

Practical Guide to the New Oral Anticoagulants

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New Oral Anticoagulants

Over the last few years, new oral anticoagulants (NOACs) have been developed and marketed for the treatment of non-Valvular Atrial Fibrillation (NVAf), Deep Venous Thrombosis (DVT) and, more recently, for pulmonary embolism (PE).

The rationale underlying these new therapies is that they reduce the risks of embolic stroke and bleeding. Standard dicumarol therapy is characterised by a narrow therapeutic window that is reflected in the need for frequent monitoring of the international normalized ratio (INR). The therapeutic INR range in these diseases is between 2 and 3 because an INR of >3 increases the risk of bleeding, whereas an INR of <2 means the a suboptimal prevention of ischaemic stroke [1] (Figure 1), and only a small percentage of patients fall into this category. Furthermore, the anticoagulant power of dicumarols is modified by food, drugs and malabsorption syndromes.

The risks of embolism and bleeding are respectively assessed using the: CHA₂DS₂Vasc score [2] and the HAS-BLED score [3] (Tables 1 and 2).

Dabigatran, rivaroxaban and apixaban are three new drugs that have different mechanisms of action, daily doses, and metabolic and elimination profiles.

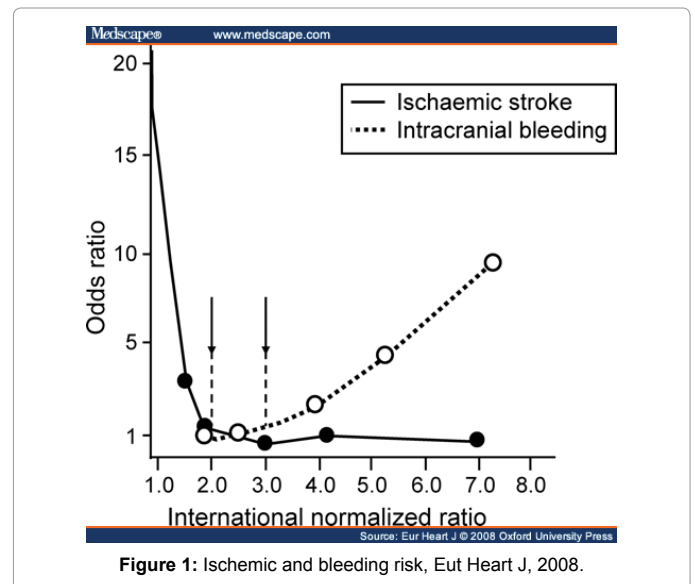
- Dabigatran (Pradaxa) is a direct thrombin inhibitor (it inhibits factor II) that has a half-life of about 12-14 hours and needs to be administered twice daily. It partially binds plasma proteins and can therefore be partially dialysed. Pradaxa is only eliminated renally: it is therefore contraindicated in patients whose creatinine clearance is <35 mL/min, and a reduced dose is mandatory when it is <50 mL/min.
- Rivaroxaban (Xarelto) is a direct factor X inhibitor with a half-life of 5-13 hours, but completely binds plasma proteins. It is administered once daily with evening meal in NVAf patients, and twice daily in those with DVT or PE. It is eliminated by the kidney and liver, and can be used at a lower dose if creatinine clearance is <50 mL/min and >15 mL/min in NVAf patients; its use should be avoided in DVT/PE patients whose creatinine clearance is <30 ml/min.
- Apixaban (Eliquis) is a direct factor X inhibitor with a half-life of 9-14 hours, but completely binds plasma proteins. It is administered twice daily and eliminated by kidney and liver. It should not be used if creatinine clearance is <15 mL/min, and the dose should be reduced if it is <30 mL/min.

The efficacy (primary endpoint: ischaemic or hemorrhagic stroke, systemic embolism) and safety (major bleeding) of these new drugs have been assessed in three clinical trials, [4-6] the results of which are summarised in Table 3.

According to the ESC guidelines, [7] NOACs should be preferred to dicumarols in all patients with NVAf and a CHA₂DS₂Vasc score of >1 (Figure 2).

ESC guideline indications

- 1) Antithrombotic therapy (thromboembolism prophylaxis) is recommended for all male and female patients with atrial fibrillation (AF), except those at very low risk (age <65 years and AF alone) or with contraindications (class IA).
- 2) The choice of antithrombotic therapy should be based on an evaluation of the absolute risk of stroke/embolism and bleeding in each patient (class IA).
- 3) The CHADS VASc score is recommended for risk evaluation in patients with NVAf.
- 4) Females aged <65 years with AF alone (a CHADS VASc score of 1 taking gender into account) are at low risk and antithrombotic therapy should not be considered (class IIa B).
- 5) Antithrombotic therapy is not recommended in patients with a CHADS VASc score of 0 (age <65 years with AF alone) who are low risk or without risk factors (class IB).
- 6) Unless contraindicated (and after evaluating bleeding risk and patient preference), antithrombotic therapy one of the following is recommended in patients with a CHADS VASc score of >2:



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CHA ₂ DS ₂ Vasc	Score (0-9)	Ischaemic risk
C=Cardiac Failure*	1	0=Low risk 1=Intermediate risk >1=High risk
H=Hypertension**	1	
A=Age (≥75 years)	2	
D=Diabetes	1	
S=Stroke (previous)	2	
V=Vascular disease***	1	
A=Age (65>years<75)	1	
Sc=Sex category****	0 or 1	

*EF <40% or a history of chronic cardiac failure

**New onset or previous diagnosis

***Involving aorta and large vessels

****Female=1, male=0

Table 1: CHA₂DS₂Vasc score.

HAS-BLED	Score (0-9)	Bleeding risk
H=Hypertension°	1	<2=Low risk 2=Intermediate risk >2=High risk
A=Abnormal liver/renal function°°	1 or 2	
S=Stroke	1	
B=Bleeding°°°	1	
L=Labile INR°°°°	1	
E=Elderly°°°°°	1	
D=Drugs/alcohol°°°°°°	1 or 2	

°SBP >160 mmHg

°°AST/ALT >3 times normal values, or serum creatinine >2.27 mg/dL

°°°Prior or predisposition

°°°°Time in therapeutic range <60%

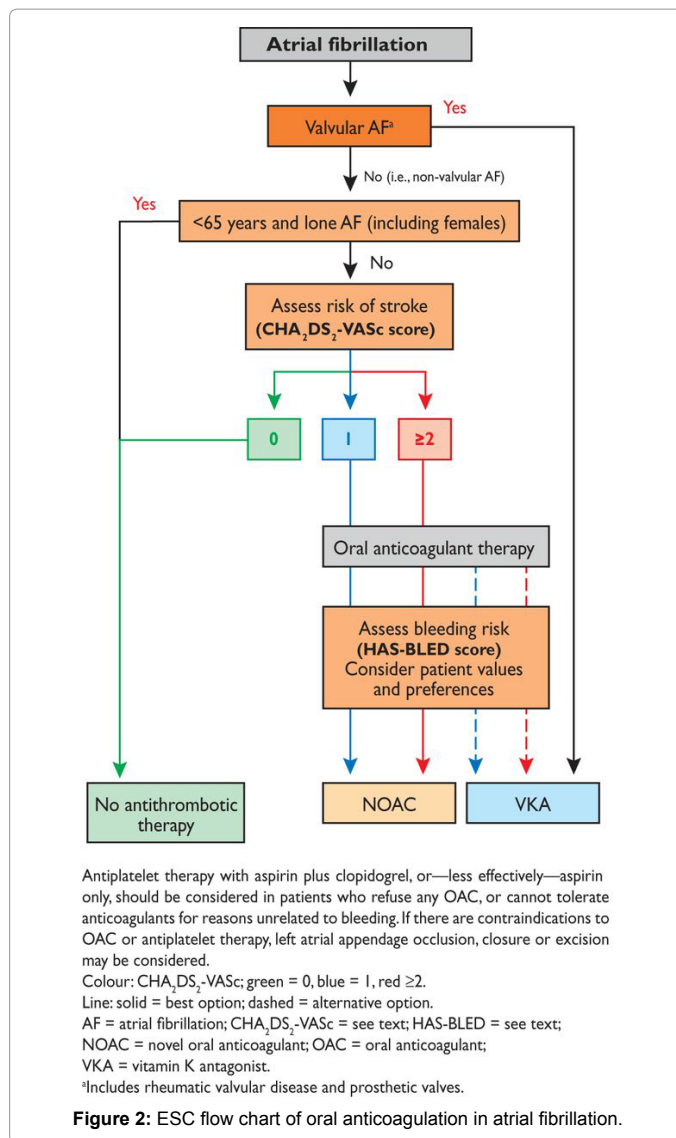
°°°°°Age >65 years

°°°°°°FANS or alcohol intake >8 units/week

Table 2: HAS-BLED score.

	RE-LY	ROCKET-AF	ARISTOTLE
Drug	Dabigatran	Rivaroxaban	Apixaban
Dose	150 mg, 110 mg b.i.d.	20 mg/day (15 mg/day)	5 mg (2.5 mg) b.i.d
Patients	18111	14264	18201
Mean CHA ₂ DS ₂ Vasc	2.1	3.5	2.1
Primary endpoint (stroke, systemic embolism) (%/y)	Dabigatran 110 mg: 1.53% (not worse than warfarin) Dabigatran 150 mg: 1.11% (superior to warfarin) Warfarin: 1.69%	Rivaroxaban 20 mg: 1.7% Warfarin: 2.2% (P<0.001 inferiority; 0.12 superiority intention-to-treat)	Apixaban 5 mg: 1.27% Warfarin: 1.60% (P<0.001 non-inferiority; P<0.01 superiority)
Hemorrhagic stroke (%/y)	Dabigatran 110 mg: 0.12% Dabigatran 150 mg: 0.10% Warfarin 0.38% P<0.0001	Rivaroxaban 20 mg: 0.26% Warfarin: 0.44% P=0.024	Apixaban 5 mg: 0.24% Warfarin: 0.47% P<0.001
Major bleeding (%/y)	Dabigatran 110 mg: 2.87% Dabigatran 150 mg: 3.32% Warfarin: 3.57% P=0.003 (110 mg) P=0.32 (150 mg)	Rivaroxaban 20 mg: 3.60% Warfarin 3.45% P=0.58	Apixaban 5 mg: 2.13% Warfarin: 3.45% P<0.001

Table 3: Results of the RE-LY, ROCKET-AF and ARISTOTLE trials.



- Vit. K inhibitor on the basis of INR
 - Direct thrombin inhibitor (dabigatran)
 - Oral factor Xa inhibitor (rivaroxaban, apixaban).
- 7) In patients with a CHADS VASc score of 1, antithrombotic therapy is recommended using one of the following:

- Vit. K inhibitor on the basis of INR
- Direct thrombin inhibitor (dabigatran)
- Oral factor Xa inhibitor (rivaroxaban, apixaban).

If a patient rejects dicumarol or NOAC therapy, double antiplatelet therapy should be considered: ASA 75-100 mg and clopidogrel 75 mg in the case of low bleeding risk, or ASA 75-325 mg alone (less effective) (class IIa B).

The choice of NOAC should be guided by a risk/benefit evaluation, clinical profile, and concomitant therapies. After prescription, a careful follow-up is essential: the first after 30 days, and then every three months.

It is necessary to evaluate:

- haemoglobin, renal and liver function
- indications for proton pump inhibitors
- the patients' educational level
- patient compliance
- previous ischaemic/hemorrhagic events
- any side effects

The European Heart Rhythm Association (EHRA) [8] recommends using a "Patient Card".

NOACs do not require routine coagulation monitoring; however, a quantitative evaluation of drug exposure and anticoagulation effect may be necessary in emergency situations.

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