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ANMCO Position Paper: direct oral anticoagulants for stroke prevention in atrial fibrillation: clinical scenarios and future perspectives

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It is now 4 years since the introduction of the new direct oral anticoagulants into clinical practice. Therefore, the Italian Association of Hospital Cardiologists (ANMCO) has deemed necessary to update the previous position paper on the prevention of thrombo-embolic complications in patients with non-valvular atrial fibrillation, which was published in 2013. All available scientific evidence has been reviewed, focusing on data derived from both clinical trials and observational registries. In addition, all issues relevant to the practical clinical management of oral anticoagulation with the new direct inhibitors have been considered. Specific clinical pathways for optimal use of oral anticoagulation with the new directly acting agents are also developed and proposed for clinical implementation. Special attention is finally paid to the development of clinical algorithms for medium and long-term follow-up of patients treated with new oral direct anticoagulants.

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The foundations of clinical practice

Elements of the practical clinical pharmacology of DOACs

During the last few years, anticoagulant therapy has been reinforced through the introduction of a number of drugs which act directly on some of the factors in the coagulation enzymatic cascade. In fact, unlike Vitamin K Antagonists (VKAs), these drugs act directly and selectively, inhibiting just one factor in the coagulation cascade, and they are therefore defined as 'direct oral coagulation inhibitors' (DOACs).[1]

From the pharmacological point of view, there are two classes of DOACs[1,2]:

- direct thrombin inhibitors (dabigatran),
- direct activated X factor inhibitors (rivaroxaban, apixaban, and edoxaban).

Their main pharmacological characteristics are summarised in *Table 1*.

Overall, these drugs share a number of fundamental characteristics:

- pharmacokinetic and pharmacodynamic stability;
- no significant effects on platelet aggregation and primary haemostasis;
- predictable pharmacodynamic factors which are stable over time (bio-availability, half-life, plasma peak after oral administration);
- low potential interaction with foods and commonly used drugs;
- quick onset of action;
- restoration of normal coagulation within short times after suspension.

The combination of these factors means that the variation in individual response is minimal, allowing use in fixed doses and overcoming the need to monitor coagulation over time.

Their rapid onset of action makes them particularly useful in the management of anticoagulation therapy in patients with atrial fibrillation (AF), since an effective anticoagulant action is guaranteed just 2–4 h after administration. This avoids the need for bridging with unfractionated heparin sodium or low molecular weight heparin at the start of treatment. Moreover, their action ends quickly, with rapid restoration of normal coagulation (on average 12–24 h with normal kidney function).[1,2]

The pharmacokinetic and pharmacodynamic stability of DOACs makes monitoring of coagulation inadvisable and potentially misleading. However, in some circumstances it may be necessary to assess these drugs' impact on coagulation, as in the case of haemorrhages or emergency surgery. *Table 2* details the effects of the different DOACs on the various coagulation tests and their possible practical uses.[3] However, when assessing the single tests it is always essential to consider the time since the drug was last administered and its half-life. Therefore, tests performed within 3–6 h after administration reflect the drug's concentration peak, while tests after 12–24 h may be useful for assessing its residual effect.

Effectiveness and safety of DOACs

AF is the most common sustained cardiac arrhythmia and involves an average risk of stroke of about 4–5% per annum, more than 5 times that of individuals without this condition.[4-6] VKAs have been the main therapy for many conditions at high risk of thrombo-embolism, including AF, for more than 60 years. Randomised, controlled clinical studies have shown that VKAs reduce the relative risk of stroke by 64% (absolute reduction of 2.8% in primary and 8.5% in secondary prevention) compared with placebo in patients with non-valvular AF (NVAF).[5]

DOACs have proved to be a valid alternative to VKAs,[7-10] demonstrating their 'non inferiority' to warfarin and opening the way to new strategies for the prevention of embolic events in NVAF (*Table 3*). In particular, considered as a group and compared with conventional treatment with warfarin,[11] DOACs have been shown to provide:

- a further reduction of 19% in the combined risk of stroke and embolic events (RR 0.81, 95% confidence interval 0.73–0.91; $P < 0.0001$);
- a further reduction of 10% in the combined risk of death from all causes (RR 0.90, 95% confidence interval 0.85–0.95; $P < 0.0003$);
- 52% reduction in the risk of cerebral haemorrhage (RR 0.48, 95% confidence interval 0.39–0.59; $P < 0.0001$);

In fact, in terms of safety, compared with conventional treatment with warfarin, DOACs considerably reduce the risk of cerebral haemorrhage events[11] and would appear to be associated with a small increase in the risk of digestive haemorrhages, which however is at the limits of statistical significance (RR 1·25, 95% confidence interval 1.01–1.55; $P = 0.04$).

The data of the major studies undertaken for registration have been confirmed by the various observational studies conducted after the introduction of the DOACs into clinical practice in the 'real world'.[12-16] These studies show DOACs to be consistently superior to warfarin in terms of both efficacy, with reduction of cerebrovascular and embolic events,[12-16] and safety,[12-16] with a lower risk of both major and minor haemorrhagic events, including digestive haemorrhages,[14,15] although there are some discrepancies in the data regarding these.

Therefore, the information emerging from clinical practice is strongly in favour of the use of DOACs in patients with NVAF.

Pharmacological interactions

DOACs show a lower rate of pharmacological interactions compared with traditional VKAs.

All DOACs are absorbed in the intestine, with an extremely variable bio-availability, from 3–7% (dabigatran) to 100% (rivaroxaban, on a full stomach). *Dabigatran* is absorbed as dabigatran etexilate (inactive) and converted in the liver and plasma into active dabigatran, about 80% of which is eliminated by the kidneys and only a minimal proportion by the liver, without interfering with the P450 cytochrome system.[17] *Rivaroxaban* is rapidly absorbed by the intestine in its active form and about 65% metabolised in the liver, involving the P3A4, P3A5, and P2J2 cytochrome

Table 1 Main pharmacological characteristics of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Direct Xa factor inhibitor	Direct Xa factor inhibitor	Direct Xa factor inhibitor
Prodrug	Yes Converted into active form by esterase	No	No	No
Bio-availability	6-7%	70% without food >90% with food	50-66%	60%
Bond to plasma proteins	35%	90-95%	80-90%	40-50%
Plasma peak after oral administration	1-2 h	2-4 h	1-3 h	1-2 h
Half-life	12-17 h Increase in case of kidney dysfunction (23-35 h)	5-9 h Increase with age and in case of kidney dysfunction (11-13 h)	8-15 h Increase with age and in case of kidney dysfunction	10-14 h Increase with age and in case of kidney dysfunction
Elimination through kidneys	80-85%	35%	25-30%	35% of dose administered and 50% of dose absorbed
Non-renal elimination	15-20%	65%	70-75%	50%
Dialisability	Yes	No	No	No
Administration advice	With or without food Capsules must be taken intact; if a capsule is broken, bioavailability may be increased	With food recommended	With or without food	With or without food
Interaction with hepatic cytochromes	No	Yes	Yes	Low
Interaction with P Glycoprotein	Yes	Yes	Yes	Yes
Dose	150 mg every 12 h (twice-daily) 110 mg every 12 h for: • age >80 years, • glomerular filtrate 30-50 ml/min • Verapamil therapy • high haemorrhage risk (HAS-BLED >3)	20 mg per day in single administration (QOD) 15 mg per day for: • glomerular filtrate 15-50 ml/min • high haemorrhage risk (HAS-BLED >3)	5 mg every 12 h (twice-daily)mg every 12 h if 2 of the following criteria are met: • age >80 years • weight <60 kg • glomerular filtrate 15-30 ml/min	60 mg per day in single administration (QOD) 30 mg per day for glomerular filtrate 15-50 ml/min • weight ≤ 60 Kg • Concomitant therapy with: • Cyclosporine • Dronedarone • Erythromycin • Ketoconazole
Contraindications	Chronic liver disease (Child class B and C) Glomerular filtrate <30 ml/min Use of strong P-Glycoprotein inhibitors (dronedarone, ketoconazole, cyclosporine, itraconazole.	Chronic liver disease (Child class B and C) Glomerular filtrate <15 ml/min Use of strong P Glycoprotein and P450 3A4 Cytochrome inhibitors/activators (HIV Protease inhibitors, carbamazepine, phenobarbital, ketoconazole, cyclosporine)	Chronic liver disease (Child class B and C) Glomerular filtrate <15 ml/min Use of strong P Glycoprotein and P450 3A4 Cytochrome inhibitors/activators (HIV Protease inhibitors, carbamazepine, phenobarbital, ketoconazole, cyclosporine)	Severe chronic liver disease Glomerular filtrate <15 ml/min Use of strong P-Glycoprotein inhibitors, carbamazepine (caution) and phenobarbital (caution)

Table 2 Effects of the different DOACs on the coagulation tests and their possible practical uses

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
INR	Do not use Generates unreliable values	Do not use Generates unreliable values	Do not use Generates unreliable values	Do not use Generates unreliable values
Prothrombin time (PT)	Do not use Generates unreliable values	Unpredictably prolonged. Normal values mean the drug is not effective.	Unpredictably prolonged. Normal values mean the drug is not effective.	Unpredictably prolonged. Normal values mean the drug is not effective.
Activated partial thromboplastin time (aPTT)	Prolonged Provides a qualitative assessment of the drug's efficacy. Normal values mean the drug is not effective. Values higher than twice the normal level 12 h after the last dose suggest an increased risk of haemorrhage	Can be unpredictably prolonged	Can be unpredictably slightly prolonged	Can be unpredictably prolonged
Diluted thrombin time (dTT)	Prolonged with linear correlation with drug concentration. Normal values mean the drug is not effective.	Do not use Generates unreliable values	Do not use Generates unreliable values	Do not use Generates unreliable values
Ecarin clotting time (ECT)	Prolonged with linear correlation with drug concentration. Normal values mean the drug is not effective. Values higher than 3 times the normal level 12 h after the last dose suggest an increased risk of haemorrhage	Do not use Generates unreliable values	Do not use Generates unreliable values	Do not use Generates unreliable values
Assessment of anti-Xa activity by chromogenic method	Do not use Generates unreliable values	Provides quantitative information about the presence and concentration of the drug. Data on the thresholds value which imply an increase in haemorrhage risk are not available.	Provides quantitative information about the presence and concentration of the drug. Data on the thresholds value which imply an increase in haemorrhage risk are not available.	Provides quantitative information about the presence and concentration of the drug. Data on the thresholds value which imply an increase in haemorrhage risk are not available.

systems, with no active metabolites.[18] *Apixaban* is absorbed by the intestine in its active form (50% in the distal part of the small intestine and ascending colon) and is about 73% metabolised in the liver, involving essentially the P3A4 and P3A5 cytochrome systems, with no active metabolites.[19] *Edoxaban* is rapidly absorbed by the gastrointestinal system and about 50% metabolised in the liver, although with little involvement of the P3A4 cytochrome system,[20] and about 50% in the kidneys.[20]

All DOACs are substrates for P glycoprotein (P-gp), an important membrane glycoprotein made of 1280 amino acids and belonging to the ABC membrane transporter (ATP-Binding Cassette) family, operating as a pump for the transmembrane outflow of its substrates from the inside to the outside of cells. P-gp consists of two equivalent halves which include six transmembrane substrates and an ATP-binding site, since the transmembrane transportation of the substrates requires energy consumption. P-gp is found

Table 3 Phase III studies on DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Patients included	18 113	14 266	18 201	21 105
Age	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female gender	37%	40%	35%	38%
Paroxystic atrial fibrillation	32%	18%	15%	25%
CHADS2 Score	Average 2.1 0-1: 32% 2: 35% 3-6: 33%	Average 3.5 0-1: 0% 2: 13% 3-6: 87%	Average 2.1 0-1: 34% 2: 36% 3-6: 30%	Average 2.8 0-1: 0% 2: 47% 3-6: 53%
Study design	PROBE (prospective, randomized, open-label, blinded end point evaluation)	Double blind—double dummy	Double blind—double dummy	Double blind—double dummy
Primary endpoint	Incidence of stroke or systemic embolism	Incidence of stroke or systemic embolism	Incidence of stroke or systemic embolism	Incidence of stroke or systemic embolism
Patients randomized to warfarin	6022	7013	9081	7036
Target INR in patients randomized to warfarin	2.0-3.0	2.0-3.0	2.0-3.0	2.0-3.0
Median TTR in patients randomized to warfarin	67%	58%	66%	68%
NOAC dose	150 mg every 12 h (6067 patients) or 110 mg every 12 h (6015 patients)	20 mg per day in single administration (7131 patients) Reduction of dose to 15 mg per day in case of Creatinine Clearance of 30-49 ml/min.	5 mg twice a day (9120 patients) Reduction of dose to 2.5 mg twice a day in patients with at least two of the following risk factors: • age >80 years, • severely impaired kidney function, • weight <60 kg	60 mg per day in single administration (7035 patients), or 30 mg per day in single administration (7034 patients). Reduction of dose by half in case of > • Creatinine Clearance of 30-50 ml/min • weight <60 kg • use of verapamil, quinidine or dronedarone.
Median follow-up	2.0 years	1.8 years	1.9 years	2.8 years
Primary endpoint Events/100 patients/year	Dabigatran 150: 1.12% Dabigatran 110: 1.54% Warfarin: 1.72%	Rivaroxaban: 1.7% Warfarin: 2.2%	Apixaban: 1.27% Warfarin: 1.60%	Edoxaban 60 mg: 1.18% Edoxaban 30 mg: 1.61% Warfarin: 1.5%
Tests	Intention to treat	As per protocol	Intention to treat	Modified intention to treat
P indicating non-inferiority of DOACs compared with warfarin	$P < 0.001$ for both doses	$P < 0.001$	$P < 0.001$	$P < 0.001$ for 60 mg dose. $P < 0.005$ for 30 mg dose.
P indicating superiority of DOACs compared with warfarin	$P < 0.001$ for 150 mg dose.		$P = 0.01$	$P = 0.02$ for 60 mg dose.
Haemorrhagic stroke Events/100 patients/year	Dabigatran 150: 0.12% Dabigatran 110: 0.10% Warfarin: 0.38% $P < 0.001$ for both doses	Rivaroxaban: 0.26% Warfarin: 0.44% $P = 0.02$	Apixaban: 0.24% Warfarin: 0.47% $P < 0.001$	Edoxaban 60 mg: 0.26% Edoxaban 30 mg: 0.16% Warfarin: 0.47% $P < 0.001$ for both doses
Major bleeding Events/100 patients/year	Dabigatran 150: 3.40% Dabigatran 110: 2.92% Warfarin: 3.61% $P = 0.003$ for 110 mg $P = 0.41$ for 150 mg	Rivaroxaban: 3.6% Warfarin: 3.40% $P = 0.58$	Apixaban: 2.13% Warfarin: 3.09% $P < 0.001$	Edoxaban 60 mg: 2.75% Edoxaban 30 mg: 1.61% Warfarin: 3.43% $P < 0.001$ for both doses

	Mechanism	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Amiodarone	Limited competition with P-gp	+ 12-60%	"Minor" effects Caution if GFR<50 ml/min	No data	+40%
Digoxin	Competition with P-gp	No effects	No effects	No data	No data
Diltiazem	Competition with P-gp Slight CYP3A4 inhibition	No effects	"Minor" effects Caution if GFR 15-50 ml/min	+ 40%	No data
Dronedarone	Competition with P-gp CYP3A4 inhibition	+70-100% **USE: 75 mg twice daily if GFR 30-50 ml/min**	No data: caution	No data: caution	+85% Reduce dose by 50%
Quinidine	Competition with P-gp	+53%	No data: caution	No data	+77%
Verapamil	Competition with P-gp Slight CYP3A4 inhibition	+ 12-180% Reduce dose and take simultaneously	"Minor" effects Caution if GFR 15-50 ml/min	No data	+ 53%
Atorvastatin	Competition with P-gp CYP3A4 inhibition	+18%. No effects	No effects	No data	No effects

Figure 1 Interaction between non-vitamin K antagonist oral anticoagulants drugs and some cardiovascular drugs.

in many normal tissues and acts as a protective agent against substances which are potentially toxic for the intracellular environment. P-gp is able to transport a considerable variety of chemical compounds even with very different structures, many of which are also substrates of the CYP3A4 isoenzyme. P-gp limits the absorption of various drugs at different levels: in the *intestine* by transferring them from the enterocytes to the intestinal cavity, in the *kidneys* by transferring them from the tubular cavity cells to the urine and in the *liver* by moving them from the hepatocytes to the bile. P-gp performs equivalent functions in the *testicles* and the central *nervous system*.

Therefore, all drugs which inhibit P-gp and/or the mainly P3A4 cytochrome system are potentially capable of increasing the bio-availability of DOACs, increasing their concentrations in the blood and consequently the haemorragic risk. Conversely, all drugs capable of inducing (strengthening) P-gp and the P3A4 cytochrome system may reduce the bioavailability of DOACs, with consequent low plasmatic levels of DOACs and an increase in the risk of thrombo-embolic events.

Figures 1, *2*, and *3*, modified from the European Heart Rhythm Association Guidelines,[21] show the effects of some drugs on plasma concentrations of DOACs, due to competition with both P-gp and the hepatic cytochrome system.

With regard to cardiovascular drugs (*Figure 1*), dronedarone, a powerful P-gp inhibitor, is able to increase plasma concentrations of dabigatran by up to 70–100% and is therefore not recommended in association with this NOAC. However, it must be stated that the *Food and Drug Administration's Adverse Reporting System Database* does not record any increase in haemorrhagic complications in patients taking dabigatran and dronedarone in association.[22] Other drugs commonly used in patients with atrial fibrillation, such as digoxin and atorvastatin, capable of slightly inhibiting P-gp, do not show any significant effects on plasma concentrations of dabigatran, while amiodarone, quinidine and verapamil may increase them slightly. A substudy of the ENGAGE-AF-TIMI 48 study showed that the simultaneous administration of amiodarone reinforces the antithrombotic effect of the low dose of edoxaban (30 mg), by increasing its plasma levels, without changing the risk of haemorrhagic complications. Conversely, the efficacy and tolerability of the high dose of edoxaban (60 mg) were not affected by the administration of amiodarone.[23] Verapamil should be administered about 2 h after dabigatran, but here again no increase in haemorrhagic complications was reported in patients who were taking dabigatran in combination with verapamil or amiodarone.[24] Rivaroxaban, 30% of which is eliminated by the kidneys, should be used with caution in patients co-treated with amiodarone, diltiazem, dronedarone, quinidine or verapamil, especially if the glomerular filtration rate is between 15 and 50 ml/min.

Other antibiotic, antineoplastic, and antitumor drugs which inhibit P-gp and also the hepatic cytochrome system in general interact with DOACs (*Figure 2*). It is estimated that plasma concentrations of dabigatran may increase by up to 138% after a single dose and up to 153% after repeated doses of 400 mg of ketoconazole.[25] The effects on the other DOACs are similar. Conversely, rifampicin acts as a strong inducer of P-gp and hepatic cytochromes P3A4 and P2, meaning that it has a strongly opposite effect, reducing plasma levels of DOACs. As regards edoxaban, in the ENGAGE-AF TIMI 48 study doses were halved in patients who were taking strong P-gp inhibitor drugs, including ketoconazole.[10] This could therefore be suggested in clinical practice, although with great caution. In addition, an interaction study has shown plasma levels of edoxaban about 35% lower in patients co-treated with rifampicin.[26]

H_2, receptor antagonist, proton pump inhibitor and antacid drugs may delay intestinal absorption of DOACs to a lesser extent, although without inducing significant pharmacological or clinical interferences (*Figure 3*).

	Mechanism	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Erythromycin Clarithromycin	Competition with P-gp Slight CYP3A4 inhibition	+ 15-20%	+ 30-54%	No data	+90%. Reduce dose by 50%
Rifampicin	P-gp /BCRP and CYP3A4/CYP2 inducer	-66%	Up to -50%	-54%	-35% (with increase in active metabolites)
HIV protease inhibitors (Ritonavir,1etc)	Competition with P-gp /BCRP, CYP3A4/CYP2, CYP3A4 inhibition	No data	+ 153%	Strong increase	No data
Fluconazole	Slight CYP3A4 inhibition	No data	+ 42% (systemic administration)	No data	No data
Ketoconazole Itraconazole Posaconazole Voriconazole	Powerful P-gp inhibition Competition with BCRP CYP3A4 inhibition	+140-150% USE: 75 mg twice daily if GFR 30-50 ml/min	Up to +160%	+ 100%	+87-95% Reduce dose by 50%
Cyclosporine Tacrolimus	Competition with P-gp	Not recommended	Not known	No data	+ 73%

Figure 2 Interaction between non-vitamin K antagonist oral anticoagulant drugs and some antibiotic, antiviral and antineoplastic drugs.

	Mechanism	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Naproxen	Competition with P-gp	No data	No data	+55%	Increase in bleeding time
H_2 blockers Proton pump inhibitors Al-Mg hydroxide	Gastrointestinal absorption	-12-30%	No effects	No effects	No effects
Carbamazepine Phenobarbital Fentoine St John's wort	P-gp /BCRP and CYP3A4/CYP2 inducer	- 66%	Up to -50%	-54%	-35%

Figure 3 Interaction between non-vitamin K antagonist oral anticoagulant drugs and other commonly used drugs.

There are also substances capable of inducing the activity of P-gp and the hepatic cytochrome system. These include rifampicin, some antiepileptic drugs (carbamazepin, Phenobarbital, and phenytoin) and *Hypericum perforatum* (with antidepressive and antiviral properties, known as 'St John's wort'). By inducing increased P-gp activity, these substances lead to an increase in the elimination of DOACs from the body, with a consequent reduction in their plasma concentrations.

Management of haemorrhages during NOAC therapy

One of the greatest fears concerning the use of DOACs amongst professionals is the risk of, post-traumatic or spontaneous haemorrhagic complications

This is another reason why antithrombotic therapy should only be prescribed after careful assessment of the ratio between thrombotic and haemorrhagic risk (CHA2DS2 VASc—HAS-BLED).

According to the definition of the International Society of Thrombosis and Haemostasis (ISTH), bleeding events can be subdivided into major and minor, where a 'major bleeding' event is one of the following:

- fatal bleeding;
- symptomatic bleeding involving a crucial area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial):
- haemoglobin reduction of 2 g/dL, or more, or necessity of transfusion of 2 or more units of fresh blood or packed red blood cells.

All events apart from those listed above are classified as 'minor bleeding'.

DOACs have shown a better safety profile with a lower incidence of bleeding than VKAs.

When faced with a patient with a haemorrhagic event in progress, both a correct assessment of the medical history and a thorough physical exams are necessary, considering a number of variables which help to stratify the risk:

- type of anticoagulant therapy being taken;
- dose being taken;

- any other concomitant drug such as antiplatelet drugs or other drugs which may interfere with the anticoagulant pharmacokinetics and pharmacodynamics.
- possible kidney and/or liver failure;
- hypertensive crisis;
- traumatism, ...

Moreover, an appropriate clinical approach to the patient should provide indications as to whether major bleeding is imminent or in progress. Unfortunately diagnosis is not always easy, such as in case of trauma. Often the diagnostic pathway is more difficult, for example when spontaneous haemorrhages are not immediately obvious (retroperitoneal, intracerebral,...), as can happen with drug overdose.

Therefore, when dealing with an haemorrhagic event in a patient receiving anticoagulant therapy, blood coagulation must be assessed with the aid of an emergency blood test. With most of the molecules used until just recently (unfractionated heparin, VKAs), the standardisation of doses was difficult, requiring continuous adjustments in relation to the measured parameters (PTT, INR). DOACs and low molecular weight heparin have made it possible to establish a standardised dose and effect relation but in the case of a haemorrhagic event it is still necessary to find out the level of anticoagulant activity in the specific moment concerned. With DOACs, INR measurement is of no use, but Xa factor inhibition is closely correlated to the plasma concentrations of Apixaban, Rivaroxaban and Edoxaban, and the aPTT value and plasma diluted thrombin time (dTT) show a good level of correlation with the plasma concentration of Dabigatran (*Table 2*).

Normally, thanks to the short half-life of DOACs, interrupting the drug allows physiological coagulation to be restored within a few hours.

Further therapeutic measures can be considered depending on the type of NOAC:

- reduction of intestinal absorption by rapid administration (within 2–3 h after administration of the NOAC) of activated charcoal;
- delay or interruption of administration of the next dose of drug;
- dialysis to increase the rate of elimination;
- administration of liquids to restore blood volume and haemodynamic compensation;
- mechanical haemostasis by direct compression, surgery or endovascular embolization procedure;
- administration of blood products (erythrocyte concentrates, frozen fresh plasma, platelets);
- use of 4-factor Prothrombin Complex Concentrate (PCC);
- administration of recombinant factor VIIa (rFVIIa)[10];
- Activated prothrombin complex – aPCC (FEIBA).

Now that DOACs efficacy has been firmly established, several studies are focusing their attention on searching molecules which can act as quick antagonists to the anticoagulant effect of DOACs. Adexanet and idarucizumab are among the molecules which antagonize DOACs. In case of acute major bleeding adexanet, is a molecule studied (used) to antagonize the anticoagulant effects of both direct and indirect inhibitors of the Xa factor.[27] Of all the new anticoagulant molecules, the only one which currently has an approved antidote (idarucizumab), is Dabigatran. The indication using idarucizumab is relegated to the rare cases in which rapid inactivation of the anticoagulant effect of Dabigatran is necessary, in the event of emergency surgery (see 'management of anticoagulant therapy in patients who are to undergo surgical procedures'), in urgent procedures or in the case of potentially fatal or uncontrolled bleeding. The Idarucizumab molecule is a humanised monoclonal antibody fragment (Fab), which bonds to dabigatran with a very strong affinity, sharply higher than the bonding affinity of dabigatran with thrombin, forming a very stable idarucizumab-dabigatran complex which neutralises the anticoagulant effect. For Edoxaban, the RCP describes how to manage haemorrhages with 4-factor PCC.

General indications for the use of DOACs in clinical practice

The various types of AF

According to the 2014 AHA/ACC/HRS guidelines,[28] paroxystic AF is defined as that with restoration of the sinus rhythm within 7 days, with or without cardioversion, while under the ESC guidelines AF is paroxystic if the sinus rhythm is restored spontaneously within a maximum of seven days. The guidelines classify AF as 'persistent' when cardioversion is required.[29]

In the literature, there are fairly divergent findings with regard to the relationship between the type of AF and the risk of stroke. Some studies find no difference in stroke risk between patients with paroxystic and permanent AF,[30-33] while in other studies, patients with paroxystic AF showed a lower risk of stroke than those with persistent or permanent AF.[5-39,50]

Some sub-studies of the main outcome studies performed on the DOACs report the behaviour of every single NOAC, compared with warfarin, in patients with paroxystic, persistent or permanent AF:

Dabigatran In a sub-study of the RE-LY[39] study, 5943 patients are defined as having paroxystic AF, 5789 persistent AF and 6375 permanent AF at the time of their recruitment to the study. Combining the antithrombotic treatments used in the study (warfarin, dabigatran), the incidence per 100 patient/year of primary endpoint (stroke/systemic embolism) was found to be 1.32 for paroxystic, 1.55 for persistent and 1.49 for permanent AF. Similarly, the incidence of major haemorrhages was reported as 3.57 for paroxystic, 3.29 for persistent and 2.92 for permanent AF. The highest dose of dabigatran (150 mg twice daily) was found to be superior to warfarin in terms of reduction of the primary endpoint, in the same way for all three different types of AF. Conversely, the lowest dose of dabigatran (110 mg twice daily) was found to be effective in comparison with warfarin in reducing the primary endpoint in patients with paroxystic AF (HR 0.60) more than in patients with persistent (HR 0.96) and permanent (HR 1.13) AF. The statistical significance of the p value for interaction term analysis ($P = 0.0465$) was found to be considerable, since this analysis had a power of over 80% for detecting an interaction between randomised treatments and type of AF in terms of relative difference of effectiveness (compared with warfarin) of over 65%.

Rivaroxaban In the ROCKET AF study, 2490 patients had paroxystic, 11 485 persistent and 196 recently diagnosed AF.[8] In the intention-to-treat analysis, the incidence of primary endpoint (stroke/systemic embolism) was found to be 3.41% in patients randomised to rivaroxaban and 3.42% in patients randomised to warfarin within the group with paroxystic AF, 3.91% in patients treated with rivaroxaban and 4.45% in those assigned warfarin in the group with persistent AF, and 2.08% in patients receiving rivaroxaban and 8.0% in those receiving warfarin in the permanent AF group. The interaction analysis *P*-value was not statistically significant ($P = 0.218$), suggesting that rivaroxaban and warfarin are equivalent for all three types of AF.[8]

Apixaban In the ARISTOTLE study, the definition of paroxystic AF was taken from the AHA/ACC/AHRA guidelines (restoration of sinus rhythm within 7 days, whether spontaneous or induced). A recent sub-study of the ARISTOTLE study made a detailed examination of the various types of AF.[35] In this sub-study, 2786 patients were found to have paroxystic and 15412 persistent or permanent AF out of the total population recruited (patients with persistent and permanent AF were studied as a single group).

The incidence of the primary endpoint (stroke/systemic embolism) was significantly lower in patients with paroxystic than with persistent or permanent AF. Conversely, there was no significant difference in the incidence of major haemorrhages between the two groups. It is possible that the decision to group patients with persistent and permanent AF together might have given the study greater statistical power in identifying differences in outcome compared with the group with paroxystic AF. When the effects of apixaban were compared with those of warfarin in the groups of patients with different types of AF, no significant interactions between the groups emerged. The interaction analysis *P*-value was not statistically significant ($P = 0.71$), suggesting that apixaban and warfarin are equivalent in effectiveness for all three types of AF.[35]

Edoxaban In the ENGAGE-AF TIMI 4 study, 5366 patients were defined as having paroxystic AF, 4868 persistent AF and 10865 permanent AF at the time of their recruitment to the study.[10] The differences between warfarin and the two doses of edoxaban in terms of incidence of the primary endpoint (stroke or systemic embolism) were identical in patients with paroxystic, persistent and permanent AF (p value for interaction analysis 0.050 for edoxaban 60 mg and 0.42 for edoxaban 30 mg). Therefore, these results again suggest that edoxaban is equivalent to warfarin for the three types of FA.[10]

Patient selection

Which patients should be treated with anticoagulants

The selection of AF patients who are to receive anticoagulant therapy requires thorough assessment of the risk/benefit ratio through careful stratification of the thrombotic and haemorrhagic risk profile.[40-42] Patients with mechanical cardiac prostheses and major valve defects are all subgroup at high risk of thrombosis, and require conventional oral anticoagulant therapy with VKAs (OAT).[50]

For NVAF, the latest main guidelines recommend the use of the CHA_2DS_2-VASc and bleeding risk scores[43] so as to assess the risk of thrombo-embolism and haemorrhage, respectively.[41,43,45-47] It should be underlined that the risk of haemorrhage is not necessarily a contraindication to anticoagulant therapy, but should be grounds, in patients with HASBLED ≥ 3, for regular checks (IIa recommendation) aiming to treatment of any correctible factors (uncontrolled hypertension, labile INR, concomitant medications) (IIaB recommendation). In consideration of the fact that 30% of AF patients suffer concomitant ischaemic heart disease, it was considered necessary to start a study to evaluate the risk/benefit ratio of a triple antithrombotic therapy (DAPT plus oral anticoagulant) for patients who underwent percutaneous coronary intervention.

Both the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) and the Intracoronary Stenting and Antithrombotic Regimen: Testing of a 6-week vs. a 6-month Clopidogrel treatment Regimen in Patients with concomitant Aspirin and Oral Anticoagulant Therapy Following Drug - Eluting Stenting (ISAR-TRIPLE), have shown that the association of a single antiplatelet with VKA, seems to have the same effect, when compared with a triple antithrombotic therapy, but with a lower risk of bleeding.

The Pioneer AF PCI Trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) which started immediately after the introduction of DOACs compared, in three different groups, the antithrombotic therapy in patients subjected to percutaneous coronary intervention.

Group 1: with a reduced dose of Rivarozaban (15 mg daily) plus P2Y12 inhibitor monotherapy for 1 year;

Group 2: with rivarosaban (2.5 mg twice a day) plus DAPT per 1, 6, 12 months;

Group 3: VKA plus DAPT for 1, 6, 12 months.

This Trial has shown no statistical difference in the three groups with regard to efficacy whereas Group 1 and Group 2 have shown a minor incidence in minor and major bleeding compared with Group 3.[48]

The latest ESC Guidelines[43] recommend:

- Patients with AF after ACS:
- *with low bleeding risk* triple therapy (TT) (IIaB) (aspirin plus clopidogrel-oral anticoagulation (OAC) for further 6 months followed by OAC monotherapy (IB);
- *with high bleeding risk* TT (IIaB) for a month followed by dual therapy (IIaC) (aspirin or Clopidogrel+OAC) fino a 12 mesi followed by OAC therapy.
- For patients with AF after elective PCI with stent:
- *with low bleeding risk* TT (IIaB) (aspirin + cloidogrel + OAC for a month followed by Dual Therapy (IIaC) (aspirin or Clopidogrel+oral anticoagulation) up to 12 months followed by OAC monotherapy (IB);
- *with high bleeding risk* TT (IIaB) for a month followed by Dual Therapy (IIaC) (aspirin or clopidogrel+OAC) up to 6 months followed by OAC monotherapy (IB)

The contraindications for OAT can be subdivided into:

- Absolute contraindications:
  - pregnancy
  - documented hypersensitivity to VKAs/DOACs
  - current major haemorrhage

Table 4 Variables which suggest treatment with VKAs or DOACs

In favour of VKAs	In favour of DOACs
TTR >70% in patients already treated	TTR <60% in patients already treated with VKAs
Absence of high risk of thrombosis/haemorrhage	Presence of high risk of thrombosis/haemorrhage
Serious valve defects or valve prostheses	history of intracranial haemorrhage
Serious kidney or liver failure	History of major non-gastrointestinal haemorrhages
Severe neoplasias	Logistical problems for INR monitoring
Patients for whom poor adherence can be predicted	difficulty in adjusting doses of VKAs when they are very low
Need for dual antiplatelet therapy (studies with lower doses of DOACs are also in progress)	KVA intolerance
Treatment with drugs which have shown significant interference with DOACs	Current treatment with drugs which have shown significant interference with VKAs
NOAC intolerance	Patient's preferences
Patient's preferences	

- haemorrhage diathesis
- seriously low platelet count (<30 000/μl)

- Relative contraindications:
  - Recent major surgery or traumas
  - propensity to haemorrhage due to active ulcers or current bleeding in the gastrointestinal, urogenital and respiratory systems
  - cerebrovascular haemorrhage
  - cerebral aneurysm
  - dissecting aortic aneurysm
  - pericarditis and pericardial effusion
  - active bacterial endocarditis
  - medical history of intracranial, intraocular, spinal or retroperitoneal haemorrhage

How to choose between vitamin K antagonists and DOACs

The choice of anticoagulant drug (*Table 4*) must be made on the basis of:

- clinical condition,
- comorbidity,
- risk factors,
- cost,
- tolerability,
- patient's preferences,
- risk of pharmacological interactions,
- Time in Therapeutic Range (TTR),[41]

With Warfarin, the main anticoagulant for stroke prevention in patients with AF[29] in the last 60 years, stroke rates have gradually fallen in the US Medicare population.

However, it is well known that warfarin is correlated to major problems, above all:

- interactions with food and/or drugs which cause side-effects, often requiring hospitalisation;
- unpredictable responses, which require routine monitoring of the INR and frequent adjustments to dosages, with consequent logistical problems.[44]

The difficulty of keeping the INR within therapeutic range is confirmed by a large study of over 20 000 patients treated with warfarin in the United States, which revealed an average TTR of 55%.[45] Moreover, warfarin is associated with an increased risk of haemorrhages, especially intracranial,[44] often with the INR within the therapeutic range.

In the real world, as many surveys and registry studies from the last 10 years have documented,[49] OAT is used in fewer than 60% of the patients for whom it is indicated. Two main reasons can explain iy:[42]

- fear of haemorrhagic complications;
- practical and logistic difficulties in actually implementing the treatment.

The introduction of DOACs may overcome the underuse of anticoagulant therapy in AF, in all patients not treated with warfarin as indicated, often only treated with acetylsalicylic acid.[49]

All in all, the most important benefits of DOACs compared with VKAs are:

- lower rate of intracranial haemorrhage; much more predictable drug effect;
- fewer interactions with foods and other drugs, with no need for constant laboratory monitoring[29,50];
- quick onset of action and quick disappearance of effects;
- better cost/effectiveness ratio.

The patients who should be given the highest priority in the use of DOACs might include[42,44]:

- patients not on any anticoagulant therapy (because refusing warfarin or because their AF has only recently been diagnosed);
- patients with a history of intracranial haemorrhage;
- patients with at high risk for stroke recurrence;
- patients where satisfactory INR monitoring is difficult due to logistical problems
- patients with 'labile' INR;
- patients who state a specific preference for treatment with DOACs.

A labile INR has been identified as a risk factor for haemorrhage worthy of inclusion in the HASBLED score, and patients with an unsatisfactory TTR are excellent candidates for DOACs.[42,44] In these cases, the switch from

warfarin to DOACs is safe and has been validated by the large trials. However, this switch is not necessary if patients are stable, under control and happy with their therapy.

However, DOACs have some limitations:

- contraindicated for serious liver failure (Child Pugh class C): dabigatran 150 mg is safe in Child Pugh class B; rivaroxaban is contraindicated in Child Pugh class B; apixaban must be used with caution in Child Pugh classes A and B.
- adherence: omission of even a single dose may cause loss of protection against thrombo-embolism.
- kidney failure or obesity: dose adjustments.

When is anticoagulant therapy recommended?. According to the ESC guidelines,[43] in patients with:

- CHA_2DS_2-VASc $=1$ in male and CHA_2DS_2-VASc$=2$ in female: a VKA (target INR between 2 and 3), a direct thrombin inhibitor or an oral FXa inhibitor should be considered in relation to haemorrhage risk, the ability to support adjusted anticoagulation safely and patient preferences (IIaB recommendation);

CHA_2DS_2-VASc ≥ 2 in male and CHA_2DS_2-VASc ≥ 3 in female: unless contraindicated, anticoagulation therapy is recommended (IA). A direct thrombin inhibitor or oral FXa inhibitor should be taken into consideration as an alternative to VKAs for most patients (IIaA recommendation), both when a VKA cannot be used because of difficulty in maintaining a therapeutic dose and due to side effects or the impossibility of INR monitoring (IB).

According to the latest US guidelines[28] the options include warfarin (INR 2.0- 3.0) with IA recommendation, while dabigatran, rivaroxaban and apixaban have IB recommendation. Conversely, DOACs are recommended (IC recommendation) for patients who are unable to maintain a therapeutic INR level. In patients with moderate or severe renal insufficiency, treatment with low doses of DOACs can be considered, but the safety and efficacy of this practice have not been established (IIbC recommendation).

Under the NICE[51] guidelines, apixaban, dabigatran, and rivaroxaban are recommended as options for the prevention of stroke and systemic embolisms in AF patients.

Are there any differences between the individual DOACs?

There are no direct comparisons, but the trials on the individual DOACs do not show clear data in favour of one or the other NOAC.

The NICE[51] guidelines refer to the indications for the individual molecules:

- Dabigatran etexilate can be used in the presence of one or more risk factors such as previous stroke, TIA or systemic embolism, ejection fraction below 40%, age over 75, or age 65 or above with diabetes mellitus, arterial hypertension or coronary heart disease.
- Apixaban and Rivaroxaban can be used in the presence of one or more risk factors such as previous stroke or TIA, age over 75 years, arterial hypertension, diabetes mellitus and cardiac insufficiency.

The European guidelines[29] also provide indications on dosages: for dabigatran the dosage of 150 mg twice daily should be preferred, with four main exceptions for which the dose of 100 mg twice daily is recommended:

- patients over 80 years of age;
- drugs with risk of interactions (verpamil);
- HAS-BLED score ≥ 3
- impaired kidney function (CrCl 30–49 ml/min) (IIaB recommendation).

In the same conditions of high haemorrhagic risk or impaired kidney function, when rivaroxaban is prescribed the dosage of 15 mg should be preferred to 20 mg (IIaC recommendation). The halved dose (2.5 mg twice daily) is also preferred for Apixaban for patients over 80 years of age, with weight <60 kg and with creatininaemia ≥ 1.5 mg/dL (133 mmol/L).

Treatment plans

In some countries, there are national, regional and local restrictions on the prescription of DOACs.[51] This is due to their cost, even though cost-effectiveness studies results are in favour of DOACs compared with warfarin.[52]

Some examples:

- Scottish National Health Service: the prescription of rivaroxaban is restricted to patients with poor INR control and those with allergies or intolerances to warfarin, even though the United Kingdom Department of Health follows the NICE guidelines, which provide the same level of recommendation for DOACs as for warfarin.[45] In Ireland and some parts of England, justification forms must be filled in when prescribing these drugs.[41]
- Hungary: the prescription of DOACs is limited to patients who have already had a stroke or with poor INR control. The drugs are prescribed by filling in an e-form and only a limited number of specialists are allowed to prescribe them.
- Spain: in case of INR out of range on three consecutive occasions.[41]
- Italy: with regard to the prescription of DOACs under the National Health Service [Servizio Sanitario Nazionale (SSN)], the Italian Drugs Agency [Agenzia Italiana del Farmaco (AIFA)] has made their provision conditional on prescription by authorised specialists (cardiologists, internists, geriatricians, neurologists and haematologists working at thrombosis and haemostasis centres) who have to fill in an e-form for the Treatment Plan which helps in identifying eligible patients.

How to recognise non-valvular atrial fibrillation?

Clinical criteria. The level of thrombo-embolic risk varies within the population of patients with AF. In fact, an annual incidence of stroke and systemic embolic events varying from $<1\%$ to $>20\%$ is described.[46] depending on the clinical characteristics of the population examined. The first evidence of the efficacy of anticoagulant therapy in the prevention of AF-related thrombo-embolism derives from studies conducted on populations with a high incidence of rheumatic valve defects.[53] A succession of epidemiological studies showed a significant difference in the risk of stroke

in AF patients with and without rheumatic disease.[54] One of the first studies to introduce the concept of non-valvular AF used the term 'non-rheumatic non-valvular heart disease'[47] to refer to AF patients without a history of rheumatic heart disease or clinical or radiological signs of significant valve defects. The difference in incidence of thrombo-embolic episodes in AF associated to rheumatic valve defects and other types of AF suggests that a different antithrombotic approach is needed in these two forms of AF.[54]

Although AF is associated with a valve defect in about 30% of cases,[55] not all valve diseases involve a significant increase in thrombo-embolic risk. The normal evolution of mitral valve stenosis, mainly of rheumatic origin, is associated with a high risk of even fatal thrombo-embolic events.[56]

NVAF definition for clinical practice

The definition of NVAF is still an open question and a matter of work in progress, and it is expected that the distinction between NVAF and Valvular Atrial Fibrillation (VAF) will be significantly revised during the next few years, with consequences on therapeutic practice.

The need for nosographic clarity is obvious, since on the one hand the definition of the type, characteristics and degree of a concomitant valve disorder affects our therapeutic decisions with regard to AF, on the other hand the very large variation in the epidemiology of NVAF, estimated as from 6 to 40%, must be corrected.[4,57]

The term valvular/non-valvular itself is confusing because it groups together widely varying categories which, however, share a similar risk of thrombo-embolic events. None of the criteria used so far is considered satisfactory and the anatomic, clinical and haemodynamic characteristics of every single valve disorder should be defined as clearly as possible, considering the thrombo-embolic risk independently of the valve disease.[58]

Therefore, it seems obvious that patients with NVAF are those who *do not have* a 'significant' valve defect. But who belongs the other category? If we analyse the exclusion criteria used in the large trials, they are:

- patients with mechanical or biological valve prosthesis;
- patients with moderate-severe rheumatic mitral valve stenosis;
- patients with an haemodynamically significant valve defect (in the RELY study, history of valve disease, valve prosthesis or haemodynamically significant valve defect; ROCKET-AF, valve prosthesis or mitral valve stenosis; ARISTOTLE, valve prosthesis, moderate or severe mitral valve stenosis; ENGAGE AF, valve prosthesis, moderate-severe mitral valve stenosis).

In practice: patients with mechanical valve prosthesis and haemodynamically significant valve defects, or who have undergone valve surgery.

The 2014 EHRA Practical Guide defines non-valvular AF as AF in the absence of rheumatic mitral valve stenosis (but without defining the degree of severity), a mechanical or biological cardiac prosthesis or a mitral valve repair.[21]

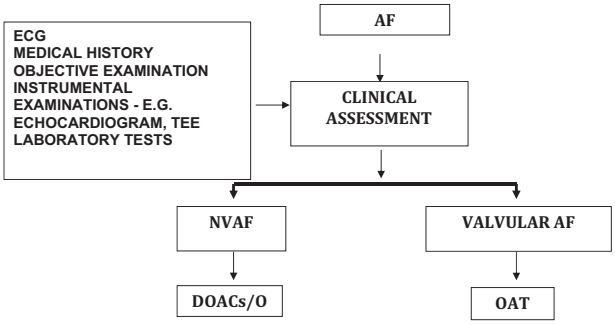

Figure 4 Essential clinical and instrumental assessment for definition of NVAF/VALVULAR AF.

From the clinical point of view, the initial assessment of a patient with diagnosed or suspected AF for whom the presence of a concomitant significant valve defect has to be confirmed/ruled out, should be made on the basis of in-depth knowledge of the medical history and a thorough medical examination. It also requires a transthoracic or, if indicated, transoesophageal echocardiogram to define the structural-haemodynamic nature of the valve defect (*Figure 4*).

What can be done in cases of valvular AF and patients with valve prosthesis?

Some studies have helped to point out that the thrombo-embolic risk is only significantly increased in AF associated with moderate/severe rheumatic mitral valve stenosis or mechanical prosthesis, while in the case of other valve defects, biological prosthesis or valvuloplasty, the thrombo-embolic risk is equivalent to that of patients with lone AF.[58] Therefore, the term Mechanical And Rheumatic Mitral Valvular AF (MARM AF) has been coined to define the categories which must be treated with VKAs. In all other cases, there is no scientific evidence of a thrombo-embolic risk different from that of lone AF, so patients can be treated with the DOACs.[59]

It should be remembered that some patients with valve defects, biological prostheses or mitral valvuloplasty were recruited to the trials on DOACs for the treatment of AF. In the RELY study, the exclusion criteria were very strict with regard to the non-recruitment of patients with a history of valve disease, excluding patients with prostheses, previous valvular surgery or a valve defect classified as more than slight.[7] Analysing the population recruited to the ROCKET AF study, Breithardt *et al.* reveal that out of 14 171 patients, 1992 (14.1%) had a significant mitral or aortic valve defect.[60] Treatment with rivaroxaban vs. warfarin did not show any significant differences in efficacy endpoint in patients with and without concomitant valve defects, while for the safety endpoints fewer haemorrhagic events were recorded, although the difference was not statistically significant ($P = 0.084$).[60] Avezum *et al.* examined the characteristics of the patients recruited to the ARISTOTLE[61] study and treated with apixaban vs. warfarin and found that 4808 (26.4%) had at least a moderate valve defect or had undergone valve surgery (251 patients). There are no differences in the safety and efficacy endpoints in patients

with and without valve defect treated with apixaban. The ENGAGE AF trial, in which patients were treated with edoxaban vs. warfarin, also recruited patients with moderate/severe valve defects or biological prosthesis or valvuloplasty, but no data are available.

In the REALIGN study, dabigatran was compared with warfarin for prophylaxis against thrombo-embolic events in patients with mechanical prosthesis. The results were an increase in thrombo-embolic events (9 (5%) in dabigatran vs. 0 in warfarin) and in haemorrhages (7 (4%) vs. 2 (2%)) in patients treated with dabigatran vs. warfarin and the trial was interrupted after the recruitment of only 252 patients.[62]

In the recent update to the EHRA guidelines on treatment with DOACs, it is underlined that the use of DOACs is authorised for NVAF. In post-biological prosthesis implantation or post-valvuloplasty patients, it is reasonable, if necessary, to switch to an NOAC after 3–6 months of treatment with VKAs. It would also seem to be feasible to use DOACs if VKA therapy is not possible in patients with TAVI, who have basically been implanted with a biological prosthesis in the aorta.[21]

Trials are currently planned on specific populations of valvular AF patients, such as:

- biological mitral valve prosthesis: rivaroxaban vs. warfarin (RIVER: Rivaroxaban for Valvular heart disease and atrial fibrillation);
- biological mitral and/or aortic valve prosthesis: dabigatran vs. warfarin (DAWA study);
- post-TAVI: apixaban vs. warfarin vs. warfarin+dual/single antiplatelet therapy (in the Apixaban study in patients who underwent a clinically successful TAVI procedure-ATLANTIS).

How to respond to an initial episode of AF

The 2010 ESC and more recent 2014 ACC/AHA guidelines suggest that the antithrombotic strategy to be adopted should be irrespective of the number of episodes and type of AF.[29,63] A high percentage of AF episodes are asymptomatic (from 6 to 38% depending on the population studied and the method of study). Moreover, the mortality risk of patients undergoing their first AF episode is higher than in paroxystic and persistent forms of AF. Therefore, the first documented episode, whether symptomatic or asymptomatic, requires a clearly defined procedure:

- stratification of thrombo-embolic risk;
- stratification of haemorrhagic risk;

definition of the most suitable prophylactic antithrombotic therapy.

The need for this approach becomes even clearer if we remember that paroxystic AF is often the start of a process leading to persistent or permanent forms. Moreover, in the paroxystic type the distribution of recurrent episodes is not random but usually evolves, in response to variables such as age, specific comorbidities and echocardiographic characteristics.

As the AFFIRM study showed, although they involve less cardiac insufficiency and hospitalisation than symptomatic forms, occasional episodes of asymptomatic AF have a higher thrombo-embolic risk.[64]

However, there are some conditions in which AF can undoubtedly be correlated to:

(1) reversible cause:
(2) alcohol consumption;
(3) dysthyroidism;
(4) surgery;
(5) electrolytic defects.
(6) intercurrent cause:
(7) acute myocardial infarction;
(8) cardiac and non-cardiac surgery;
(9) sepsis;
(10) pulmonary embolism.

Any diagnosis of AF, regardless of the number of episodes, must always be assessed on the basis of its presentation and duration (*Table 5*). However, the risk of thrombo-embolism and stroke in Paroxystic AF seems to be less well defined, partly because these patients appear in lower percentages both in the trials and in the registry studies (usually $<30\%$). In the SPAF study population, the annual incidence of ischaemic stroke is similar in the intermittent (3.2%) and persistent (3.3%) forms and there is no change with regard to the patient's thrombo-embolic risk.[65] The same results are provided by the Stockholm Cohort study, which confirmed that there are no significant differences in terms of ischaemic stroke between paroxystic and permanent AF.[66]

Similar results are reported by the ACTIVE[31,39] study and in the patients of the large trials conducted with the DOACs, NAO, RE-LY, and ARISTOTLE. However, as a survey[67] recently pointed out, the guidelines do not refer to analyses deriving from trials such as ACTIVE-A, AVERROES and the sub-studies of the ROCKET-AF trial and the J-RHYTM registry, and this undoubtedly restricts their real applicability.[30]

One particular area where this is the case is study of the burden of AF, as analysed in the TRENDS study, in which an AF burden of 5.5 h/day significantly increased the thrombo-embolic risk.[59,68,69]

Risk stratification, scores, and limits

Thrombo-embolic and haemorrhagic risk stratification is performed with the aid of conventional scores: CHADsVASC for the definition of thrombo-embolic risk and HAS-BLED for haemorrhagic risk.[70]

Although they were widely used in the European observational study (83.7 and 78.2%, respectively) and the Guidelines recommend that they should be used regardless of the type of AF and the number of episodes, physicians often give consideration to other factors not currently included in the standard scores (dimensions of atrium, kidney failure, AF burden).

In the post-hoc ARISTOTLE analysis, the stroke risk, but not the bleeding risk, was different in the low risk category depending on whether it was calculated with the CHADs score or the CHADsVASC score (in CHADs 1 HR 0.85, in CHADsVASC 1 HR 1.18, CHADs 2 HR 0.90, CHADsVASC 1.26), while it was more or less equivalent in high thrombo-embolic risk.[71] It is possible that CHADsVASC is not sufficient for stratifying thrombo-embolic risk, meaning that additional information concerning the association with other

Table 5 AF classification

Newly diagnosed AF	Initial onset of arrhytdmia regardless of symptoms and duration
Paroxystic AF	Spontaneous restoration of sinus rhythm, generally within 48 h
Persistent AF	Forms lasting more than 7 days or requiring pharmacological or electric cardioversion to restore the sinus rhythm
Persistent, long-lasting AF	Duration > 1 year
Permanent AF	No rhythm control measures adopted
Silent symptomatic AF	Diagnosed by chance by ECG or by querying a device

predictive markers, such as biomarkers, kidney failure, AF burden and other echocardiogram parameters, is required.

In the ASSERT trial, which recruited patients with no previous history of AF and average CHADs score 2.41, in patients who reported a symptomatic or asymptomatic episode of AF lasting more than 6 min. there was an increased risk not only of recurrence of AF but especially of thrombo-embolic events. If we associate the AF episode to the thrombo-embolic risk, we can see that for patients with CHADs 1 and no episodes the thrombo-embolic risk was 0.19%/year, while in patients with AF episodes and CHASDs >2 the increase in risk was extreme. Previously, in studies of smaller groups, it had been shown that in patients with CHADsVASC1, the onset of AF episodes lasting between 5 min and 24 h significantly increased the thrombo-embolic risk.

Therefore, the recording of AF combined with CHADs or CHADsVASC score is able to modify and improve the stratification of thrombo-embolic risk.

So what should be done?
One operating hypothesis could be:

(1) *CHADsVASC 0:* in patients with age < 65 years and lone AF, no indication for antithrombotic therapy;
(2) *CHADsVASC ≥1:* in accordance with national and ESC guidelines, start anticoagulation, preferably with DOACs. The American guidelines advise the starting of anticoagulant therapy with a value >1.

Considering the low level of thrombo-embolic risk with CHADsVASC 1, (about 0.1–0.2 for women and 0.5–0.7 for men[66]) according to the standard scores, the additional consideration of other parameters such as AF burden, biomarkers, kidney failure, and other echocardiograph parameters (left ventricle hypertrophy, low left atrial appendage flow rate, multi-lobed LAA morphology) may be useful for more accurate stratification of the thrombo-embolic risk and help to guide therapeutic choices.

The role of imaging in thrombo-embolic risk stratification. Embolism is a complication in a large number of cardiovascular conditions, such as AF, infective endocarditis, valve prostheses, myocardial infarction, valve defects, etc. Various studies indicate that 15–20% of all systemic embolisms and about 25% of cryptogenic strokes or TIAs are of cardioembolic origin.[72]

Therefore, cardiac imaging plays an important role in helping the clinician to select the best therapeutic strategy. Among the diagnostic tools available, echocardiography is the most widely used, since it is convenient, suitable for bedside use and easily reproducible.

Ultrasounds allow thrombo-embolic risk to be identified and stratified in many predisposing clinical conditions (myocardial infarction leading to systolic dysfunctions, remodelling of the ventricles, arrhythmias), often with the presence of spontaneous echo contrast. However, one of the most significant underlying conditions for cardioembolism is Atrial Fibrillation.

In AF patients, transthoracic echocardiography is able to provide useful information for thrombo-embolic risk stratification, such as the identification of clinical-structural conditions responsible for the AF, which may provide guidance to the most appropriate therapeutic approach. In clinical practice, transoesophageal echocardiography (TEE) also plays an important role in the identification of underlying sources of cardioembolism (PFO, morphological, and functional characteristics of the left atrial appendage), since it is able both to provide additional information about the patient's clinical condition and to guide any procedure required, such as cardioversion. However, the main goal is to identify the potential source of embolism, which in AF is mainly endocavitary thrombosis in the left atrium.

The sensitivity of transthoracic echocardiography (TTE) is between 39 and 70% depending on whether or not the thrombus is in the left atrial appendage, the most frequent site in NVAF patients.[73]

The dimensions and volumes of the atrium are one more thrombo-embolic risk factor, probably due to the way in which the changes in shape and contractility cause an increase in blood stasis, leading to the formation of thrombi.[74]

Cardiac CT has gained a place in the diagnostic pathway for patients with suspected or known ischaemic heart disease and is, to all intents and purposes, an additional examination useful for cardioembolic risk stratification, mainly for the identification of thrombosis in the left atrial appendage and/or ventricle. Furthermore, this technique could be a useful method for screening for LAA thrombosis in patients in whom TEE is contraindicated, since its sensitivity is excellent, although there are real difficulties in distinguishing between severe echo contrast and thrombosis.[75]

Lastlyt, Cardiac Magnetic Resonance (CMR) plays a less relevant role in searching for sources of embolism. In fact, a pilot study has revealed that TEE is more effective than CMR for identifying potentially embolism-generating lesions in patients with cryptogenic stroke.[67]

How to manage follow-up in patients on DOACs therapy?

A well structured, 'logical' treatment plan

The follow-up in patients on DOACs therapy must consider:

- the patient's characteristics (frailty, comorbidity, age if $>$ 75–80 years, multiple therapies, etc.);
- the drug administered (specific administration characteristics, interactions and metabolism/elimination) and any potential related dangers;
- adherence to therapy;
- the presence of family members, caregivers or a care network;
- the health care organisation and services in the area where the patient lives.

When the therapy is started, the patient (and/or family members and caregivers) must be informed about the drug's specific characteristics, whether it should be taken at or separately from meals, any possible side-effects, and the fact that health care staff and the family doctor must always be informed before the therapy is interrupted for any reason or if new drugs are prescribed.

1–2 months after the start of the therapy, a check can be scheduled at the cardiology outpatient clinic (or nursing clinic with specialist staff) to check:

- any thrombo-embolic and/or haemorrhage events;
- adherence and persistence with the therapy;
- the possible side-effects or complications;
- blood tests (liver and kidney function, complete blood count) agreed with the General Practitioner (GP) to assess any need to reduce the dose or even suspend administration.

As for adherence to treatment (proportion of days in which the patient is covered by the therapy $\geq$80%) after the start of the therapy, some data are available in favour of DOACs compared with therapy with VKAs, especially in patients who were previously taking VKAs. In non-adherent patients, longer, stricter control on accuracy in assuming therapy, with the physician's involvement, have been shown to improve the rate of adherence.[76] The Assessment of an Education and Guidance program for Eliquis Adherence in Non-valvular atrial fibrillation (AEGEAN) trial, in which adherence to treatment with apixaban at 6 months is assessed through electronic monitoring of the number of tablets used, is now in progress. The initial results appear to indicate that patient education and an aggressive strategy of reminders (SMS messages on smartphones) to ensure that the drug is taken, compared with education and awareness-raising alone, are correlated with very high adherence and persistence at 6 months (88 and 90.8%, respectively).

The appropriately trained and informed GP (or specific nursing clinic) is able to manage the medium-long term follow-up.[65] The patient should come back for regular checks (e.g. every 3 months) which can be planned and scheduled depending on individual characteristics. A patient aged 75–80 years, or a particularly frail patient, with score $\geq$3, established on the basis of unplanned weight loss, history of asthenia, poor handgrip rest result, reduction in speed/gait test result and little physical exercise should be checked more often than a younger or a 'healthy' elderly patient'.[21,76]

A year after the start of the therapy the patient will return to the cardiology clinic to renew the therapy plan, and this will give the cardiologist the opportunity to review any thrombo-embolic and/or haemorrhage events, check the blood tests performed for monitoring and decide whether the treatment can be continued and at which dose.

The laboratory parameters to be monitored

The regular blood tests to be performed and checked at least once a year are:

- kidney function with calculation of creatinine clearance (ClCr) using the Cockchroft-Gault formula;
- liver function with transaminase and total bilirubin;
- complete blood count to check haemoglobin stability and platelet count.

If there is a moderate worsening in renal function (ClCr 30–49 ml/min/m^2) or in patients who are frail or $>$75–80 years old, ClCr should be checked every 6 months. Amongst the blood tests, special attention should be paid to renal function, since all DOACs are eliminated, in varying percentages, in this way (this is especially true for dabigatran, since it is 80% eliminated by the kidneys), especially in case of:

- the frailest patients;
- fever;
- high ambient temperatures;
- inadequate hydration;
- gastroenteritis with diarrhoea and possible dehydration;
- any situation in which a reduction in ClCr is possible.

In the main European guidelines on AF[31] the use of DOACs is said to be contraindicated in pts with ClCr $<$ 30 ml/min, while in the technical data for apixaban and rivaroxaban it is stated that they should be used at a lower dose (2.5 mg[2] and 15 mg/day, respectively) in the event of significantly reduced renal function (CrCl 15–30 ml/min/m^2). This advice should be viewed as a strategy for avoiding the interruption of treatment of a patient with kidney function which becomes impaired during the follow-up and stabilises on these values; naturally, this will require more frequent checks (every 1.5–3 months). A tip recommended in the EHRA guidelines[77] concerning renal function is the ratio 'ClCr/10', which gives the number of months after which the parameters should be checked again (e.g. if ClCr 60 ml/min, 60/10 = 6, meaning renal function check within 6 months is needed). Another value which could be assessed before starting therapy with an NOAC is the prothrombin time (PT) or activated partial thromboplastin time

(aPTT), which may provide useful guidance in emergency-urgent situations (bleeding, unpostponable surgical operations or procedures), because these parameters can give a qualitative idea of whether or not the patient has taken the therapy during the follow-up (aPTT for dabigatran and PT for rivaroxaban).[21,78]

Documents to be supplied to the patient

It is useful to provide the patient with the following:

informative material with instructions on what to do in case of:

- the most common pharmacological interactions;
- a forgotten dose;
- an incorrect dose;
- minor bleeding;

card or document with:

- name of the drug;
- starting date;
- dose;
- time of the day when drug should be taken;
- name of any other concomitant therapies
- interruption procedure to be adopted for the specific NOAC in case, for example, of surgery
- results of the latest blood tests performed and due dates when to schedule next laboratory tests.

Management of anticoagulant therapy in patients who are scheduled for surgical procedures

The management of NOAC therapy in patients who are scheduled to undergo invasive procedures or elective surgery is based on three factors:

- renal function (creatinine clearance with Cockcroft-Gault);
- NOAC taken (once or twice daily, elimination pathway);
- haemorrhagic risk of the procedure: negligible, low, high.

In case of an urgent/emergency procedure, the strategy requires the adoption of specific methods for the reduction of haemorrhagic risk, such as the use of an antidote. The EMA (European Medicines Agency) has approved the use of Praxabind in Europe in cases of life-threatening or uncontrolled haemorrhages and urgent procedures/emergency surgery. This approval was issued after the publication of the good results on the first 90 patients in therapy with dabigatran who received the antidote after life-threatening haemorrhage or in preparation for unpostponable (within 8 h) surgical procedures or operations. Research has reached an advanced stage on the development of antagonists which block FXa inhibitors and their arrival on the market appears to be imminent (Andexanet alfa), while the development of the 'universal' antagonist (Cirapantag) is at an earlier stage of research.

The assessment of the haemorrhagic risk related to an operation/procedure (*Table 6*) should be combined with an evaluation of renal function to establish the correct timing for interruption of the therapy.

If the risk of haemorrhage is negligible, it is advisable to start the operation at the time when the NOAC concentration is lowest or skip the scheduled dose and wait 18–24 h, restarting the therapy 6 h after the procedure.

The timing for interrupting a NOAC before a surgical procedure/operation varies (*Table 7*). It should be remembered that if the patient is on therapy with apixaban or rivaroxaban the proportion eliminated through the kidneys (27 and 35%, respectively) is about one third of the figure for dabigatran (80%). If the patient's renal function is severely impaired (15–30 ml/min, for which dabigatran is contraindicated), it is advisable to wait up to 4–5 days for low risk surgery or as much as >5 days before a high risk procedure.[21,79] Using a bridge therapy vs. no bridge therapy seems to increase the risk of haemorrhage (6.5 vs. 1.8%, $P < 0.001$) and does not reduce the (low) risk of thrombo-embolic events and systemic embolisms (1.2 vs. 0.6%, $P = 0.16$ and 0.5 vs. 0.3%, $P = 0.46$, respectively).[77]

If all bleeding has stopped, the therapy can be restarted 6–8 h after the operation/procedure. If haemorrhagic risk is considered high, it is advisable to wait 48–72 h or until the risk itself lowers below that of any possible thrombo-embolic complications related to the immobilisation. If the patient is immobilised for a considerable time after the procedure/operation, to minimize the risk of venous thrombo-embolic event, low molecular weight heparin can be started at a prophylactic dose after 6–8 h, postponing the restarting of the NOAC by 48–72 h.[21,79]

Table 6 Haemorrhage risk of procedures

Negligible risk
Dental procedures (extraction of 1–3 teeth, paradental surgery, lancing of abscesses, implantology)
Ophthalmology (cataract or glaucoma surgery)
Non-interventionist endoscopic procedures
Superficial surgery (e.g. lancing of abscesses, removal of small skin lesions, etc.)
Low risk
Endoscopic procedures with biopsy
Bladder and prostate biopsies
Electrophysiological studies or transcatheter ablation in right chambers
Non-coronary angiography
Implantation of pacemaker or defibrillator (if anatomy is not complex)
High risk
Transcatheter ablation in left cardiac chambers (WPW ablation, pulmonary vein ablation*, ablation of some ventricular tachycardias*)
Spinal or epidural anaesthesia, lumbar puncture
Major thoracic, abdominal or orthopaedic surgery
Liver or kidney biopsy
Transurethral prostate removal
Lithotripsy with shockwaves

*Consider when to suspend therapy, bearing in mind the increased thrombo-embolic risk of these procedures.

Appendix: Consensus Document Approval Faculty

Alunni Gianfranco, Amico Antonio Francesco, Amodeo Vincenzo, Angeli Fabio, Aspromonte Nadia, Audo Andrea, Azzarito Michele, Battistoni Ilaria, Bianca Innocenzo, Bisceglia Irma, Bongarzoni Amedeo, Bonvicini Marco, Cacciavillani Luisa, Calculli Giacinto, Caldarola Pasquale,

Table 7 DOACs interruption times before surgical procedures/operations with low or high haemorrhagic risk, considering kidney function

DOACs	ClCr ml/min	In case of low haemorrhagic risk (hours after last intake)	In case of high haemorrhagic risk (hours after last intake)
Dabigatran*	≥80	≥24	≥48
	≥50–80	≥36	≥72
	≥30–50	≥48	≥96
Apixaban-Rivaroxaban**	≥30 ml/min	≥24	≥48
	<30 ml/min	≥36	≥48

*ClCr: creatinine clearance; contraindicated if ClCr < 30 ml/min;
**contraindicated if ClCr < 15 ml/min.

Capecchi Alessandro, Caporale Roberto, Caretta Giorgio, Carmina Maria Gabriella, Casazza Franco, Casolo Giancarlo, Cassin Matteo, Casu Gavino, Cemin Roberto, Chiarandà Giacomo, Chiarella Francesco, Chiatto Mario, Cibinel Gian Alfonso, Ciccone Marco Matteo, Cicini Maria Paola, Clerico Aldo, D' Agostino Carlo, De Luca Giovanni, De Luca Leonardo, De Maria Renata, Del Sindaco Donatella, Egidy Assenza Gabriele, Egman Sabrina, Fattirolli Francesco, Francese Giuseppina Maura, Gabrielli Domenico, Geraci Giovanna, Giardina Achille, Greco Cesare, Gregorio Giovanni, Iacoviello Massimo, Khoury Georgette, Ledda Antonietta, Lucà Fabiana, Macera Francesca, Marini Marco, Mascia Franco, Masson Serge, Maurea Nicola, Mazzanti Marco, Mennuni Mauro, Menotti Alberto, Menozzi Alberto, Mininni Nicola, Molon Giulio, Moreo Antonella, Moretti Luciano, Mortara Andrea, Mureddu Gian Francesco, Murrone Adriano, Musumeci Giuseppe, Navazio Alessandro, Nicolosi Gian Luigi, Oliva Fabrizio, Oreglia Jacopo, Parato Vito Maurizio, Parrini Iris, Patanè Leonardo, Pini Daniela, Pino Paolo Giuseppe, Pirelli Salvatore, Procaccini Vincenza, Pugliese Francesco Rocco, Pulignano Giovanni, Radini Donatella, Rao Carmelo Massimiliano, Rasetti Gerardo, Roncon Loris, Rossini Roberta, Ruggieri Maria Pia, Rugolotto Matteo, Sanna Fabiola, Sauro Rosario, Scalvini Simonetta, Scherillo Marino, Severi Silva, Sicuro Marco, Silvestri Paolo, Sisto Francesco, Tarantini Luigi, Themistoclakis Sakis, Uguccioni Massimo, Urbinati Stefano, Valente Serafina, Vatrano Marco, Vianello Gabriele, Vinci Eugenio, Zuin Guerrino.

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