

ANMCO position paper ‘Appropriateness of prescribing direct oral anticoagulants in stroke and systemic thromboembolism prevention in adult patients with non-valvular atrial fibrillation’

David Mocini^{1*}, Stefania Angela Di Fusco¹, Leonardo De Luca², Pasquale Caldarola³, Manlio Cipriani⁴, Marco Corda⁵, Andrea Di Lenarda⁶, Alfredo De Nardo⁷, Giuseppina Maura Francese⁸, Cosimo Napoletano⁹, Alessandro Navazio¹⁰, Carmine Riccio¹¹, Loris Roncon¹², Emanuele Tizzani¹³, Federico Nardi¹⁴, Stefano Urbinati¹⁵, Serafina Valente¹⁶, Michele Massimo Gulizia^{8,17}, Domenico Gabrielli², Fabrizio Oliva¹⁸, and Furio Colivicchi¹

¹Division of Clinical and Rehabilitation Cardiology, Emergency Department, P.O. San Filippo Neri - ASL Roma 1, Via G. Martinotti, 20, 00135, Roma, RM, Italy

²Cardiology, Department of Cardio-Thoraco-Vascular, Ospedale San Camillo, Circonvallazione Gianicolense, 87, 00152, Roma, RM, Italy

³Cardiology-ICU Department, Ospedale San Paolo, Via Caposcardicchio, 1, 70123, Bari, BA, Italy

⁴Cardiology 2-Heart Failure and Transplants, ASST Ospedale Metropolitan Niguarda, Piazza Ospedale Maggiore, 3, 20162, Milano, MI, Italy

⁵Cardiology Department, Arnas G. Brotzu, Piazzale Alessandro Ricchi, 1, 09134, Cagliari, CA, Italy

⁶Cardiovascular and Sports Medicine Department, Asugi Trieste, Via Slataper, 9, 34125, Trieste, TS, Italy

⁷Cardiology-ICU Department Ospedale Civile G. Jazzolino Piazza Fleming 89900 Vibo Valentia, VV, Italy

⁸Cardiology Department, P.O. Garibaldi-Nesima - Arnas Garibaldi, Via Palermo, 636, 95122, Catania, CT, Italy

⁹Cardiology-ICU Department - Cath Lab, Ospedale Civile G. Mazzini, Piazza Italia, 64100, Teramo, TE, Italy

¹⁰Hospital Cardiology Department, Po Santa Maria Nuova - Ausl RE IRCCS, Viale Risorgimento, 80, 42100, Reggio Emilia, RE, Italy

¹¹Follow-up of the Post-Acute Patient, Cardio-Vascular Department, Azienda Ospedaliera S. Anna E S. Sebastiano, Via Palasciano, 1, 81100, Caserta, CE, Italy

¹²Cardiology Department, Ospedale Santa Maria Della Misericordia, Viale Tre Martiri, 140, 45100, Rovigo, RO Italy

¹³Cardiology Department, Ospedale Degli Infermi, Strada Rivalta, 29, 10098, Rivoli, TO, Italy

¹⁴Cardiology Department, Ospedale Santo Spirito, Casale Monferrato (AL), Italy

¹⁵Cardiology Department, Ospedale Bellaria, Via Altura, 3, 40139, Bologna, BO, Italy

¹⁶Cardio-Thoracic Department, AOU Senese Ospedale S. Maria Alle Scotte, Viale Mario Bracci, 13, 53100, Siena, SI, Italy

¹⁷Fondazione per il Tuo cuore - Heart Care Foundation, Via La Marmora, 36, 50121, Firenze, FI, Italy; and

¹⁸Unit of Intensive Cardiological Care, Cardiology 1-Hemodynamics, Cardiothoracovascular Department, "A. De Gasperis" ASST Grande Ospedale Metropolitan Niguarda, Piazza Ospedale Maggiore, 3, 20162, Milano, MI, Italy

*Corresponding author. Tel: +39 06 3306 2344, Email: david.mocini@gmail.com

KEYWORDS

Apixaban;
 Atrial fibrillation;
 Dabigatran;
 Direct oral anticoagulants;
 DOACs;
 Edoxaban;
 Rivaroxaban

The appropriateness of prescribing direct oral anticoagulants [dabigatran, rivaroxaban, apixaban, and edoxaban (DOACs)] is regulated on the criteria established in Phase III trials. These criteria are reported in the summary of the product characteristics of the four DOACs. In clinical practice, prescriptions are not always in compliance with established indications. In particular, the use of lower doses than those recommended in drug data sheets is not uncommon. Literature data show that the inappropriate prescription of reduced doses causes drug underexposure and up to a three-fold increase in the risk of stroke/ischaemic transient attack, systemic thromboembolism, and hospitalization. Possible causes of the deviation between the dose that should be prescribed and that prescribed in the real world include erroneous prescription, an overstated haemorrhagic risk perception, and the presence of frail and complex patients in clinical practice who were not included in pivotal trials, which makes it difficult to apply study results to the real world. For these reasons, we summarize DOAC indications and contraindications. We also suggest the appropriate use of DOACs in common clinical scenarios, in accordance with what international guidelines and national and international health regulatory bodies recommend.

Introduction

In reference to the provision of health care, the term ‘appropriateness’ appears with considerable frequency in the official documents of the public administration in our country. However, despite the many citations, a precise and shared definition of this particular concept does not seem to exist. Indeed, even the World Health Organization has difficulty in defining appropriateness in an unequivocal manner and merely sustains that ‘a specific health intervention is to be considered appropriate if the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing excluding considerations of monetary cost’.¹

As for the medications, the term appropriateness is generally associated with the prescription and it refers to ‘a proper use’ of the drug.² Generally, the appropriateness of therapeutic prescriptions implies the efficacy of the drug, previously demonstrated in clinical trials. Furthermore, the drug should be used in the same conditions as those studied during the clinical trials that verified its efficacy. However, in clinical practice, it is often very difficult to find the same identical conditions to those of the clinical trials, where patients are selected and do not present major comorbidities. This type of approach, however, totally focused on the drug does not take into consideration the patients, their attitude towards medical therapy, or their autonomous decisions.³

The concept of prescriptive appropriateness appears, therefore, complex and elusive, with a wide margin of interpretation both for clinicians and for the Regional and National Control Agencies.

In summary, elements influencing the appropriate use of a drug are potentially identifiable as follows:

- Patient-related factors:
 - (1) the evaluation of the patient’s specific therapeutic needs in relation to the clinical diagnosis;

- (2) the evaluation of the severity and the duration of the treatment in relation to the patient’s overall clinical profile (severity of the disease and comorbidities); and
 - (3) the evaluation of the patient’s individual preferences and choices.
- Drug-related factors:
 - (1) the selection of the most effective and safest active substance;
 - (2) the evaluation of the potential treatment risks in relation to the expected benefits;
 - (3) the evaluation of the monetary costs of the treatment in relation to the expected benefits; and
 - (4) verification of the effective adherence and continuation of the treatment.

To confirm this general direction, the considerations mentioned above are indicated in the Medical Deontological Code that regulates the professional behaviour of the medical community in Italy.⁴ Indeed, Art. 6 of the Code foresees that ‘The physician bases the exercise of her/his technical-professional skills on the principles of effectiveness and appropriateness, updating them to the available scientific knowledge and through a constant verification and revision of her/his actions’, while Art. 13 underlines how ‘The prescription must be based on the available scientific evidence, on the optimal use of resources and on the compliance with the principles of clinical efficacy, safety and appropriateness’.

On the whole, in a health context such as the one in our country, the physician should always combine the full protection of the patient’s clinical needs (favourable risk/benefit ratio) with the correct allocation of available resources (favourable cost/benefit ratio). Ultimately, various regional public health authorities agree to highlight how the basic principle of prescriptive appropriateness should be as follows: ‘with equal documented efficacy and with the applicability of different medications to the individual patient, the

least expensive must be preferred'. The professionals who operate in the National Health Service need to agree on this principle to safeguard public resources equity of intervention and sustain the introduction of innovative therapies.

The non-appropriate use of 'low' dose of the direct oral anticoagulants (DOACs) in the prevention of thromboembolism in patients with non-valvular atrial fibrillation (NVAF), presumably intended to contain a potential risk of bleeding, is a relatively frequent event in daily clinical practice,⁵⁻¹¹ estimated between 10% and 57%⁵⁻⁷ of the prescriptions. However, this inappropriate prescription, without a proportional reduction of bleeding risk,¹² could lead to an increase in stroke risk, systemic embolization, hospitalization, and sometimes even death. This specific issue is fuelled by the common perception that bleeding represents an iatrogenic event directly connected to the prescribed therapy. Thromboembolism is instead part of the natural history, not directly attributable to the physician. Failure to reduce the dose, which appears as a rare event, on the contrary, could cause overexposure to the drug and to an unacceptable increase in the bleed risk.¹³

The intent of this document is to define the boundaries of prescriptive appropriateness for DOACs, by following the indications, the correct dose, the contraindications, and the common scenarios of clinical practice.

The main sources to define the prescriptive appropriateness criteria, here understood as the formal and substantial correctness in clinical use, are represented by the official documents filed with the national and international regulatory authorities, the European Medicines Agency (EMA), and the Italian Drug Agency for the authorization to place DOACs on the market. These documents are integrated, but not replaced, by the main referring guidelines for the management of NVAF edited, for example by the European Society of Cardiology (ESC) and the National Institute for Health and Care Excellence (NICE).

The physician, by the laws in force in our country, when prescribing a drug must follow the therapeutic indications and the ways and methods of administration envisaged in the issued authorization to place the drug on the market, having been evaluated in the drug clinical trial. In fact, Art. 3 comma 1 of the D.L. 23/1998, converted to Law 94/1998 states: 'the physician, when prescribing a medicinal product or other industrially produced medicinal product, shall comply with the therapeutic indications, ways and methods of administration provided for in the authorization to place in commerce issued by the Ministry of Health'.

Therapeutic indications

The clinical indications of the use of DOACs, dabigatran, rivaroxaban, apixaban, and edoxaban, listed in the summary of the product characteristics (SmPCs) for the prevention of stroke and systemic embolism in adult patients suffering from NVAF, are as follows:

- Presence of (NVAF) with one or more risk factors, such as:
 - (1) previous stroke or transient ischaemic attack (TIA);
 - (2) age ≥ 75 years;

- (3) systemic arterial hypertension;
- (4) diabetes mellitus; and
- (5) symptomatic heart failure with functional class \geq II of the New York Heart Association (NYHA).

By NVAF, we mean atrial fibrillation without mechanical heart valve prosthesis and moderate or severe mitral stenosis.^{18,19}

Small and non-relevant differences are present in the four SmPCs, as for example the non-disclosure of the NYHA functional class for rivaroxaban ed edoxaban. In the guidelines published by the NICE,²⁰ the conditions for the use of dabigatran are slightly different compared to the other three DOACs and, in particular, are:

- previous ictus, TIA, or systemic embolism;
- $<40\%$ ejection fraction;
- symptomatic heart failure NYHA functional class \geq II;
- age >75 years; and
- age ≥ 65 years with one of the following conditions: diabetes mellitus, arterial hypertension, or coronary heart disease.

These indications derive from the enrolment criteria of the controlled randomized trials of III²¹⁻²⁴ phase and from their use of CHADS Score.²⁵ As the CHA₂DS₂-VASc²⁶ has replaced CHADS¹⁸⁻²⁰ in clinical practice, the current indication in the ESC guidelines is as follows:

- presence of NVAF in males with CHA₂DS₂-VASc ≥ 2 and in females with CHA₂DS₂ ≥ 3 (class I indication with A level of evidence).

Male patients with CHA₂DS₂-VASc = 1 and female patients with CHA₂DS₂-VASc = 2 may qualify for the anticoagulant treatment considering their specific clinical conditions and their preferences after they have been informed on the risk and benefit connected to the treatment (class IIa indication).¹⁸

There is no indication for anticoagulant treatment for male patients^{18,19} with CHA₂DS₂-VASc = 0 and female patients with CHA₂DS₂-VASc = 1.

The NICE guidelines²⁰ present a few slight differences compared to the ESC guidelines,¹⁸ which can be summarized as follows:

- with due regard to the bleed risk, offer DOAC treatment to all patients with CHA₂DS₂-VASc ≥ 2 ;
- take into consideration DOAC treatment in male patients with CHA₂DS₂-VASc = 1; and
- do not offer DOAC treatment to male patients with CHA₂DS₂-VASc = 0 and to female patients with CHA₂DS₂-VASc = 1.

Contraindications

Clearly identifying the contraindications to the use of DOACs is a very complex issue and ill-suited to synthesis. In fact, in the four SmPCs, different terms are used to define the use, legitimate or otherwise, in reference to the same clinical conditions and in the presence of essentially similar data from the literature.

Taking as an example the use of DOACs in pregnancy, we note that this condition is generally an exclusion criterion

in Phase III trials, and women of childbearing potential needed to use contraception to take part in those studies. Furthermore, the number of pregnant women in treatment with any DOAC is very limited in the literature and the available data are only observational.³¹

Nevertheless, there is no uniform indication in the four SmPCs but rather it is stated that:

- rivaroxaban and edoxaban are contraindicated^{15,17};
- it is 'preferable to avoid the use of apixaban'¹⁶; and
- dabigatran 'must not be used unless clearly necessary'¹⁴.

Despite these indications included in the four SmPCs, we believe that in accordance with the *ESC guidelines for the diagnosis and management of atrial fibrillation*,¹⁸ the *guidelines for the management of cardiovascular diseases during pregnancy*,³¹ and the *practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation*,¹⁹ all these drugs should be considered contraindicated in pregnancy.

In Table 1, we collected the contraindications shared by all four DOACs, along with other situations particularly relevant in clinical practice, such as thrombocytopenia and antiphospholipid syndrome. For further details mainly related to drug interactions, it is recommended to refer to the four specific SmPCs,¹⁴⁻¹⁷ the European guidelines,^{18,20} or, in the absence of specific indications in the previous documents, the practical guide to the use of DOACs published by the European Heart Rhythm Association (EHRA).¹⁹

Dabigatran

Pharmaceutical forms

Dabigatran is available in 150, 110, and 75 mg capsules. Only 150 and 110 mg capsules are indicated in stroke prophylaxis and systemic embolism in adult patients with NVAf.¹⁴

Posology

The recommended dose is 300 mg/day with two 150 mg administrations every 12 h (bid).¹⁴

Appropriate criteria for the use of the lower dose

A dose of 220 mg/day is recommended in SmPC, divided into two 110 mg administrations every 12 h in the case of concomitant treatment with verapamil or in patients aged ≥ 80 years.¹⁴ In the SmPC, it is also recommended to consider a reduction in dose to 220 mg/day in case of¹⁴:

- patients between 75 and 80 years of age;
- patients with moderate renal impairment [creatinine clearance (ClCr) 30-50 mL/min];
- patients with gastritis, esophagitis or gastroesophageal reflux; and
- other patients at increased risk of bleeding.

In these four cases, the use of the daily 300 or 220 mg dose can be decided by the clinician on the basis of the assessment of thromboembolic risk and haemorrhagic risk.¹⁴ Renal function must be estimated using the Cockcroft-Gault (CG) method.

With regard to the issue of defining the increased risk of bleeding, in the SmPC,¹⁴ there are four categories that contain the majority of the conditions identifiable as being able to increase the haemorrhagic risk:

- age;
- factors that increase plasma levels of dabigatran;
- drug interactions; and
- congenital or acquired pathologies and medical and surgical interventions with haemorrhagic risk.

The ESC guidelines for the diagnosis and management of atrial fibrillation¹⁸ include the presence of a more generic 'increase of bleeding risk' among the indications to the use of the lower dose. To better manage the bleeding risk, the ESC guidelines recommend, in addition to the identification of non-modifiable and modifiable risk factors, the use of the HAS-BLED^{18,32} score while the NICE guidelines recommend the ORBIT^{20,33} score.

Dabigatran is the only one of the four DOACs currently on the market in which the choice between the available doses can be determined by the physician on the basis of his own

Table 1 Main contraindications/non-recommendations to the use of direct oral anticoagulants shared by all products

| Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|--|-------------|---------------------------------|----------|
| 'Valvular' atrial fibrillation | | | |
| Hypersensitivity to the active substance or to any of the excipients—pregnancy and feeding antiphospholipid syndrome—concomitant treatment with any other anticoagulant except in specific circumstances—clinically significant active bleeding. thrombocytopenia <20 000/ μ L | | | |
| Creatinine clearance <30 mL/min | | Creatinine clearance <15 mL/min | |
| Injury or condition considered a significant risk factor for major bleeding. May include ongoing or recent gastrointestinal ulcer, the presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent cerebral, spinal or ophthalmic surgery, recent intracranial haemorrhage, established or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities | | | |
| Severe liver disease or disease associated with coagulopathy at the risk of clinically relevant bleeding | | | |

^aAtrial fibrillation in the presence of mechanical heart valve prostheses and/or moderate or severe rheumatic mitral stenosis, as defined by the European Society of Cardiology.¹⁸ For further details, it is recommended to refer to the respective Summaries of Product Characteristics.¹⁴⁻¹⁷

clinical judgement to evaluate whether the specific patient benefits most from a dose of 150 mg bid favouring the prevention of thromboembolism or on the contrary, from a dose of 110 mg bid to favour the reduction of haemorrhagic risk.

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy)^{21,27} study was designed to have three distinct patient groups: the first group was administered with dabigatran 150 mg bid, the second group was administered with dabigatran 110 mg bid and the third group was administered with warfarin. Both dabigatran treatment groups proved not to be inferior to warfarin. The 150 mg group demonstrated equivalent safety and better efficacy while the 110 mg group had equivalent efficacy and a lower number of haemorrhagic event compared to warfarin. For this reason, the choice between the two doses can be made by the clinician on the basis of the factors expressed above, or even on the basis of her/his personal experiences. On the contrary, in the phase III studies conducted for the evaluation of rivaroxaban^{22,28} and apixaban,^{23,29} the reduced dose of, respectively, 15 mg/day and 2.5 mg bid was tied to the presence of precise clinical, demographic, and/or laboratory characteristics. In the case of edoxaban, although in the ENGAGE AF-TIMI⁴⁸ study (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48)^{24,30} three treatment groups were programmed with warfarin, edoxaban 60/30 mg/day, and edoxaban 30/15 mg/day, only the first of the two edoxaban groups were placed on the market.

Therefore, as for other factor Xa inhibitors, we have to decide what the appropriate dose is for the patient, based on precise clinical criteria.^{17,24,30}

This aspect factually places a precise obligation on the prescription of the reduced dose.

For this reason, it is necessary to distinguish between:

- *Low dose*, as in the case of dabigatran 110 mg, the use of which may be a medical choice in addition to a recommendation in specific contexts.
- *Reduced dose*, 15 mg once a day (QD) for rivaroxaban, 2.5 mg bid for apixaban and 30 mg QD for edoxaban (15 mg QD only in the case of transition from edoxaban to vitamin K antagonists (AVK)), which instead constitute a prescriptive obligation bound by precise objective conditions. The use of the reduced dose, in the absence of the conditions defined in the randomized clinical trials, detailed in the different SmCPs,¹⁴⁻¹⁷ and well defined in the documents of the Scientific Societies,¹⁸⁻²⁰ could lead to underexposure of the drug, a reduced anticoagulant effect and an increase in thrombotic risk.

Contraindications to the use of dabigatran

In addition to what is stated in Table 1, it is necessary to recall the presence of the contraindication to its use in case of concomitant treatment with the following strong inhibitors of P-glycoprotein (P-gp): ketoconazole for systemic use, cyclosporine, itraconazole, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir.

Suspension prior to surgical intervention

To eliminate the effect, the suspension of dabigatran before surgery should be prolonged for a variable period of time and which depends on two factors:

- the haemorrhagic risk of the intervention/procedure to which the patient is candidate and
- the patient's renal function.

For surgery/procedure with low haemorrhagic risk, the withdrawal interval of the drug in patients with normal renal function may be 24 h, while for intervention with a high haemorrhagic risk in patients with ClCr between 50 and 30 mL/min, 4 days of suspension are required.^{14,19} In case of urgent and mandatory intervention, it is possible to use a rapid and effective antidote (idarucizumab).³⁴ It determines the loss of the anticoagulant effect in about 5 min.

Use in specific clinical settings

Elderly

See criteria for the use of the lowest dose.

Renal impairment

See criteria for dose reduction and Table 1.

Hepatic impairment

See contraindications. Hepatic enzyme values over twice the upper reference limit (ULN) are to be considered a contraindication to the use of the drug mainly because patients with these characteristics were excluded from randomized and controlled trials.^{14,27}

Rivaroxaban

Pharmaceutical forms

Rivaroxaban pharmaceutical forms are registered with the EMA in numerous forms. Of all those available, only 20 mg tablets and in special cases 10 and 15 mg tablets are indicated in the prevention of stroke and systemic embolism in adult patients with NVAf with one or more risk factors.¹⁵

Posology

The recommended dose is 20 mg QD during a meal.¹⁵

Appropriate criteria for the use of the reduced dose

The use of 15 mg in substitution of 20 mg/day in the context of prevention of stroke and systemic embolism in adult patients with NVAf is considered appropriate only under two conditions:

- (1) In patients with moderate/severe renal impairment (ClCr from 49 to 15 mL/min calculated with the CG formula). The phase III pivotal study did not provide for the use of rivaroxaban in the case of ClCr <30 mL/min.^{22,28} The possibility of using rivaroxaban also in patients with ClCr between 15 and 30 mL/min is a result of the incorporation of pharmacokinetic data into the SmPC.¹⁵

(2) In patients with NVAF who have undergone a percutaneous coronary procedure (PCI), in whom treatment is planned in combination with antiplatelet agents, usually clopidogrel. In this case, the scientific evidence derives from the PIONEER AF-PCI Study (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)³⁵ that has demonstrated an advantage in terms of safety of rivaroxaban 15 mg [or 10 mg/day QD for patients with moderate renal impairment (CrCl 30-49 mL/min)] in addition to a P2Y¹² inhibitor for up to a maximum of 12 months. The results are significant with regard to the reduction of bleeding events even when rivaroxaban 2.5 mg is used together with a dual antiplatelet. The study however does not have the dimension to demonstrate an equivalent or even superior efficacy of these innovative therapies compared to the traditional therapeutic strategy with anticoagulant and dual antiplatelets. The EHRA practical guide on the use of DOACs concurs with these indications.¹⁹ In contrast to the contents of the SmPC and the EHRA guide, the ESC guidelines suggest instead the use of the full dose (20 mg/day) of rivaroxaban in patients with NVAF undergoing PCI, suggesting a reduction of the dose to 15 mg/day in patients with HAS-BLED score ≥ 3 (class IIa recommendation).¹⁸ However, the same guidelines do not clarify what the approach should be in case of reduced renal function. In fact, as mentioned, in this case, the SmPC and the EHRA practical guide indicate the dose of 10 mg/day.

Contraindications on the use of rivaroxaban

See Table 1.

Suspension prior to surgical interventions

Prior to a surgical intervention or an invasive procedure, rivaroxaban must be suspended when possible, and on the basis of the physicians' judgement, at least 24 h before.¹⁵ The EHRA¹⁹ practical guide proposes an approach based on the type of drug, the haemorrhagic risk of the procedure/intervention and the renal function. For rivaroxaban as with the other two inhibitors of the Xa factor, the interventions at minor bleeding risk can be carried out without suspending the therapy, preferably when the plasma concentrations are lower (trough). For procedures/interventions at low haemorrhagic risk, a suspension of 24 h is proposed for all CrCl values ≥ 30 mL/min and a 36-h suspension in patients with CrCl included between 29 and 15 mL/min.¹⁹ For all interventions at high haemorrhagic risk, a 48-h washout is suggested, regardless of the renal function.¹⁹ In case of non-deferrable surgeries or more generally of bleeding that threatens survival, andexanet alfa is available, a drug with antidote functions registered for rivaroxaban and apixaban.³⁶

Use in specific clinical settings

Elderly

Age is not considered an independent variable and therefore does not influence the dose directly. Of course, indirectly, it affects the determination of the dose, being a parameter included in the CG formula.

Hepatic impairment

In patients with a mild hepatic impairment (classified as Child-Pugh A), only slight differences have been observed in the pharmacokinetics when compared to the control group and, therefore, there are no contraindications to the use or need to reduce the dose. Rivaroxaban is contraindicated in patients with hepatic diseases associated with coagulopathy and clinically relevant haemorrhagic risk, including patients with liver cirrhosis in Child-Pugh B and C class.¹⁵

Renal impairment

The dose suggested in patients with moderate (CrCl 30-49 mL/min) and severe (CrCl 15-29 mL/min) renal impairment is 15 mg/day in a single administration.¹⁵ Special attention should be paid in case of severe impairment or in case of moderate renal impairment if drugs that increase the plasma concentration of rivaroxaban are in use. The SmPC does not specify what this attention consists of, but we could summarize it as a more frequent clinical or laboratory control (blood count) or, possibly, in the plasma dosage of the peak and trough concentration of the drug.

Apixaban

Pharmaceutical forms

Apixaban is available in 5mg and 2.5 mg tablets.¹⁶

Posology

The recommended dose in NVAF is 5 mg bid.¹⁶

Appropriate criteria for the use of the reduced dose

The dose of apixaban must be reduced to 2.5 mg bid in the following cases:

- (1) When a glomerular filtration rate is between 15 and 29 mL/min. Patients with CrCl <25 mL/min were excluded from the pivotal trial. The indication for the use up to a CrCl of 15 mL/min derives from pharmacokinetic studies¹⁶;
- (2) The presence of two of the three following criteria:
 - age ≥ 80 years;
 - weight ≤ 60 kg; and
 - creatinine >1.5 mg/dL (133 μ mol/L).

The use of reduced dose in the absence of the above criteria is inappropriate.

Contraindications to the use of apixaban

See Table 1.

Temporary discontinuation before surgery

The SmPC indicates that apixaban should be suspended at least 48 h before an invasive intervention/procedure at moderate-high risk of bleeding.¹⁶ Twenty-four hours of suspension are required before an invasive intervention/procedure at low or even minimal risk of bleeding.¹⁶

This last statement is not consistent with the practical guide on the use of non-AVK anticoagulants, which, similarly to rivaroxaban and edoxaban, suggests not to suspend the drug if the procedure is at minimal risk of bleeding.¹⁹ Andexanet alfa can be used as an antidote if necessary.³⁶

Use in specific clinical settings

Elderly

See dose-reduction criteria.

Renal impairment

See dose-reduction criteria. Unlike the other pivotal studies, the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)^{23,29} Study did not use the CrCl but a plasma creatinine cut-off of 1.5 mg/dL for dose reduction as specified above. However, CrCl was an exclusion criterion when <25 mL/min, such as creatinine plasma value of >2.5 mg/dL²⁹ creatinine.

Hepatic impairment

See contraindications. Laboratory tests for the hepatic function must be performed before the prescription of apixaban. The drug is not recommended in severe hepatic impairment and must be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B).¹⁶ Patients with elevated hepatic enzymes (alanine aminotransferase/aspartate aminotransferase) >2 × ULN or total bilirubin ≥1.5 × ULN were excluded from the ARISTOTLE Study.^{16,23,29}

Edoxaban

Pharmaceutical forms

Edoxaban is available in 15 mg, 30 mg, and 60 mg tablets. The 15 mg tablet is indicated, in patients candidates to 30 mg, in an NVAf when switching from edoxaban to AVK until an *international normalized ratio* (INR) of ≥2¹⁷ is achieved.

Posology

The recommended dose for NVAf is 60 mg/day.¹⁷

Appropriate criteria for the use of the reduced dose

The dose of edoxaban must be reduced to 30 mg in a single daily administration and in the presence of one of the three following conditions¹⁷:

- (1) Mild or severe renal impairment (CrCl 15-50 mL/min calculated with the CG formula). As with rivaroxaban, patients with CrCl <30 mL/min were excluded from the referring pivotal trial; therefore, the indication for the use of up to CrCl 15 mL/min derives from pharmacokinetic studies¹⁷;

- (2) Low body weight ≤60 kg; and
- (3) Co-administration of P-gp inhibitors, such as cyclosporine, dronedarone, erythromycin, or ketoconazole.

Contraindications to the use of edoxaban

See Table 1. In SmPC, the presence of severe uncontrolled hypertension is also reported as a contraindication.¹⁷

Use in specific clinical settings

Elderly

As for rivaroxaban, it does not influence the dose directly.

Renal impairment

As with other DOACs, the CG formula was used to estimate renal function (CrCl in mL/min) during the clinical development of edoxaban. As already mentioned, in the case of CrCl between 51 and 80 mL/min, the recommended dose is 60 mg/day. In the case of CrCl between 15 and 50 mL/min, the recommended dose is 30 mg/day.

Hepatic impairment

Edoxaban is contraindicated in patients with hepatic pathologies that are associated with coagulopathy and clinically significant bleeding risk. In general, in patients with severe hepatic impairment, the use of edoxaban is not recommended. If the liver impairment is mild or moderate, the drug should be used with caution, increasing clinical surveillance and the frequency of laboratory tests.

Other factors that condition appropriateness

Treatment duration

The SmPCs of the four DOACs do not indicate a precise duration for anticoagulant treatment but report that 'therapy should be continued for a long time'.¹⁴⁻¹⁷ Some specific contexts, such as the post-cardioversion period, are very articulated and are examined in the European guidelines,¹⁸ or in the practical guide to the use of DOACs.¹⁹

Ethnicity and gender

No dose modification is required for any of the four DOACs.

Weight categories

- Dabigatran. No dose modification is required but close clinical monitoring of patients with a bodyweight of <50 kg¹⁴ is recommended;
- Rivaroxaban: no dose change is required.¹⁵
- Apixaban: use the reduced dose (2.5 mg bid) in case of bodyweight ≤60 kg, if associated with at least one of the following criteria: ≥80 years of age or ≥1.5 mg/dL¹⁶ creatinine.
- Edoxaban: use the reduced dose (30 mg/day) if the bodyweight is <60 kg.¹⁷

There are no specific indications for patients with overweight or obesity. Theoretically, patients weighing >60 kg should be treated with the same DOAC dose regardless of their body mass index or weight.¹⁴⁻¹⁷ This indication has generated a heated debate. In fact, it has been emphasized that the increase in the volume of distribution and

the absorption changes, which are present in patients with severe obesity, may lead to a sub-optimal exposure to the drug and a reduced anticoagulant effect. Since there are no randomized clinical trials that compare the population of patients with obesity exposed to DOAC or AVK, the problem can only be evaluated on the basis of pharmacokinetic studies, *post hoc* data extracted from randomized trials, prospective observational studies, or retrospective studies. However, the outcomes reported by these studies are inconsistent. For a more in-depth analysis of this topic, see the ANMCO position paper on DOACs in patients with obesity and atrial fibrillation.³⁷

Pregnancy and nursing

Dabigatran, rivaroxaban, apixaban, and edoxaban are contraindicated or not recommended in pregnancy. The ESC guidelines^{18,31} and the practical guide on the use of DOACs¹⁹ consider these drugs contraindicated in pregnancy.

Breastfeeding is contraindicated when taking DOAC since they are excreted in breast milk or there is no certainty that they are not. Therefore, in this setting, either breastfeeding or DOAC must be discontinued.

Thrombocytopenia

Thrombocytopenia is reported as a rare side effect of dabigatran,¹⁴ uncommon with the use of rivaroxaban,¹⁵ apixaban,¹⁶ and edoxaban.¹⁷

It represents a haemorrhagic risk factor if it precedes the use of DOAC. Patients with platelet count $<100\,000/\mu\text{L}$ require a multidisciplinary evaluation. Indeed, this value constitutes a haemorrhagic risk factor that requires the search for reversible causes.

In the absence of data from randomized controlled trials, in the case of platelet values $<100\,000/\mu\text{L}$, each patient should be evaluated individually by an expert team.¹⁹ Platelet values $<20\,000/\mu\text{L}$ are a contraindication to the use of DOACs.¹⁹ Values between $100\,000$ and $20\,000/\mu\text{L}$ require a progressively increasing degree of surveillance.¹⁹

Switching from vitamin K antagonist to direct oral anticoagulant

It is recommended to start dabigatran, rivaroxaban, apixaban, or edoxaban when the INR value is <2 ,¹⁴ ≤ 3 ,¹⁵ <2 ,¹⁶ or <2.5 ,¹⁷ respectively. To standardize behaviour, in the practical guide on the use of DOACs, the EHRA proposed to start each drug immediately when the INR value is ≤ 2 and immediately or the next day if it is between 2 and 2.5 and to re-evaluate the INR value within 1-3 days if it is between 2.5 and 3.¹⁹

Switching from direct oral anticoagulant to vitamin K antagonist

When you plan to suspend one of the four DOACs and start treatment with an AVK, a period of overlap between the two anticoagulants is necessary, due to the slowness of the latter category of drugs in achieving the desired anticoagulant effect. The suspension of the DOAC should take place only after reaching an INR value of ≥ 2 .¹⁴⁻¹⁷

Since all four drugs are able to modify the INR value, it is necessary to perform blood sampling for INR control immediately before DOAC administration to limit interference as much as possible. In any case, the INR values should be interpreted with caution. In the case of edoxaban, half DOAC dose should be used during the period of simultaneous administration with AVK. Therefore, 30 mg of edoxaban will be administered if the patient had an indication of 60 mg and 15 mg if he had an indication of 30 mg. This is the only setting in which edoxaban can be prescribed 'on-label' at 15 mg^{17,19} in the context of the prevention of thrombosis and systemic embolism in NVAf.

Direct oral anticoagulant plasma levels

Evaluating DOAC plasma concentrations could seem like a simple solution in specific cases where there is a suspicion of underexposure or overexposure to the drug. However, currently, there are no data on the possible benefit, in terms of efficacy and safety, of a possible DOAC dose adjustment based on plasma concentrations. For this reason, and also in view of the incomplete knowledge of the trough and peak optimal plasma levels, the systematic assessment of DOAC plasma concentration is not recommended by the guidelines nor by practical guides of European scientific societies.^{18,19}

Patients undergoing electrical or pharmacological cardioversion

Patients on dabigatran, rivaroxaban, apixaban, and edoxaban should not interrupt the anticoagulant before electrical cardioversion.¹⁴⁻¹⁷ Before cardioversion, the patient should be expressly asked to confirm the intake of DOAC as prescribed. If the patient is not on anticoagulant treatment, it is possible to start one of the four DOACs and program elective cardioversion after 3 weeks of regular intake.¹⁴⁻¹⁷

After a transesophageal echocardiogram, if the intention is to use the accelerated pathway, it is possible to start one of the three inhibitors of factor Xa,¹⁵⁻¹⁷ always provided that the doses and times deriving from studies specifically conducted with DOACs in the context of cardioversion indicated below are respected. EMANATE (Eliquis evaluated in acute cardioversion compared to usual treatments for Anticoagulation in subjects with NVAf) for apixaban,³⁸ X-Vert (eXplore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with nonvalvular atrial fibrillation scheduled for cardioversion) for rivaroxaban,³⁹ and ENSURE-AF (Edoxaban vs. warfarin in subjects Undergoing cardioversion of Atrial Fibrillation) for edoxaban⁴⁰ demonstrated the safety of DOACs administered for <3 weeks before electrical cardioversion, as compared to VKA. The use of dabigatran in early electrical or pharmacological cardioversion programmes is not contemplated, as a specific study exploring the safety of such an approach has never been conducted. Therefore, for the use of this drug, 3 weeks are needed to perform electrical or pharmacological cardioversion in the election.¹⁴

Apixaban

The first dose to be administered should be 10 mg (5 mg if the criteria for the use of the reduced dose exist) with subsequent maintained dose according to indications (5 or 2.5 mg bid). Cardioversion can be performed between 2 and 12 h from the loading dose. If the administration of the loading dose is not considered cautious, it is necessary to wait for the required time to administer 5 doses (2.5 days) using the dose based on the patient's characteristics.

Rivaroxaban

It is administered according to the dose based on the patient's characteristics and cardioversion can be performed 4 h after the first administration. It is important to remember that the drug is better absorbed with food and that therefore the timing of a possible transesophageal echocardiogram will have to take into account the food intake associated with the administration of the drug.

Edoxaban

It is administered according to the dose based on the patient's characteristics and cardioversion can be performed 2 h after administration.

Conclusions

The choice of the appropriate DOAC and the correct dose for a given patient is a complex process, not always reducible to the simple knowledge of the SmPC, as indicated by the ESC¹⁸ or NICE²⁰ guidelines, or by what is indicated in the EHRA practical guide for the use of these drugs.¹⁹ In general, however, identifying the appropriate dose for the individual patient is relatively simple. This dose must be carefully respected to guarantee the best efficacy and ensure greater safety. It should also be noted that, for three of the DOACs (rivaroxaban, apixaban, and edoxaban), the choice of the 'reduced' dose is closely linked to precisely defined criteria (renal function, body weight, age, concomitant medical therapy), which impose an unavoidable constraint on the prescriber. For dabigatran, however, as already mentioned, the prescribing physician has greater freedom of judgement and the choice of the dose can be personalized based on a clinical evaluation of the individual case. Basically, the 'lower dose' exists only for one of the DOACs, dabigatran, and can be prescribed through a conscious choice of the physician, based on an articulated clinical judgement. In fact, in this case, 'the doctor decides'. For the other DOACs, rivaroxaban, apixaban, and edoxaban, there are 'reduced doses', which can only be prescribed in compliance with precise predefined criteria. In fact, for the reduced dose, 'the patient's profile decides'. Any prescription that does not comply with these criteria is 'off-label', i.e. not in compliance with the provisions of the SmPC, in violation of the law currently in force.^{41,42} If the physician decides to proceed with an 'off-label' prescription, he can do so, but he will have to follow precise rules, assuming direct responsibility for this decision. In particular, the physician should obtain the patient's informed consent, explain the rationale for the therapy, define the risk of possible adverse events, and present

what efficacy data are available in the off-label use of the drug to be administered.^{41,42}

In daily clinical practice, the boundaries of appropriateness for anticoagulant drugs are not always easily determined.⁷ A careful evaluation by the prescribing physician is necessary, who must take into consideration all the clinical variables of the individual patient and correctly identify the specific haemorrhagic risk. This assessment will have to be repeated over time, with the knowledge that the clinical features and risk profile can change significantly.^{18-20,32,33,43}

Acknowledgements

This position paper was originally published in the Italian language as 'Position paper ANMCO: Appropriately prescriptive degli anticoagulanti orali diretti nella prevenzione dell'ictus e dell'embolia sistemica nei pazienti adulti affetti da fibrillazione atriale non valvolare', in the official journal of the Italian Federation of Cardiology (IFC) 'Giornale Italiano di Cardiologia', published by Il Pensiero Scientifico Editore. This paper was translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted with permission of IFC and Il Pensiero Scientifico Editore.

Funding

This research was funded by Associazione Nazionale Medici Cardiologi Ospedalieri. Centro servizi ANMCO srl societa' benefit. Via A. La Marmora, 36. Firenze 50121. Italy.

Conflict of interest: The authors declare no conflict of interest.

Disclaimer

This Position Paper was originally published in the Italian language as 'Position paper ANMCO: Appropriately prescriptive degli anticoagulanti orali diretti nella prevenzione dell'ictus e dell'embolia sistemica nei pazienti adulti affetti da fibrillazione atriale non valvolare', in the official journal of the Italian Federation of Cardiology (IFC) 'Giornale Italiano di Cardiologia', published by Il Pensiero Scientifico Editore. This paper was translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted with permission of IFC and Il Pensiero Scientifico Editore.

Appendix: ANMCO faculty of approval

Antonio Francesco Amico, Michela Barisone, Claudio Bilato, Irma Bisceglia, Edoardo Bonsante, Raimondo Calvanese, Roberto Caporale, Giancarlo Casolo, Mario Chiatto, Giuseppe Di Tano, Doriana Frongillo, Giovanna Geraci, Rossella Gilardi, Edoardo Gronda, Daniele Grosseto, Gabriele Guardigli, Massimo Iacoviello, Fabiana Lucà, Antonia Mannarini, Marco Marini, Antonella Maurizia Moreo, Adriano Murrone, Federico Nardi, Giuseppe Pajes, Daniela Pavan, Claudio Picariello, Serena Rakar, Roberta Rossini,

Marino Scherillo, Gerolamo Sibilio, Stefano Strano, Giovanni Tarsi, Paolo Trambaiolo, Tullio Usmiani, Annalisa Viele, Massimo Zecchin, Filippo Zilio, and Giuseppe Zuccalà.

References

- World Health Organization. Regional Office for Europe. *Appropriateness in Health Care Services: Report on a WHO Workshop, Koblenz, Germany, 23-25 March 2000*. WHO Regional Office for Europe; 2000. <https://apps.who.int/iris/handle/10665/108350> (31 October 2021).
- Hicks NR. Some observations on attempts to measure appropriateness of care. *BMJ* 1994;**309**:730-733.
- Britten N, Jenkins L, Barber N, Bradley C, Stevenson F. Developing a measure for the appropriateness of prescribing in general practice. *Qual Saf Health Care* 2003;**12**:246-250.
- CODICE DI DEONTOLOGIA MEDICA 2014_aggiornato_febbraio_2020.pdf. https://www1.ordinemediciroma.it/images/Ordine/Deontologia/CODICE%20DI%20DEONTOLOGIA%20MEDICA%202014_aggiornato_febbraio_2020.pdf (16 February 2022).
- Godino C, Bodega F, Melillo F, Rubino F, Parlati ALM, Cappelletti A, Mazzone P, Mattiello P, Della Bella P, Castiglioni A, Alfieri O, De Bonis M, Montorfano M, Tresoldi M, Filippi M, Zangrillo A, Salerno A, Cera M, Margonato A; INSIgHT (Italian NOACs San Raffaele Hospital) registry investigators. Inappropriate dose of nonvitamin-K antagonist oral anticoagulants: prevalence and impact on clinical outcome in patients with nonvalvular atrial fibrillation. *J Cardiovasc Med* 2020;**21**:751-758.
- Jacobs MS, van Hulst M, Campmans Z, Tieleman RG. Inappropriate non-vitamin K antagonist oral anticoagulants prescriptions: be cautious with dose reductions. *Neth Heart J* 2019;**27**:371-377.
- Vedovati MC, Giustozzi M, Paciaroni M. Patients with Atrial Fibrillation receiving NOACs: the boundary between appropriate and inappropriate dose. *Eur J Intern Med* 2021;**88**:25-27.
- Steinberg BA, Gao H, Shrader P, Pieper K, Thomas L, Camm AJ, Ezekowitz MD, Fonarow GC, Gersh BJ, Goldhaber S, Haas S, Hacke W, Kowey PR, Ansell J, Mahaffey KW, Naccarelli G, Reiffel JA, Turpie A, Verheugt F, Piccini JP, Kakkar A, Peterson ED, Fox KAA; ORBIT-AF Investigators. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *Am Heart J* 2017;**194**:132-140.
- Haas S, Camm AJ, Bassand J-P, Angchaisuksiri P, Cools F, Corbalan R, Gibbs H, Jacobson B, Koretsune Y, Mantovani LG, Misselwitz F, Panchenko E, Ragy HI, Stepinska J, Turpie AG, Sawhney JP, Steffel J, Lim TW, Pieper KS, Virdone S, Verheugt FW, Kakkar AK; GARFIELD-AF Investigators. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Am Heart J* 2019;**213**:35-46.
- Mazurek M, Halperin JL, Huisman MV, et al. Antithrombotic treatment for newly diagnosed atrial fibrillation in relation to patient age: the GLORIA-AF registry programme. *EP Eur* 2020;**22**:47-57.
- Maura G, Billionnet C, Drouin J, Weill A, Neumann A, Pariente A. Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016. *BMJ Open* 2019;**9**:e026645.
- Paciaroni M, Agnelli G, Caso V, Silvestrelli G, Seiffge DJ, Engelter S, De Marchis GM, Polymeris A, Zedde ML, Yaghi S, Michel P, Eskandari A, Antonenko K, Sohn S-I, Cappellari M, Tassinari T, Tassi R, Masotti L, Katsanos AH, Giannopoulos S, Acciarresi M, Alberti A, Venti M, Mosconi MG, Vedovati MC, Pierini P, Giustozzi M, Lotti EM, Ntaios G, Kargiotis O, Monaco S, Lochner P, Bandini F, Liantinioti C, Palaodimou L, Abdul-Rahim AH, Lees K, Mancuso M, Pantoni L, Rosa S, Bertora P, Galliazzo S, Ageno W, Toso E, Angelini F, Chiti A, Orlandi G, Denti L, Flomin Y, Marcheselli S, Mumoli N, Rimoldi A, Verrengia E, Schirinzi E, Del Sette M, Papamichalis P, Komnos A, Popovic N, Zarkov M, Rocco A, Diomedes M, Giorli E, Ciccone A, Mac Grory BC, Furie KL, Bonetti B, Saia V, Guideri F, Acampa M, Martini G, Grifoni E, Padroni M, Karagkiozi E, Perlepe K, Makaritsis K, Mannino M, Maccarrone M, Ulivi L, Giannini N, Ferrari E, Pezzini A, Doronin B, Volodina V, Baldi A, D'Amore C, Deleu D, Corea F, Putaala J, Santalucia P, Nardi K, Risitano A, Toni D, Tsigoulis G. Causes and risk factors of cerebral ischemic events in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants for stroke prevention. *Stroke* 2019;**50**:2168-2174.
- Paciaroni M, Agnelli G, Giustozzi M, Caso V, Toso E, Angelini F, Canavero I, Micieli G, Antonenko K, Rocco A, Diomedes M, Katsanos AH, Shoamanesh A, Giannopoulos S, Ageno W, Pegoraro S, Putaala J, Strbian D, Sallinen H, Mac Grory BC, Furie KL, Stretz C, Reznik ME, Alberti A, Venti M, Mosconi MG, Vedovati MC, Franco L, Zeponi G, Romoli M, Zini A, Brancaloni L, Riva L, Silvestrelli G, Ciccone A, Zedde ML, Giorli E, Kosmidou M, Ntaios E, Palaodimou L, Halvatsiotis P, Tassinari T, Saia V, Ornello R, Sacco S, Bandini F, Mancuso M, Orlandi G, Ferrari E, Pezzini A, Poli L, Cappellari M, Forlivesi S, Rigatelli A, Yaghi S, Scher E, Frontera JA, Masotti L, Grifoni E, Caliendo P, Zauli A, Reale G, Marcheselli S, Gasparro A, Terruso V, Arnao V, Aridon P, Abdul-Rahim AH, Dawson J, Saggese CE, Palmerini F, Doronin B, Volodina V, Toni D, Risitano A, Schirinzi E, Del Sette M, Romoli P, Monaco S, Mannino M, Tassi R, Guideri F, Acampa M, Martini G, Lotti EM, Padroni M, Pantoni L, Rosa S, Bertora P, Ntaios G, Sagris D, Baldi A, D'Amore C, Mumoli N, Porta C, Denti L, Chiti A, Corea F, Acciarresi M, Flomin Y, Popovic N, Tsigoulis G. Risk factors for intracerebral hemorrhage in patients with atrial fibrillation on non-vitamin K antagonist oral anticoagulants for stroke prevention. *Stroke* 2021;**52**:1450-1454.
- Pradaxa. European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/pradaxa> (19 February 2022).
- Xarelto. European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto> (19 February 2022).
- Eliquis. European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/eliquis> (19 February 2022).
- Lixiana. European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/lixiana> (19 February 2022).
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castellà M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373-498.
- Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haessler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ, Heidbüchel H; External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612-1676.
- Overview | Atrial fibrillation: diagnosis and management | Guidance | NICE. <https://www.nice.org.uk/guidance/ng196> (31 October 2021).
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139-1151.
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM; the ROCKET AF Steering Committee. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883-891.
- Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Gerasides M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981-992.
- Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093-2104.

25. Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864-2870.
26. Lip GYH, Nieuwlaet R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263-272.
27. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 2009;**157**:805-810, 810.e1-2.
28. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 2010;**159**:340-347.e1. doi:10.1016/j.ahj.2009.11.025
29. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, Gersh BJ, Granger CB, Hanna M, Horowitz J, Hylek EM, McMurray JJV, Verheugt FWA, Wallentin L; ARISTOTLE Investigators. Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010;**159**:331-339.
30. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;**160**:635-641.
31. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cifková R, De Bonis M, Jung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA; ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:3165-3241.
32. Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093-1100.
33. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;**36**:3258-3264.
34. Praxbind. European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/praxbind> (19 February 2022).
35. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Janus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GYH, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423-2434.
36. Ondexxya. European Medicines Agency. Published February 27, 2019. <https://www.ema.europa.eu/en/medicines/human/EPAR/ondexxya> (15 March 2022).
37. Mocini D, Di Fusco SA, Mocini E, Donini LM, Lavallo C, Di Lenarda A, Riccio C, Caldarola P, De Luca L, Gulizia MM, Oliva F, Gabrielli D, Colivicchi F. Direct oral anticoagulants in patients with obesity and atrial fibrillation: position paper of Italian National Association of Hospital Cardiologists (ANMCO). *J Clin Med* 2021;**10**:4185.
38. Ezekowitz MD, Pollack CV, Halperin JL, England RD, VanPelt Nguyen S, Spahr J, Sudworth M, Cater NB, Breazna A, Oldgren J, Kirchhof P. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J* 2018;**39**:2959-2971.
39. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma C-S, Le Heuzey J-Y, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346-3355.
40. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GYH. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**:1995-2003.
41. Off-Label. Bollettino d'informazione sui Farmaci, Vol. 13; 2006. p140-141.
42. L 94/98. <https://www.camera.it/parlam/leggi/98094.htm> (1 November 2021).
43. Di Fusco SA, Colivicchi F, Santini M. The hemorrhagic risk: how to evaluate it. *Pacing Clin Electrophysiol* 2013;**36**:1191-1197.