Taking Non-vitamin K Oral Anticoagulants

aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII. ^aWith dabigatran.
From: Camm et al, 2012.²¹ By permission of Oxford University Press on behalf of European Society of Cardiology. © ESC 2014. www.escardio.org

the NOAC dose by half, start warfarin and stop the NOAC when the INR is ≥ 2 . When the patient is on warfarin, the NOAC is started after cessation of therapy and three-daily INR measurements to detect a value < 2 .⁵⁶

Conclusion

In conclusion, the new, non-vitamin K dependent oral anticoagulants, ie direct thrombin or Xa inhibitors, appear to be safer and more effective than warfarin in preventing thromboembolism in patients with non-valvular AF (ie absence of prosthetic valves or rheumatic mitral valve disease). ■

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