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Italian intersociety consensus on DOAC use in internal medicine

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Abstract The direct oral anticoagulants (DOACs) are drugs used in clinical practice since 2009 for the prevention of stroke or systemic embolism in non-valvular atrial fibrillation, and for the treatment and secondary prevention of venous thromboembolism. The four DOACs, including the three factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and one direct thrombin inhibitor (dabigatran) provide oral anticoagulation therapy alternatives to Vitamin K antagonists (VKAs). Despite their clear advantages, the DOACs require on the part of the internist a thorough knowledge of their pharmacokinetic and pharmacodynamic characteristics to ensure their correct use, laboratory monitoring and the appropriate management of adverse events. This document represents a consensus paper on the use of DOACs by representatives of three Italian scientific societies: the Italian Society of Internal Medicine (SIMI), the Federation of the Associations of Hospital Managers (FADOI), and the Society for the Study of Haemostasis and Thrombosis (SISET). This document formulates expert opinion guidance for pragmatic managing, monitoring and reversing the anticoagulant effect of DOACs in both chronic and emergency settings. This practical guidance

Members of SIMI (Italian Society of Internal Medicine), FADOI (Federation of Associations of Hospital Doctors on Internal Medicine) and SISET (Italian Society for the Study of Haemostasis and Thrombosis) are listed in Acknowledgement.

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may help the internist to create adequate protocols for patients hospitalized ion internal medicine wards, where patients are often elderly subjects affected by poly-morbidities and renal insufficiency, and, thus, require particular attention to drug–drug interactions and peri-procedural protocols.

Keywords Atrial fibrillation · Venous thromboembolism · Pulmonary embolism · Venous thrombosis · Internist · Drug interactions · Elderly · Direct oral anticoagulant · Novel oral anticoagulant

Introduction and aim

The direct oral anticoagulants (DOACs) are becoming more commonly used in clinical practice for the prevention of stroke in non-valvular atrial fibrillation (NVAF) and the acute treatment and secondary prophylaxis of venous thromboembolism (VTE). The availability of a number of agents with similar efficacy and safety profiles offers different alternatives to improve individual therapeutic strategies, but also requires an appropriate knowledge to select optimal choices.

Although anticoagulant treatment with vitamin K antagonists (VKAs) has represented the standard of care for a long time, the use of the DOACs has rapidly become supported by robust and comprehensive evidence, which needs to be adequately translated into clinical practice with standardized approaches. This prompted the Italian Society of Internal Medicine (SIMI), the Italian Federation of Hospital Internists (FADOI) and the Italian Society for the Study of Haemostasis and Thrombosis (SISET) to set up a working group with the aim to define an inter-society consensus statement on practical issues related to the daily management of patients on DOACs.

The process included reviewing up-to-date evidence and existing high-quality evidence-based international guidelines. After a single meeting held in Rome in June 2015 to decide the general strategy, five groups wrote the five parts of the draft. Further revisions were made by consensus through email. All the members of the panel are the authors of this article.

The application of this statement is in particular intended to assist the management of patients on DOACs on internal medicine wards.

Prescription and follow-up planning

According to the indications of the Italian national regulatory authority (AIFA), physicians working on Internal Medicine wards are authorized to prescribe DOACs to patients with NVAF and with VTE.

The choice of the anticoagulant (VKAs or DOACs; type of DOAC) has to be made on the basis of approved indications by national regulatory authorities, current evidence and guidelines by professional societies [1, 2]. Before prescribing a DOAC to a patient with NVAF or with VTE, physicians should evaluate the risk/benefit threshold of introducing an anticoagulant. In general, DOACs have a better efficacy and safety profile than VKAs in NVAF and VTE patients [3, 4]. However, NVAF patients evaluated by Internal Medicine have some peculiar characteristics that should be considered before DOAC prescription (Table 1) [5–8]. As previously specified, DOACs have been studied in NVAF only. A clear definition of NVAF, as AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis, usually of rheumatic origin, has been recently suggested by the expertise of the EHRA guidelines) [1]. However, the definition of NVAF varied widely in the original studies, "Appendix".

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Table 1 Peculiar characteristics of NVAF patients evaluated in Internal Medicine in comparison to patients evaluated in Cardiology [5, 6]

Older age
Higher prevalence of:
A. Heart failure
B. Diabetes Mellitus
C. Prior stroke/TIA,
D. Peripheral embolism
E. Peripheral artery disease
F. Renal failure
G. COPD
H. Anemia
I. Cognitive deficit/dementia
J. Need of assistance
Lower prevalence of
A. Valvular heart disease
B. Hypercholesterolemia
Higher CHA_2DS_2VASc score
Higher HAS-BLEED score
More concomitant medications

The risk of short-term complications should be evaluated before the introduction of DOACs in patients with acute VTE. Patients presenting with acute PE with shock or hypotension (defined as systolic blood pressure <90 mm Hg, or a systolic pressure drop >40 mm Hg for at least 15 min, if not caused by new onset dysrhythmia, hypovolemia or sepsis) are at high risk of short term complications, and should be urgently reperfused using intravenous thrombolytic therapy, if not contraindicated, or embolectomy, and they should managed in the intensive care setting [8]. Moreover, close monitoring is recommended in patients with intermediate–high risk PE to allow an early detection of haemodynamic decompensation, and timely initiation of rescue reperfusion therapy [8]. In general, patients with high or intermediate–high risk of short-term complications were not included in randomized controlled trials evaluating the safety and efficacy of DOACs in the treatment of acute VTE. Thus, it seems reasonable to treat these patients with intravenous unfractioned heparin for the first 48 h, and to introduce a DOAC only when the patient is completely stabilized.

Although DOACs seem as effective and safe as VKAs for the prevention of VTE recurrence in cancer patients with acute PE or DVT [9], the evidence on the role of DOACs in this setting is limited, and to date, no study has compared these compounds to low molecular weight heparin (LMWH) that is considered the treatment of reference. Moreover, drugs used for treatment of active cancer may have important pharmacological interactions with DOACs, and cancer patients on chemotherapy frequently develop thrombocytopenia and liver or kidney insufficiency, complications that may contraindicate the use of these compounds. Thus, until solid evidence is produced, it may be reasonable to avoid the use of DOACs in cancer patients with VTE when they are on chemotherapy, and to prefer LMWHs.

Evidence on the role of DOAC in cancer patients with VTE is even more limited since RCTs comparing DOAC and VKA during the acute phase have a relatively short-term follow-up, and only one study that included a very small number of patients with cancer has compared a DOAC, namely dabigatran, to VKA after the acute phase of VTE treatment [10]. Current guidelines suggest to leave unchanged the initial anticoagulant treatment [11]. However, long-term use of LMWH is often associated with bruising and deterioration of injection sites, and thus many patients prefer an oral antithrombotic drug. DOACs appear a reasonable alternative, especially in patients who have completed chemotherapy.

In patients with acute VTE, DOACs have to be prescribed according to the product label for this indication, namely patients should be treated for at least 5 days with LMWH, fondaparinux or unfractionated heparin (UFH) before the introduction of dabigatran and edoxaban, whereas an initial treatment with LMWH, fondaparinux or UFH is not necessary when apixaban or rivaroxaban are used. However, in the treatment of acute VTE, a loading dose of apixaban (10 mg bid) or rivaroxaban (15 mg bid) should be prescribed for 7 and 21 days, respectively.

Baseline hemoglobin, renal and liver function studies should be obtained in all patients.

Renal function should be expressed by a Cockcroft–Gault estimate of glomerular filtration rate (GFR), and for liver function bilirubin and alanine transferase (ALT) measurement is suggested.

Generic coagulation assays [activated partial thromboplastin time (aPTT) and prothrombin time (PT)] should be assessed before introducing DOACs since this information may be useful in case of the necessity for evaluating the presence or absence of a DOAC effect in an emergency setting (see "Bleeding or thromboembolic event-related hospitalization").

According to the Italian National regulatory authority (AIFA) indications, DOACs are reimbursed in NVAF patients only if they have a high risk of bleeding (HAS-BLED ≥3), if INR control under VKA has been shown to be suboptimal (i.e., after a failed 'trial of VKA'), or if patients are unable to comply with a long-term therapy with VKAs. Although there is no direct comparison among different DOACs, differences in the product characteristics (e.g., renal clearance, daily dosing, drug–drug interactions) do exist.

Future follow-up visits of patients taking DOACs should be carefully specified and discussed with the patients at the

time of first therapy prescription. Patients should be invited to return on a regular basis for ongoing review of their treatment, preferably after 1 month initially, and later every 3 months at least for the first visits, then every 6 months.

During each visit, the physician should assess: the patient's compliance with treatment; the occurrence of thromboembolic and bleeding complications and of other complications potentially related to the prescribed DOACs; and any new co-medications (including over-the-counter medications). Time of blood sampling for hemoglobin, renal and hepatic function should be chosen on an individual patient basis. For example, renal function should be assessed more frequently in patients with pre-existing chronic renal failure, in the elderly (age >80 years) and frail patients, and every time in which an intercurrent condition potentially affecting renal function (e.g., diarrhea) does occur.

In case of renal function deterioration, DOACs dosage should be adapted according to European label.

Non-serious adverse events, food and drug–drug interactions which may change patients' management

One of the major advantages of DOACs over VKAs is their easier management, which contributes to the increasing therapeutic use of these drugs. Nevertheless, minor adverse drug reactions, drug–drug interactions, and concomitant non-severe common clinical conditions may influence the pharmacological properties of DOACs and ultimately their clinical effects. The prescription of DOACs requires an in-depth knowledge of the pharmacology of these drugs.

Non-serious adverse events/reactions

Major bleeding is the most fearsome adverse drug reaction related to DOACs, but also non-major bleeding events may become relevant during treatment with these drugs. Yet, most of these events (epistaxis, hematuria, skin hematomas, gingival bleeding, etc.) are generally self-limited, do not require hospitalization, systematic drug interruption or change in dosage, which can be decided on a case-by-case basis.

In addition, similarly to the majority of drugs, patients receiving DOACs may experience other non-serious adverse events or reactions, including gastrointestinal: (nausea, emesis, dyspepsia, diarrhea, abdominal pain, less frequently dysphagia, gastroesophageal reflux, stipsis), cutaneous: (skin rush, itch), hematological: (anemia, less frequently thrombocytopenia), cardiovascular and neurological: (hypotension, tachycardia, syncope, vertigo, headache) effects [11]. Dyspepsia is one of the most common adverse events during treatment with dabigatran. It can occur in up to 10% of subjects treated with this drug, and may lead to early discontinuation of the treatment regimen. The condition can be improved with the intake of dabigatran with food, or with the use of a proton pump inhibitor, but if the problem still exists, it is useful to change the drug.

Food interactions

Concerning food interactions, the anticoagulant activity of DOACs is less sensitive to diet variables than VKAs, which are affected by various types of food, especially products that contain vitamin K. This is important in daily life, as patients who receive these drugs do not need to consider particular diet limitations [12]. However, and more specifically, gastro-intestinal absorption of dabigatran is dependent on an acid milieu, which is provided by the formulation of the drug. Therefore, patients should intake dabigatran 2 hours removed from meals. The concomitant use of proton pump inhibitors or H2-blockers leads to reduced bioavailability of the anticoagulant (20–30%), possibly without clinically relevant effects. On the other hand, since food intake influences the absorption and bioavailability of rivaroxaban, it is recommended that this anticoagulant be administered with meals. No relevant food interactions are reported so far for apixaban and edoxaban [13, 14].

Concomitant diseases influencing pharmacokinetics

Intercurrent episodes of fever, diarrhea, even brief periods of vomiting or lack of appetite should be considered with attention, and possibly require control of renal function to avoid harmful overdose of anticoagulant. The use of DOACs in these conditions requires caution, especially in elderly patients, as this group generally has moderate (creatinine clearance 30–50 mL/min) or severe (15–30 mL/min) renal insufficiency, with the area under the concentration–time curve (AUC) increasing 2.7 to sixfold and the plasma elimination half-life increasing at least twofold [15]. Dabigatran is not recommended in patients with severe renal insufficiency [16], whereas apixaban, edoxaban and rivaroxaban are recommended with caution and dose adjustment application [17].

Drug–drug interactions

Intercurrent non-severe diseases (such as osteoarthritis, cutaneous or mucosal fungal infections, etc.) should be carefully considered since they require treatments that can interfere with DOACs. There are two major mechanisms

Table 2 Effects of drug–drug interactions on DOACs plasma levels, including recommendations for dosing of the anticoagulants released by the European Heart Rhythm Association (modified and updated from [1]

	Mechanism	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp and CYP3A4 inhibition	↑	No data yet	No effect	No effect
Digoxin	P-gp competition	No effect	No data yet	No effect	No effect
Verapamil	P-gp and CYP3A4 inhibition	↑ (reduce dose and take simultaneously)	No data yet	↑	Use with caution if CrCl 15–50 ml/min
Diltiazem	P-gp and CYP3A4 inhibition	No effect	↑	No data yet	Use with caution if CrCl 15–50 ml/min
Quinidine	P-gp competition	↑	No data yet	↑	↑
Amiodarone	P-gp competition	↑	No data yet	↑	Use with caution if CrCl 15–50 ml/min
Dronedarone	P-gp and CYP3A4 inhibition	↑	No data yet	↑ (reduce dose by 50%)	No data yet
Ketoconazole, itraconazole, voriconazole, posaconazole	P-gp and CYP3A4 inhibition	↑	↑	↑ with ketoconazole (reduce dose by 50%)	↑
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	↑ (if systemic)
Cyclosporin, tacrolimus	P-gp competition	Cyclosporin contra-indicated, tacrolimus not recommended	No data yet	↑ with cyclosporin (reduce dose by 50%)	↑
Clarithromycin, erythromycin	P-gp competition and CYP3A4 inhibition	↑	No data yet	↑ with erythromycin (reduce dose by 50%)	↑
HIV protease inhibitors	P-gp and CYP3A4 inhibition	No data yet	Strong increase	No data yet	↑
Rifampicin, carbamazepine, phenytoin, phenobarbital	P-gp/BCRP and CYP3A4/CYP2J2 inducers	↓	↓	↓	↓
Antiacids	Gastrointestinal absorption	↓	No data yet	No effect	No effect

of drug–drug interactions, one related to the metabolism by the cytochrome system, especially CYP3A4, and the other to the P-glycoprotein (P-gp) transporter mechanism. Metabolism of DOACs is influenced by P-gp in case of dabigatran and edoxaban, and by both CYP3A4 (mainly) and P-gps for the other anti-Xa compounds; therefore, it is plausible that drugs acting as strong inducers or inhibitors of CYP3A4 or P-gp may interfere with metabolism of DOACs and reduce or increase their bioavailability. Table 2 summarizes the effects on DOACs plasma levels (AUC) from drug–drug interactions, including recommendations for dosing of the anticoagulants released by the European Heart Rhythm Association [13] or information obtained by the Summary of Product Characteristics approved by the European Medicines Agency (EMA).

In some cases, during concomitant therapy with drugs inhibiting CYP3A4 or P-gp (e.g., verapamil, cyclosporin, dronedarone, erythromycin, and azoles), but also in patients with low body weight (<60 kg), aged more than 80 years, or with gastric disorders (gastritis, esophagitis, gastroesophageal reflux), a dose reduction is necessary. A practical strategy might be reducing dabigatran from 150 mg × 2/die to 110 mg × 2/die, rivaroxaban from 20 to 15 mg/die, apixaban from 5 mg × 2/die to 2.5 mg × 2/die and edoxaban from 60 to 30 mg/die. Table 3 reports on these cases with the reduced dosing when necessary.

In addition, attention should be paid in case of concomitant treatment with non-steroidal anti-inflammatory drugs as well as with antiplatelet agents, increasing the risk of bleeding (up to 60%) due to pharmacodynamic interactions [18–20]: such associations should be carefully

Table 3 Dosing recommendations for DOACs

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Body weight	No dose adjustment (but close surveillance when <50 kg)	No dose adjustment	≤60 kg: 30 mg/die	No dose adjustment
Elderly patients	• Age 75–80 years: 150 mg bid or 110 mg bid depending on individual thromboembolic and bleeding risk • ≥80 years: 110 mg bid	No dose adjustment	No dose adjustment	No dose adjustment
Concomitant medication	Verapamil: 110 mg bid	No dose adjustment	Cyclosporin, dronedarone, erythromycin, ketoconazole: 30 mg/die	No dose adjustment
Gastric disorders	110 mg bid	No label advice	No label advice	No label advice

Table 4 Potential interactions of DOACs with antibiotics (modified and updated from [19, 20])

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
As reported in the summary of product characteristics submitted to FDA	Ketoconazole Rifampicin	Clarithromycin Itraconazole Ketoconazole Rifampicin	Rifampicin	Clarithromycin Erythromycin Fluconazole Ketoconazole Rifampicin
Reported in the literature	Clarithromycin Rifampicin	None	None	Clarithromycin Erythromycin Fluconazole Ketoconazole

balanced against the potential benefit in each clinical situation, and surveillance recommended especially for high risk patients. Furthermore, caution is required with a number of anti-cancer agents, which may act as inducers, inhibitors, or substrates of CYP3A4 or P-gp, thus competing with DOACs metabolism [18].

Finally, interactions between DOACs and a number of antibiotics have been recently described, which is of importance for the very frequent use of these drugs (Table 4) [19].

Management of DOACs in patients hospitalized for medical illness

With the widespread prescription of DOACs in NVAF and VTE patients, the need to manage these agents on Internal Medicine wards has become an increasingly relevant issue.

During hospitalization, some critical issues may lead to reconsideration of DOAC treatment or dosage.Liver failure and kidney disease, in particular, are frequent comorbidities that may affect DOAC excretion. A new diagnosis of cancer and the occurrence of bleeding during hospitalization are two additional common conditions that need special attention.

Impact of therapeutic changes

DOACs interactions with other drugs prescribed during hospitalization is another relevant issue (see "Non-serious adverse events, food and drug–drug interactions which may change patients' management") that needs to be taken into consideration when patients' therapy is modified due to intercurrent disease [21, 22].

Moreover, the personal risk of bleeding of the individual patient should be considered when administering a drug that is known to increase the plasma concentration of a DOAC.

Liver disease, renal failure, cancer

Liver disease, per se or drug-induced, is very common, and often complicates other medical disorders. The clinical experience with DOACs use in patients with liver disease is very limited. The major phase III trials that evaluated DOACs did not include patients with clinically significant liver disease (acute or chronic hepatitis, cirrhosis, or transaminase elevation over three times the upper normal limit).

Very few reports of possible rivaroxaban hepatotoxicity (ALT >3× and total bilirubin >2× the upper normal value)

have been reported in the literature, and pharmaco-epidemiological studies are needed to assess whether there is indeed a hepatotoxic effect of this drug [22, 23].

Due to the limited clinical experience in patients with liver disease, it is reasonable to carefully check the hepatic profile of each patient and follow these practical suggestions during the hospitalization:

- DOACs should be avoided in case of severe liver disease (Child—Pugh C).
- It is necessary to evaluate liver function tests before prescribing/confirming DOACs.
- It is mandatory to monitor liver function during treatment, especially in elderly patients.
- It is required to monitor liver function in hospitalized patients especially if suffering from congestive heart failure, or if they are taking acetaminophen/other potentially hepatotoxic drugs.
- DOACs should be withdrawn in case of hospitalization for suspected drug-related hepatotoxicity.
- Due to the prevailing renal excretion, dabigatran may be the DOAC of choice for patients with liver disease, but there are no definitive data to support this suggestion.

Patients treated with DOACs may be at risk of bleeding if there is sudden deterioration of renal function. Renal failure is frequently observed during hospitalization, being related to several different conditions, commonly associated with a large number of medical conditions, such as hypotension, dehydration and diarrhea.

The prevalence of chronic kidney disease (CKD) [24, 25] increases to 15–30% in the elderly and exceeds 50% in patients with cardiovascular and metabolic diseases. A doubling of renal failure patients due to the increasing incidence of hypertension, diabetes and metabolic syndrome is expected over the next few years [26].Thus, renal function should be frequently assessed. Doses of DOACs in patients with moderate to severe CKD should be reduced, and DOACs should be avoided in patients with end-stage chronic kidney disease or requiring hemodialysis [27]. In case of creatinine clearance between 15 and 30 ml/min one should consider substituting dabigatran with VKAs or lower dose of rivaroxaban, apixaban or edoxaban. In patients with creatinine clearance below 15 ml/min one should treat patients with VKA only.

The new diagnosis of a malignancy is another event frequently occurring during hospitalization. Appropriate management of the DOACs is necessary while patients undergo invasive procedures as well as when patients start chemotherapy, in the light of the possible impact of cancer treatments on DOACs metabolism (many oncology drugs are substrates, inhibitors or inducers of CYP3A4 and/or P-gp). Moreover, chemotherapy is frequently associated with immunosuppression resulting in viral, bacterial or fungal infections; all these conditions require antimicrobial treatment that may modify DOACs metabolism. In particular, this occurs with almost all the systemic antifungal drugs, and specifically with Ketoconazole, itraconazole, voriconazole and posaconazole (see "Non-serious adverse events, food and drug–drug interactions which may change patients' management").

Peri-operative management of patients on DOACs

Evidence to support the peri-operative management of patients treated with DOACs is currently based on the results of post hoc analyses of randomized clinical trials, a few small observational studies, and a large prospective cohort study on patients treated with dabigatran who underwent invasive procedures or surgical interventions [28–33].

A number of Scientific Societies have proposed their recommendations on the peri-operative management of patients on DOACs, based on expert consensus [2, 34–37]. The main questions that should be answered in the peri-operative setting of patients on DOACs are: (1) when should DOACs be discontinued before an elective invasive procedure or surgery, and when should they be resumed? (2) when should bridging therapy with LMWHs and VTE prophylaxis be administered in the peri-operative period? (3) when and how should coagulation laboratory parameters be measured in patients who undergo elective or urgent invasive procedures or surgery?

The time of discontinuation of DOACs before an invasive procedure or surgery depends on creatinine clearance (CrCl) and procedure-related bleeding risk.

CrCl should be calculated by using the Cockroft-Gault formula because it was used in the majority of phase III clinical trials. Procedure-related bleeding risk is conventionally defined as low when the peri-procedural bleeding rate is lower than 2%, and high, when the bleeding rate is over 2% (Table 5) [38]. The definition of procedure or surgery-related bleeding risk should be locally reviewed at each Institution.

The interval between the last dose intake of the DOACs and an elective procedure or surgery should increase linearly with the presence and degree of renal impairment and with bleeding risk.

Caution should be used when resuming a DOAC after invasive procedures or surgical interventions. The decision on the optimal timing should be based on patient-related thromboembolic risk and procedure or surgery-related bleeding risk.

Table 6 summarizes the definition of thromboembolic risk in the settings of NVAF and VTE in patients on

Table 5 Examples of invasive procedure o surgery stratified according to bleeding risk

High bleeding risk (peri-operative bleeding rate 2–4%)	Low bleeding risk (peri-operative bleeding rate <2%)
o Trans-catheter ablation (pulmonary vein isolation)	o Requiring discontinuation of anticoagulation
o Neuroaxial anesthesia	o Angiography
o Renal biopsy	o Bladder or prostate biopsy
o Cardiac, vascular and thoracic surgery	o Urologic endoscopy
o Abdominal, urologic (comprehensive of TURP), breast, head/neck and oncologic surgery	o PM-ICD placement
	o Electrophysiological study
o Prosthetic orthopedic surgery	Not necessarily requiring discontinuation of anticoagulation
o Operative gastro-intestinal endoscopy	o Small dental intervention such as extraction of one tooth, periodontal surgery, incision of abscess, implant positioning
o Neurosurgery	o Cataract or glaucoma intervention
o PEG	o Superficial skin surgery
o All surgical interventions lasting more than 45 min	o Non operative gastro-intestinal endoscopy
o Lumbar puncture	
o Extractions >2 teeth or particular interventions even on one tooth (tooth VIII) involving bloody maneuvers (in the opinion of the surgeon dentist)	

Table 6 Thromboembolic (TE) risk stratification in patients who need to restart DOACs [41–47]

	NVAF	VTE
High TE risk	CHA_2DS_2-VASC ≥4	VTE episodes in the last three months
	Recent TIA or stroke	Severe thrombophilia (antithrombin deficiency, protein C deficiency, antiphospholipid antibodies syndrome, homozygous FV Leiden and prothrombin G20210A mutation)
Intermediate TE risk	CHA_2DS_2-VASC 2–3	VTE episodes in the last 3–12 months
		VTE recurrences
		Non severe thrombophilia (heterozygous FV Leiden and prothrombin G20210A mutation, increased homocysteinemia, protein S deficiency, high FVIII and FIX)
		Cancer
Low TE risk	CHA_2DS_2-VASC 0–1	Single provoked VTE episode >12 months without other VTE risk factors

DOACs, and for whom invasive procedures or surgery are necessary. Given the rapid onset of action of the DOACs, the first post-procedural dose should be administered only when an adequate local haemostasis is achieved, and the optimal timing can only be decided on an individual basis. In principle, resumption after 24 h should be considered only following a procedure at low risk for bleeding. For all other procedures, resumption after at least 48 h should be considered in patients at high thromboembolic risk, and after at least 72 h in all other patients. Figure 1 summarizes the schemes for discontinuation and resumption.

Due to their short half-life and their rapid onset and offset of action, DOACs do not require bridging therapy. In phase III RCTs comparing DOACs with the standard of care, about 7000 patients treated with DOACs underwent invasive procedures or surgery. Thromboembolic and major bleeding events did not differ between patients who received bridging therapy and patients who did not [39]. In the Dresden registry, bridging therapy was associated with a fivefold increased risk in major bleeding events [31]. More recently, Schulman et al. demonstrate that an approach without bridging therapy in patients on dabigatran is effective and safe [32]. Therefore, bridging therapy is not recommended in patients on DOACs undergoing invasive procedures or surgery.

Since the resumption of therapeutic doses of a DOAC may occur 48–72 h after procedures at high risk of bleeding, or later if adequate haemostasis is not achieved, patients at concomitantly high post-operative risk of VTE may require an earlier start of thromboprophylaxis. Prophylactic doses of DOACs can be used after total hip or total knee replacement surgery, while for all other high risk surgical procedures prophylactic doses of LMWH can be used until the first therapeutic dose of DOACs is administered. Mechanical prophylaxis, i.e., intermittent pneumatic compression or graduated elastic stockings can be alternative choices for VTE prevention in high bleeding risk patients or in patients who bleed.

Measuring the anticoagulant effects or plasma levels of DOACs can help to determine when it is safe to perform an intervention, in particular when urgent or unplanned [1]. A

1 High bleeding risk and high-moderate TE risk (Legend: green= administered; red= discontinued

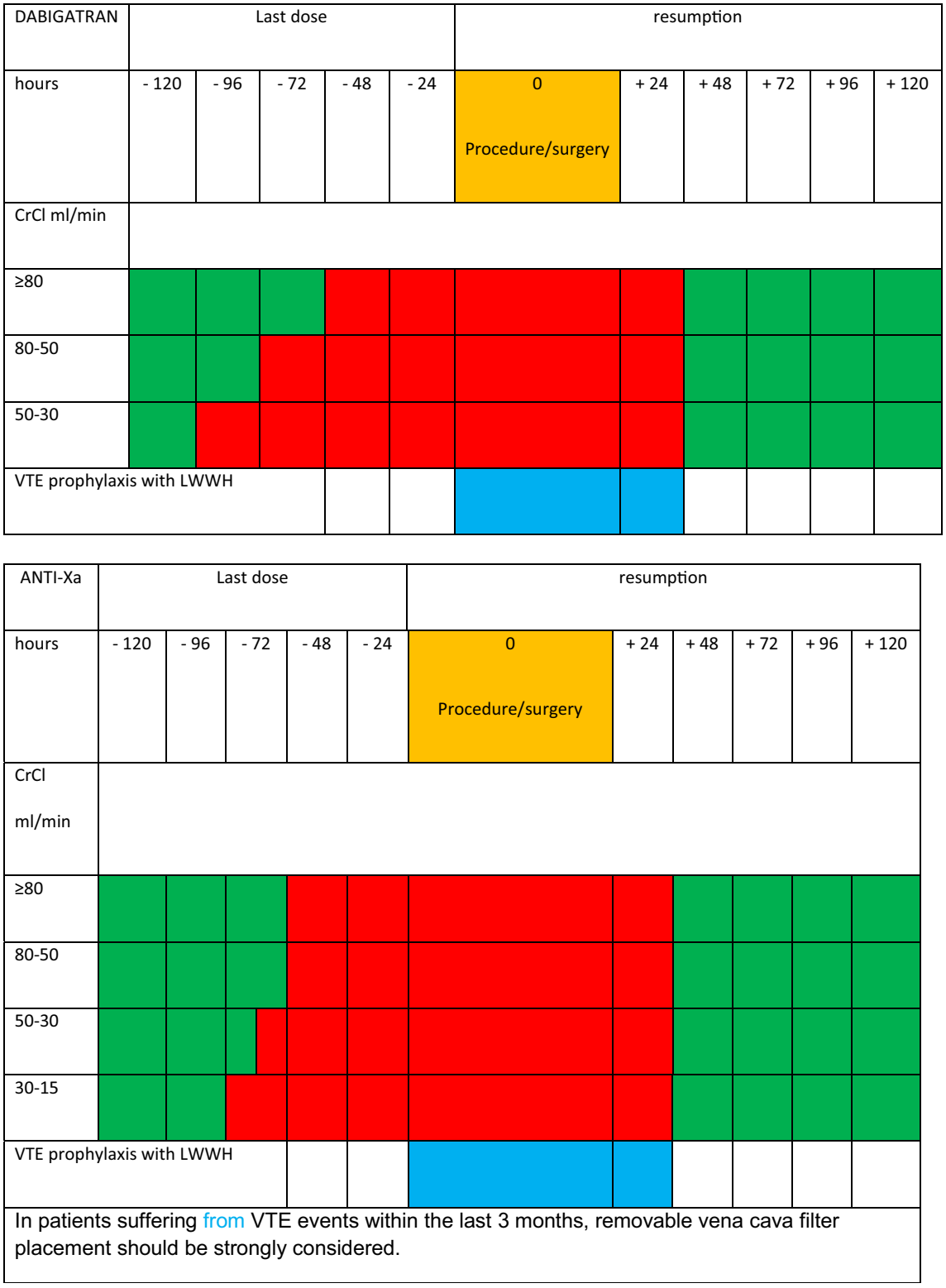


Fig. 1 Schemes for discontinuation and resumption of DOACS during the elective peri-procedural phase

2 High bleeding risk and low TE risk Legend: green= administered; red= discontinued

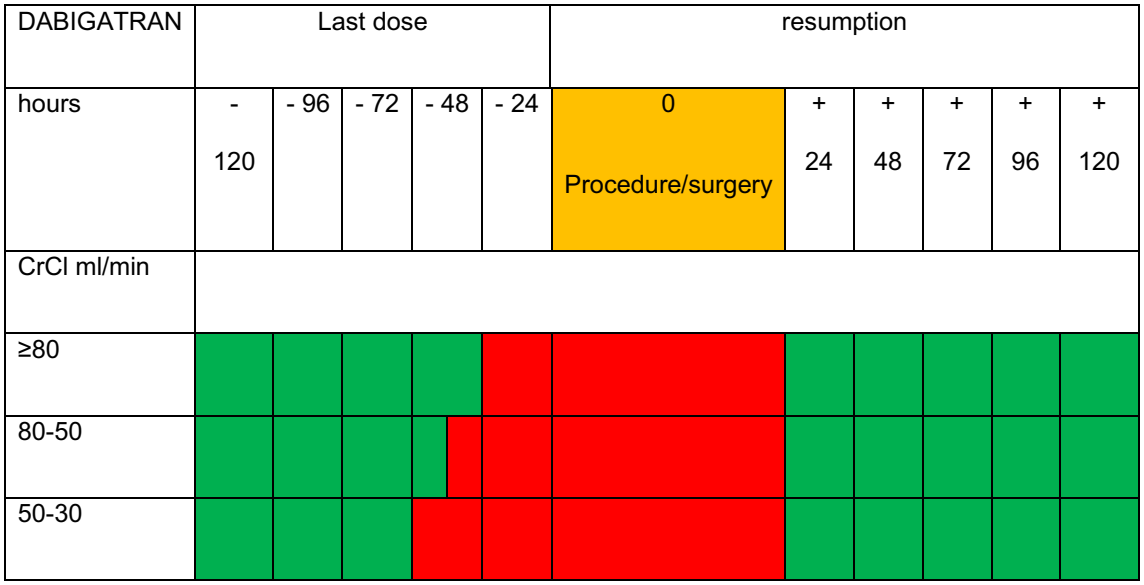
DABIGATRAN	Last dose					resumption					
hours	- 120	- 96	- 72	- 48	- 24	0 Procedure/surgery	+ 24	+ 48	+ 72	+ 96	+ 120
CrCl ml/min											
≥80											
80-50											
50-30											
VTE prophylaxis with LWWH (i.e. enoxaparin 40 mg od)											

ANTI-Xa	Last dose					resumption					
hours	- 120	- 96	- 72	- 48	- 24	0 Procedure/surgery	+ 24	+ 48	+ 72	+ 96	+ 120
CrCl ml/min											
≥80											
80-50											
50-30											
30-15											
VTE prophylaxis with LWWH											

In patients suffering from VTE events within the last 3 months, removable vena cava filter placement should be strongly considered.

Fig. 1 continued

3 Low bleeding risk irrespective of TE risk (Legend: green= administered; red= discontinued)



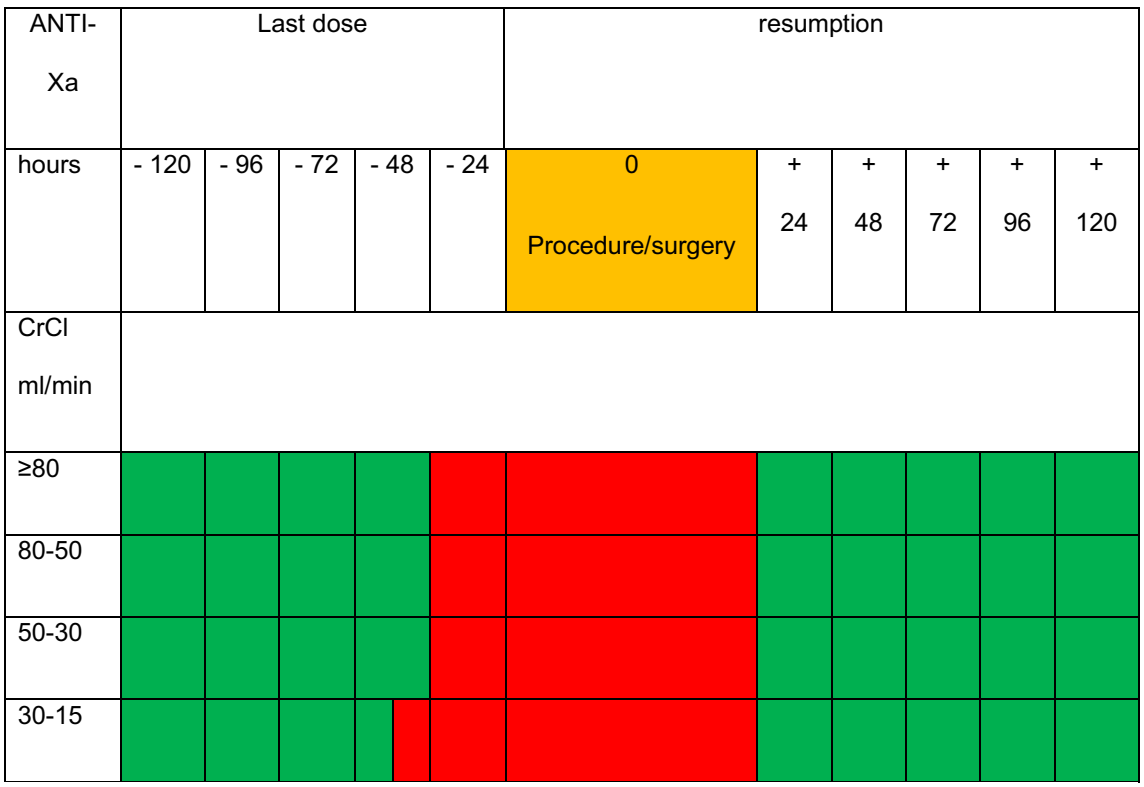


Fig. 1 continued

number of Scientific Societies or groups of experts have suggested that specific coagulation tests should be considered in these circumstances [1, 39].

Drug levels can be quantified using specific assays (see "Bleeding or thromboembolic event-related hospitalization"). Post hoc analyses of phase III RCTs show no difference in thromboembolic and major bleedings events in patients receiving DOACs or VKAs undergoing elective invasive procedures or surgery. Of note, the procedures in patients treated with DOACs were performed without coagulation monitoring, but only with strategy-based and renal function-related discontinuation [29, 40]. Moreover, neither the Dresden registry [31] nor the study by Schulman [32] supports a coagulation monitoring-based strategy for the discontinuation of the DOACs in elective patients. Therefore, for the majority of patients undergoing elective procedures or planned surgical interventions coagulation laboratory monitoring or the measurement of DOACs plasma concentrations are not needed. In patients with moderate renal failure or at high risk of renal function deterioration undergoing a procedure or surgical intervention at high bleeding risk or suffering from co-morbidity at high risk of bleeding (Table 7) it may be reasonable to perform coagulation monitoring by specific tests for DOACs the day before or some hours before invasive procedure or surgery (see "Bleeding or thromboembolic event-related hospitalization"). Invasive procedures or surgery should be delayed if coagulation tests demonstrate that activity of DOACs is present in plasma.

In patients who require urgent invasive procedures or surgery, coagulation laboratory tests that are specific for each DOAC, or the measurement of DOACs plasma concentrations might avoid unexpected and severe bleeding episodes, and therefore their execution is suggested. When possible, invasive procedures or surgery should be delayed until coagulation tests that are specific for each DOAC are normalized. Alternatively, a drug-specific antidote should be considered in these patients or when the procedure cannot be further delayed (see "Reversal").

Bleeding or thromboembolic event-related hospitalization

The patient

The clinical management of patients admitted for thrombotic or bleeding events while on treatment with DOACs should be tailored on the severity of clinical presentation. Severity assessment includes both clinical and instrumental parameters (Table 8).

International scales/models for severity assessment can be used for evaluation of bleeding events (Table 9).

Drug discontinuation

In patients admitted for thromboembolic events while on DOACs, anticoagulant treatment should be discontinued in

Table 7 Individual characteristics at high bleeding risk

o ClCr <50 ml/min
o Inherited or acquired coagulation defects
o Liver diseases with coagulopathy or history of previous bleedings
o Thrombocytopenia (platelets count <75.000 mm^3)
o Trauma
o Previous bleedings
o Treatment with concomitant drugs able to increase the bleeding risk such as antiplatelets, FANS, corticosteroids, drugs giving interference with P-gp or CYP3A4)

Table 8 Some clinical and instrumental parameters to be used for the severity assessment of patients with thromboembolic events

Clinical event	Assessment of clinical severity	Instrumental assessment of severity
Ischemic or hemorrhagic stroke	GCS°, NIHSS scale*	Extension and localization of lesion at imaging (CT or NMR)
Myocardial infarction	Hemodynamic status, Killip class	EKG (STEMI/NSTEMI), echocardiography
Pulmonary embolism	Hemodynamic status, clinical criteria (sPESI/PESI)	Echocardiography biomarkers
Critical limb ischemia or systemic embolism	Level of ischemia	Residual vascularization

° *GCS* Glasgow Coma Scale

* National Institute of Health Stroke Scale

Table 9 International scales/models to be used for the severity assessment of bleeding events

Severity of bleeding	Definition
Major	Acute, clinically overt bleeding with at least one among: associated with one of the following:
	Decrease of Hb ≥2 g/dl;
	Transfusion of ≥2 unit of red blood cells;
	Critical site bleeding as intracranial, spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal;
	Fatal bleeding
Clinically relevant non major	Any clinically overt bleeding that does not meet the criteria for major bleed but requires medical attention (e.g.: medical treatment for bleeding), or a change in antithrombotic therapy (including discontinuation or down-titration of study drug), or any other bleeding type considered to have clinical consequences for a patient

Table 10 Management of anticoagulant treatment during surgery or invasive procedures in patients on DOACs

Clinical event	Procedure	Management of anticoagulant treatment
Ischemic stroke	Systemic thrombolysis, percutaneous maneuver	Discontinuation
Transient ischemic attack	No procedure	No clear evidence in favor of discontinuation
Hemorrhagic stroke	Neurosurgical evacuation, external ventricle derivation	Discontinuation. Reverse in selected patients
Myocardial infarction	Percutaneous coronary angiography with or without stenting	DOACs discontinuation to be evaluated based on best antiplatelet therapy
Pulmonary embolism	Percutaneous pulmonary revascularization	Consider peri-procedural shift to heparin
	Systemic or loco-regional thrombolysis	Shift to heparin for 24–48 h after thrombolysis
Critical limb ischemia	Thrombectomy	Discontinuation to be evaluated based on the type of revascularization procedure
Systemic embolism	embolectomy	Continuation
Gastrointestinal bleeding	Endoscopic treatment	Discontinuation and reversal
Muscle/retroperitoneal bleeding	Percutaneous embolization	Discontinuation

particular if surgery or invasive procedures are indicated, with the exception of percutaneous procedures (Table 10). These indications are mainly based on clinical judgement, on limited data from patients included in clinical trials with DOACs, and on what is currently known in patients treated with VKAs more than on results from 'ad hoc' clinical trials [2, 41–43].

In the case of ischemic stroke, DOACs should be temporarily discontinued while assessing the need for thrombolytic treatment and the extent of ischemia [2, 41]. Thrombolytic treatment given for an acute ischemic stroke is not associated with an increase in bleeding complications when administered at least 12 h beyond the last dose of DOACs in case series. The timing for resumption of anticoagulation after ischemic stroke is controversial. The risk for recurrent cerebral ischemia is highest during the first two weeks after the acute event as is the risk of haemorrhagic transformation of the ischemic lesion. Current guidelines recommend resumption of anticoagulation after 3 days from minor stroke, and at least 14 days after a major stroke or a stroke with hemorrhagic transformation. These indications are mainly based on results from studies with VKAs and Experts' opinion. In patients with transient ischemic attack, it is conceivable that anticoagulation can be continued with no interruption. Whether the change of oral anticoagulant agent after an ischemic stroke occurring on well-conducted anticoagulation can reduce the risk for recurrent stroke is undefined.

In the case of an acute coronary syndrome, discontinuation of VKAs is not recommended even in patients who are candidatea for percutaneous coronary interventions [2, 42]. Discontinuation of DOACs may be indicated to start safe treatment with new inhibitors of P2Y12. These agents are currently recommended for the treatment of acute coronary syndromes. However, no data is available on the efficacy and safety of combined treatment with DOACs and the new P2Y12 inhibitors. If, based on the risk–benefit ratio, a decision is taken not to start a new P2Y12 inhibitor, treatment with DOACs could be continued for its improved safety profile.

The occurrence of acute pulmonary embolism is rare during anticoagulant treatment. When it occurs, it might be reasonable to shift the patient to an anticoagulant agent with

a different mechanism of action in order to overcome treatment failure.

Discontinuation of DOACs is essential in all patients having major bleeding [2]. The DOACs regimen and time of last dose intake are essential information in this setting, and this is also the case for the presence of remedial causes or predisposing factors for bleeding. Red blood cells and fresh frozen plasma should be administered based on the estimated loss of volume, and the source of bleeding should be controlled if indicated, as in patients with non-anticoagulant-associated bleeding. Active charcoal can be useful in case of last intake within the last 2 h. In patients with major bleeding, reverse strategies will be used in case of (a) last DOAC intake in the last 12 h, or (b) last DOAC intake in the last 24–48 h in the presence of renal failure (and up to 96 h in patients taking dabigatran or in patients with severe renal failure i.e. creatinine clearance <30 ml/min), or c) persistent bleeding. It is possible that the availability of laboratory tests aimed at measuring DOACs plasma levels or their anticoagulant activity are of use in the case of patients with persistent bleeding or in those with severe renal failure.

Patients with minor bleeding can be managed as outpatients; in patients with clinically relevant non-major bleeding, the need for hospitalization should be evaluated on an individual patient basis.

Reversal

Given the short half-life of DOACs, most bleeding complications—mainly if minor or clinically relevant non-major—can be safely managed only by treatment discontinuation.

Pharmacological reversal of anticoagulation is indicated in life-threatening bleeding (intracranial or in critical site), and in the case of emergency surgery. Besides the site of bleeding, the assessment of the severity of bleeding and of the need for reversal therapy should also take into account hemodynamic status, time from last DOAC intake and renal function.

Reversal therapy is different for different DOACs. Active charcoal can be administered if indicated.

Reversal strategies

Prothrombin complex concentrates (PCC) with 3 or 4 factors

No controlled study exists that has evaluated the role of PCCs in the management of anticoagulants-associated bleeding. However, PCCs are currently considered the more effective strategy for the management of bleeding associated with VKAs. Even in the absence of conclusive evidence, 4-factors PCCs are preferred over 3-factors PCCs due to the higher concentration of factor VII.

Studies in healthy volunteers find 25–50 UI/Kg to be the optimal dose [48–52].

Activated prothrombin complex concentrates (aPCC)

These agents should be used for reversal only in patients with persistent life-threatening bleeding due to the increased thrombotic risk associated to their administration. Studies in healthy volunteers find 50 UI/Kg to be the optimal dose [49, 52].

Recombinant activated Factor VII (rFVIIa)

Although included in EHRA recommendations [2], this agent should not be used for the management of DOAC-associated bleeding. Indeed, rFVIIa fails to reduce the expansion of dabigatran-associated cerebral hematoma in animal models, and is associated with an increased risk for arterial thrombosis when used in non-hemophilia patients.

Fresh frozen plasma (FFP)

There is apparently no role for FFP in the reversal of DOACs. Moreover, no efficacy studies are currently available.

Dialysis

Circulating dabigatran has low affinity for plasma proteins, and is only 35% albumin bound, while apixaban, rivaroxaban and edoxaban have a high degree of affinity for albumin. Based on these features, dialysis is effective to clear dabigatran from plasma while it is ineffective for apixaban, rivaroxaban and edoxaban [53].

Tranexamic acid

No evidence exists on the role of this agent in the management of DOAC-associated major bleeding. However, tranexamic acid reduces mortality in patients with trauma and reduces blood loss due to surgery. Thus, its use can be considered in association with PCCs. The optimal dose is: 15–30 mg/kg i.v. 3–4 times daily. It may be used for 2–4 days.

Antidotes Specific antidotes, with rapid (few minutes) neutralization of DOACs pharmacological effect have been successfully tested in Phase3 clinical studies. These are idarucizumab for dabigatran and andexanet alpha for anti-Xa agents [54, 55].

Idarucizumab is the Fab of a monoclonal antibody directed against dabigatran with 350 folds higher affinity

than that of dabigatran for thrombin; it is approved by FDA and EMA for emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding, and is now available for clinical use [54]. The recommended dose of idarucizumab is 5 g, administered i.v. in two separate doses by 2.5 g each, overall diluted in 100 mL of solvent. Limited data supports administration of an additional dose of 5 g of the antibody. In currently available clinical studies, the use of idarucizumab is tailored on clinical presentation and not on laboratory measurements. However, the use of specific tests to measure dabigatran concentration in plasma (diluted thrombin time, ecarin thrombin time with specific reference) before proceeding with idarucizumab treatment may be an option in case these tests are rapidly available, and their use will not delay the administration of a potentially life-saving antidote.

Andexanet alpha is a recombinant factor Xa devoid of the interaction domain with the phospholipid surfaces (GLA domain) and, therefore, able to compete for binding to any anti-Xa without having any procoagulant activity [55]. It has been submitted to FDA for approval.

Ciraparantag (Arapazine, PER 977) is a small hydrophilic molecule that rapidly binds and neutralizes the anticoagulant effect of heparin (UFH and LMWH), fondaparinux, and DOACs (anti-Xa and dabigatran) in vitro and in animals, with no interaction with coagulation factors and other blood proteins. A study performed in healthy volunteers shows the efficacy of ciraparantag and also in reversing the effect of edoxaban [56].

The availability of antidotes for clinical practice can improve the management of DOACs-associated major bleedings.

According to a recent ISTH statement [57] the indications for the use of antidotes are:

- Life-threatening bleeding: intracranial or uncontrollable bleeding with the usual measures.
- Bleeding in an enclosed space or in critical organ;
- Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding due to delayed clearance or overdose of DOACs;
- Emergency interventional procedures, surgery or surgery in patients at high risk of procedural bleeding: neurosurgery, lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), liver or other major surgery.

The laboratory

As is well known, DOACs, differently from VKAs [58], are recommended to be used without laboratory monitoring. Age, body weight, liver and renal function should be used to tailor the dose of DOACs, renal failure being the main factor to be considered [27].

Measuring DOACs: when and why

The role of the laboratory in the management of antithrombotic treatment might be that of "monitoring" or of "measuring." Monitoring, that is the assessment of the anticoagulant effect of the drug used for dose adjustment based on a therapeutic range, is not necessary for DOACs. Measurement is the evaluation of the anticoagulant effect of the drug, used to assess the degree of anticoagulation. It may be useful in particular conditions, such as in case of severe bleeding, because such value could be used for decision making on the use of specific antidote [51, 52]. Also in the case of emergency surgery, the knowledge of plasma concentration of DOACs might be of value to set the timing of surgery. Besides emergencies, measuring plasma concentration of DOACs mght be useful in patients with advanced age (>80 years.), chronic mild to moderate renal failure, concomitant treatment with cardiovascular agents that can significantly alter the plasma concentrations of DOACs, and in case of bleeding or thrombotic complications. Actually, a large inter-individual variability has been observed in plasma trough levels of dabigatran [27] and rivaroxaban [59], after about one week of treatment with standard doses. The inter-individual variability in the concentration of dabigatran is about 40% [60].

The clinical situations in which laboratory measurements may be useful for DOACs therapy are [61–63]:

- Before surgery/invasive procedures;
- When antidotes are administered;
- When thrombolytic treatment (for ischemic stroke) is needed.

Lab tests and the DOACs

No consensus exists on the laboratory tests to be recommended in clinical practice for the measurement of DOACs and their effect. A laboratory test simple to perform and widely available with a close correlation with the clinical activity of DOACs has not yet been developed.

There is an effect of DOACs on the common coagulation tests, but with no clear correlation with their actual anticoagulant effect [62, 63]:

a) antithrombin activity: overestimation of antithrombin activity in rivaroxaban-, apixaban- or dabigatran-treated patients is probable if the test is based on factor Xa or thrombin;

b) fibrinogen: underestimation either by Clauss method and by PT method in dabigatran-treated patients;
c) activated Protein C resistance: DOACs can alter the results;
d) Factor XIII activity: underestimation possible with chromogenic tests in dabigatran-treated patients.

Which test for DOACs?

Unfortunately, an ideal test, offering both accuracy and precision for measurement of any DOAC is not widely available. The use of a dilute thrombin time assay or ecarin-based assay are recommended for assessment of the anticoagulant effect of dabigatran and anti-Xa assays with drug-specific calibrators for assessment of the anticoagulant effects of direct Xa inhibitors. In the absence of these tests: thrombin time or APTT are recommended over PT/INR for assessment of dabigatran and PT/INR is recommended over APTT for detection of factor Xa inhibitors (more details are reported in Tables 11 and 12 for dabigatran and FXa inhibitors, respectively).

Table 11 Features of main tests for the measurement of dabigatran

Feature	Test				
	Anti-thrombin	APTT	PT	ECT*	dTCT§
Availability	–	+	+	+	+
Dose–response curve	–	±#	+	+	+
Standardization	–	–	–	?	?
Drug response°	–	+	–	+	+

* *ECT* ecarin clotting time

§ *dTCT* diluted thrombin clotting time

° Drug response: slope of the linear curve, which correlates the biological response with the concentration

Linear only at low-medium concentrations of dabigatran

Table 12 Features of main tests for the measurement of rivaroxaban

Feature	Test				
	Anti-FXa	APTT	PT	Heptest	dRVVT§
Availability	–	+	+	+	+
Dose–response curve	+	+*	+	–	–
Standardization	–	–	+§	?	?
Drug response°	+	+	+	+	+

* Linear only at concentrations >100 ng/ml [62]

§ Available but requires validation by regulatory agencies [64]

° Drug response: slope of the linear curve, which correlates the biological response with the concentration

Dabigatran

The dTCT and the ECT tests are the best tests to measure dabigatran induced anticoagulation. A through level of dabigatran between 90 and 140 ng/mL seems to have the best risk/benefit ratio [62].

Rivaroxaban

Based on currently available evidence, anti-Xa tests with plasma calibration for rivaroxaban concentration and the PT are the best tests to measure rivaroxaban induced anticoagulation.

Apixaban

Limited laboratory data are currently available for this agent. Conflicting results have been obtained concerning the correlation between PT or aPTT and plasma levels of apixaban [65, 66]. Anti-Xa test seems to have the best correlation with plasma levels of apixaban [67]. Standardization is needed before this test can be used to measure apixaban induced anticoagulation.

Edoxaban

Classical anti-Xa activity of edoxaban is linear across a broad range of drug levels, and may be used for edoxaban quantification in plasma. Anti-Xa activity increased in a concentration-dependent linear fashion.

The assay shows greater variability at above on-therapy drug concentrations [67–70]. PT is less sensitive to edoxaban. A normal PT may not exclude clinically relevant on-therapy drug levels. Finally, APTT does not reach a sufficient sensitivity to edoxaban for measurement of its anticoagulant activity [70].

Conclusions

The DOACs are increasingly used in clinical practice, in particular for the prevention of stroke or systemic embolism in AF patients, and for the treatment and long-term secondary prevention of VTE. As such, the prescription and management of these agents has rapidly become standard of practice for most internists. Despite

the undisputable advantages, the DOACs require a thorough understanding of their pharmacokinetic and pharmacodynamic characteristics to ensure their correct use. This knowledge allows the selection of the right molecule and the right dosage, the application of the correct follow-up strategies, and the appropriate management of patients experiencing adverse events. This is particularly crucial during hospitalization on Internal Medicine wards, where the large majority of patients can be defined as "fragile". This knowledge also helps hospitals to build adequate protocols for the management of patients on anticoagulant treatment, from the prescription of the drug to its management in the emergency setting. The application of guidance documents shared by scientific societies is the first step towards the development of such protocols. Monitoring the application of these protocols and measuring clinical outcomes in "real life" settings is the necessary next step that should be pursued by all clinicians and scientists.

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Compliance with ethical standards

Conflict of interest DP declares fees for participations in editorial boards and lectures by Bayer, Boehringer Ingelheim, BMS-Pfizer and Daiichi Sankyo given to his Institution. WA declares research support by Bayer and Boehringer Ingelheim; he also declare participation in advisory boards for Bayer, Boehringer Ingelheim, Daiichi Sankyo and BMS-Pfizer. CB declares speakers' fees by Bayer, Bristol Meyer Squibb and Boehringer Ingelheim. AD declares speakers' fees by Bayer, Boehringer Ingelheim, BMS-Pfizer and Daiichi Sankyo given to his Institution. FD declares a consultance activity for Bayer and Boehringer Ingelheim and participations in advisory boards of Boehringer Ingelheim, BMS-Pfizer. AF declare a role of speakers' bureau for Pfizer, Aspen and Rovi. GP declares participation in advisory board or speakers' fees by Alfa-Wassermann, Daiichi-Sankyo, Pfizer, Roche, Siemens and Werfen. PP declares speakers' fees by Bayer, Boehringer Ingelheim, BMS-Pfizer and Daiichi Sankyo FS declares fesearch support by Bayer. GD, RD, GDM, GG, LM, RMS, MS, AT, FV declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

Appendix

Trial	Exclusion criteria
RELY	History of heart valve disorder (i.e. prosthetic valve or hemodynamically relevant valve disease)
ROCKET	Hemodynamically significant mitral valve stenosis. Prosthetic heart valve. Annuloplasty with or without prosthetic ring, commissurotomy, or valvuloplasty permitted
	Planned invasive procedure with potential for uncontrolled bleeding, including major surgery (i.e. heart valve surgery)
ARISTOTELE	Moderate or severe mitral stenosis, conditions other than atrial fibrillation that require anticoagulation (e.g. a prosthetic heart valve)
ENGAGE AF	Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves or valve repair could be included)

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