Direct oral anticoagulants: a guide for daily practice

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Summary

In recent years, small oral compounds that specifically block activated coagulation factor X (FXa) or thrombin (FIIa) have become alternatives to the anticoagulants that had been used for several decades. As of today, these direct oral anticoagulants (DOACs) include dabigatran etexilate (thrombin inhibitor) and apixaban, edoxaban and rivaroxaban (inhibitors of FXa). While there is no doubt that DOACs represent a major step forward in the management of patients with venous thromboembolic disease and atrial fibrillation, new challenges have arisen. They need to be addressed with the necessary pragmatism on the basis of evidence. Indeed, a better understanding of the management of these last-generation antithrombotics will favour safer use and increase confidence of the practitioner for the prescription of these drugs. The aim of this article is to present practical suggestions for the prescription and use of these drugs in everyday clinical practice, based on clinical experience and recently updated recommendations of the European Heart Rhythm Association and the American College of Chest Physicians among other scientific organisations. We address issues such as pharmacokinetics, dosing, side effects, limitations of use, drug interactions, switching from and to other anticoagulants, renal function, concomitant administration of antiplatelet agents and perioperative use. We also address the issue of monitoring and reversal, taking advantage of the most recent development in this latter area. Rather than being one additional set of recommendations, our narrative review aims at assisting the practicing physician in his or her daily handling of these novel anticoagulant compounds, based on frequently asked questions to the authors, a group of experienced specialists in the field who have, however, no commitment to issue guidelines.

Key words: anticoagulant treatment; dabigatran etexilate; rivaroxaban; edoxaban; apixaban, thrombin; recommendations

Introduction

Over the past few years, direct oral anticoagulants (DOACs) have emerged as the first orally administered alternatives to vitamin K antagonists (VKAs) [1]. As opposed to VKAs, DOACs are direct and specific inhibitors of a single coagulation factor. The two main targets of DOACs are thrombin, also called activated factor II (FIIa) and activated factor X (FXa). Large scale phase III trials in venous thromboembolism (VTE) prophylaxis in orthopaedic surgery, in VTE treatment, in secondary prevention of VTE recurrence, and in atrial fibrillation have proven the efficacy and safety of these drugs. Overall, DOACs are at least as effective as standard treatment in all the above-mentioned indications, and are at least as safe as, or even safer than, standard treatment in terms of bleeding risk.

To date, four DOACs have been approved by Swissmedic (the Swiss Agency for Therapeutic Products): one FIIa inhibitor (dabigatran) and three FXa inhibitors (rivaroxaban, apixaban, edoxaban). With their large-scale introduction in clinical practice after approval in Europe and North America, new challenges have arisen regarding their use in everyday clinical practice. As many review papers have already been published regarding detailed pharmacological considerations and results of the main phase III trials, these will not be discussed here in detail. The aim of this article is thus rather to present practical suggestions for the prescription and use of these drugs in everyday clinical practice. In order to convey a clear and uniform message, some simplifications were necessary, and are discussed hereafter in each section.

Indications

DOACs have been studied in various clinical settings: VTE prophylaxis in medical inpatients [2, 3] and in major orthopaedic surgery patients [4–16], treatment of acute VTE [17–22], long term prevention of VTE recurrence [18, 22–24], prevention of thromboembolic events in patients with atrial fibrillation [25–28], and in acute coronary syndromes in association with antiplatelet agents [29, 30]. Results of phase III trials have not been encouraging in VTE prevention in acutely ill medical inpatients and in patients with acute coronary syndrome, in whom an excessive bleeding rate was observed. Therefore, DOACs have not been approved for use in these patients. In Switzerland, DOACs and indications that have received Swissmedic approval to date are, in chronological order:

– rivaroxaban, apixaban for VTE prophylaxis in major orthopaedic surgery;

– rivaroxaban, dabigatran, apixaban, edoxaban for VTE treatment;
– rivaroxaban, dabigatran, apixaban, edoxaban for the long term prevention of VTE recurrence;
– dabigatran, rivaroxaban, apixaban, edoxaban for atrial fibrillation.

Pharmacokinetics

As already mentioned in the introduction, DOACs are *direct* and *specific* inhibitors of a single coagulation factor, the two main targets being FIIa and FXa. Numerous review articles have already been published including detailed information on the pharmacological characteristics of DOACs [31–33]. Here, we would like to highlight pharmacological properties that have the highest clinical significance and an impact on the prescription of these drugs.

DOACs share many common pharmacokinetic properties (table 1). First of all, all DOACs have a rapid onset of action after oral ingestion, with a peak plasma level reached in approximately 2 to 4 hours. Second, all have rather short half-lives of approximately 8 to 12 hours. Third, as opposed with VKAs, they are not subject to food interactions, although some need to be taken with food to enhance absorption (see below). Fourth, drug interactions are overall minimal compared with VKAs, and will be discussed hereafter.

DOACs differ in some important pharmacokinetic properties. First, bioavailability varies widely. All FXa inhibitors are lipophilic drugs and have high bioavailability after oral ingestion, of approximately 50% for apixaban and edoxaban, and 80% for rivaroxaban. Notably, therapeutic doses of the latter need to be ingested with food for optimal absorption. In contrast, dabigatran has low oral bioavailability. Indeed, dabigatran itself is a hydrophilic molecule that cannot be absorbed in the intestinal tract. Therefore, it needs to be administered as a prodrug, dabigatran etexilate, whose oral availability is less than 10%. Also, since an acid microenvironment is required to improve solubility and absorption of dabigatran etexilate, the capsule formulation includes a tartaric acid core together with the prodrug.

Another important pharmacokinetic difference between FXa inhibitors and FIIa inhibitor is the metabolic pathway. Absorption of all DOACs is influenced by intestinal P-glycoprotein (P-gp). However, whereas metabolism of dabigatran does not depend on the cytochrome P450 pathways, the FXa inhibitors are all metabolised by the cytochrome CYP3A4 to varying extents. These differences have an impact in terms of significant drug interactions, as discussed below.

Finally, renal impairment has a different influence on the pharmacokinetics of FXa inhibitors and FIIa inhibitor. Figures regarding the percentage of renal elimination of FXa inhibitors vary in different articles [33–35]. Indeed, whereas some authors focus on the renal elimination of the active form only, others mention the overall renal elimination including active and inactive metabolites. Moreover, debate persists as to whether the percentage of renal elimination of the ingested drug or of the absorbed active drug should be considered. Therefore, and once again in order to simplify the practical message, we decided to give a very broad approximation of the renal elimination, more than 80% for dabigatran and around 50% (or even less) for FXa inhibitors. Indeed, it seemed more important to us to emphasise the major clinically significant difference between dabigatran and FXa inhibitors in a simple message: dabigatran is mainly eliminated by the kidneys, whereas FXa inhibitors are not. In the setting of this article, subtle differences between FXa inhibitors in percentages of renal elimination did not seem relevant, especially when considering the wide interindividual variation of the pharmacokinetic profile.

Dosing

The Swissmedic-approved dosages suggested in our recommendations (table 2) strictly adhere to the doses used in phase III trials, with the exception of the reduced dose of dabigatran (110 mg b.i.d) in the treatment and secondary prevention of VTE in patients with moderate renal impairment. This choice was made in order to be in line with the doses recommended by the Swiss compendium for patients with an increased bleeding risk. Of note, this dosage recommendation is based on pharmacokinetic studies [36].

Regarding dosing in patients with renal failure, we would like to emphasise that all phase III trials excluded patients with severe renal impairment, the exclusion cut-off being almost always based of the estimation of creatinine clearance calculated by use of the Cockcroft-Gault formula (CrCl C-G). In clinical practice, the CrCl C-G should thus

Table 1: Pharmacological properties of direct oral anticoagulants.

Characteristics	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Direct target	Factor Xa			Factor IIa (thrombin)
Need for monitoring	No			
Pro-drug	No	No	No	Yes
Bioavailability	>80%	≈50%	≈50%	≈6%
Time to reach peak plasma concentration (hours)	2–4	2–3	1–2	2–3
Half-life (hours)	5–13	8–15	6–11	14–17
Metabolism	P-gp CYP3A4/3A5 CYP2J2	P-gp CYP3A4/3A5	P-gp (CYP3A4)	P-gp
Renal elimination*	≈50%			>80%
P-gp = P glycoprotein * See text for details.				

be used to adapt dosing, rather than other formulas such as the Modification of Diet in Renal Disease (MDRD) [37]. At therapeutic dose, the most commonly used cut-off in phase III trials was 30 ml/min. A lower CrCl C-G was accepted for including patients in some phase III trials studying prophylactic doses after major orthopaedic surgery or in a study using therapeutic doses in patients with atrial fibrillation. However, in order to avoid confusion, we decided to suggest a contraindication to prescription of DOACs in all patients with CrCl calculated with use of the Cockcroft-Gault formula <30 ml/min, regardless of the molecule and indication.

Dose reductions have been studied in phase III trials for: (1) all DOACs in atrial fibrillation, (2) edoxaban in VTE treatment and (3) apixaban and edoxaban in long-term prevention of VTE recurrence. Criteria for dose reduction as well as the number of subjects with renal impairment included vary between studies and drugs and have been detailed in table 2. Only those patients with the corresponding criteria should be prescribed a reduced dose.

Two other noteworthy points on initiating DOACs in the acute phase of VTE are: (1) with dabigatran and edoxaban, the necessity to administer initial parenteral anticoagulation for at least 5 days before introducing the oral medication [17, 21], and (2) the necessity of a higher-dose treatment during the initial 7 days for apixaban (10 mg b.i.d.) and the initial 21 days for rivaroxaban (15 mg b.i.d.) [18–20]. Apart from the initial phase of acute VTE, which requires specific regimens of higher-dose treatment, some DOACs have been approved for once daily (o.d.) and others for twice daily (b.i.d.) prescription in all indications in spite of their similar half-lives (see table 2 for details).

Recommendations regarding drug intake and switch from or to a vitamin K antagonist, heparin or fondaparinux

In the event of a missed dose of DOACs prescribed once a day, we suggest taking the missed dose on the same day as soon as possible and continuing with the regular dosing schedule the following morning. A missed dose should not be taken on the day after (avoid double dosing). For DOACs prescribed twice a day, we suggest carrying over the missed dose until 6 hours before the scheduled next dosing.

Switching from low molecular weight heparin (LMWH) to a DOAC or vice versa is relatively easy since both anticoagulants have a similar pharmacokinetic profile. Indeed, the first dose of DOAC is to be given when LMWH is normally scheduled and vice versa. Similarly, the same switching pattern applies with fondaparinux. Regarding unfractionated heparin, the DOAC should be given when the unfractionated heparin infusion is stopped. To switch from a DOAC to unfractionated heparin, the parenteral anticoagulant should be started when the DOAC dose is scheduled. Of note, a prolonged delay between the last dose of DOAC and the start of unfractionated heparin may be necessary in cases of renal failure. Moreover, the anti-Xa assay per-

Table 2: Dosing of direct oral anticoagulants in clinical practice.

Indication	CrCL C-G (ml/min)*	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
VTE prevention in major orthopaedic surgery	≥30	10 mg o.d.; 1st dose 6–10 hrs after surgery	2.5 mg b.i.d.; 1st dose 12–24 hrs after surgery	Not approved in Switzerland	Not approved in Switzerland
	<30	Contraindicated†	Contraindicated		
VTE treatment	≥50	15 mg b.i.d. for the first 21 days, then 20 mg o.d., with food	10 mg b.i.d. for the first 7 days, then 5 mg b.i.d.	Parenteral AC for 5 days, then 60 mg o.d. [30 mg o.d. if weight ≤60 kg and/or concomitant use of strong P-gp inhibitors]	Parenteral AC for 5 days, then 150 mg b.i.d.
	30–49	15 mg b.i.d. for the first 21 days, then 20 mg o.d., with food	10 mg b.i.d. for the first 7 days, then 5 mg b.i.d.	Parenteral AC for 5 days, then 30 mg o.d.	Parenteral AC for 5 days, then 110 mg b.i.d.‡
	<30	Contraindicated	Contra-indicated	Contraindicated	Contra-indicated
Long-term prevention of VTE recurrence	≥50	20 mg o.d., with food	2.5 mg b.i.d.	60 mg o.d. [30 mg o.d. if weight ≤60 kg and/or concomitant use of strong P-gp inhibitors]	150 mg b.i.d.
	30–49	20 mg o.d., with food	2.5 mg b.i.d.	30 mg o.d.	110 mg b.i.d.‡
	<30	Contraindicated	Contraindicated	Contraindicated	Contra-indicated
Prevention of arterial thromboembolic events in patients with nonvalvular AF	≥50	20 mg o.d., with food	5 mg b.i.d.	60 mg o.d. [30 mg o.d. if weight ≤60 kg and/or concomitant use of strong P-gp inhibitors]	150 mg b.i.d. [110mg b.i.d. if age ≥80 yrs]
	30–49	15 mg o.d., with food	5 mg b.i.d. [2.5 mg b.i.d. if one or more of the following: age >80 yrs, weight <60 kg]	30 mg o.d.	110 mg b.i.d.
	<30	Contraindicated	Contraindicated	Contraindicated	Contraindicated

AC = anticoagulation; AF = atrial fibrillation; b.i.d. = twice daily; o.d. = once daily; P-gp = P-glycoprotein; VTE = venous thromboembolism.
* Renal function (creatinine clearance) estimated with the Cockcroft-Gault formula; ClCr C-G (ml/min) = [(140-age) x weight/creatinine level] x k. k in men 1.23; k in women 1.03.
† The lower limit of CrCL set at 15 ml/min suggested in the Swiss Compendium seems too risky to us.
‡ Dose not tested in phase III trials but based on pharmacokinetic studies.

formed to monitor unfractionated heparin may be influenced by residual oral anti-Xa activity from FXa inhibitors (rivaroxaban, apixaban or edoxaban) during at least the 24 to 36 hours after the last DOAC dose.

When switching from VKAs to DOACs, the first dose of DOAC may be started as soon as the prothrombin time international normalised ratio (INR) is ≤2, usually 24 to 72 h after discontinuing VKA, depending on the VKA half-life. In some instances, when the thrombotic risk is high (recent thromboembolic event) and the bleeding risk is low, starting the first dose of DOAC with an INR <2.5 may be considered [38]. Switching from a DOAC to a VKA is more problematic since DOACs may influence the INR result. Therefore, we suggest bridging with LMWH or fondaparinux after DOAC discontinuation for a few days and start the VKA thereafter. If there is no past history of thromboembolic event (such as in atrial fibrillation), VKA could be started straight away after DOAC discontinuation, without bridging with LMWH or fondaparinux.

Limitations of use

As for any new drug, DOACs have not been tested in phase III trials during pregnancy and lactation and in paediatric patients, limiting their prescription in these populations of patients. Hepatic disease, with varying definitions across studies, has also represented an important exclusion criterion in phase III trials. Therefore, we suggest not using DOACs in patients with hepatic cirrhosis (Child-Pugh B and C), and/or with abnormal liver tests (transaminase levels ≥2 times upper limit of the reference range) and/or coagulopathy secondary to hepatic disease.

DOACs are contraindicated in patients with severe renal impairment. For prescription of DOACs in patients with moderate renal impairment, please refer to the section on dosing and to table 2.

Obese patients have been under-represented in clinical trials, with less than 20% of patients with a body weight >100 kg in most trials, and, therefore, the optimal dosing for both safety and efficacy in this subgroup remains unknown [39]. We arbitrarily placed a cut-off at 130 kg above which VKAs should be preferred.

As a general consideration, for the time being, prescription of DOACs should not be extended to indications other than those tested in phase III trials. For example, DOACs have not been tested in some particular clinical situations such as the antiphospholipid syndrome. Results have been disappointing in patients with mechanical heart valves [40] and acute coronary syndrome [29, 30], and no other studies have tested DOACs in arterial thrombosis. VTE studies excluded patients with VTE in unusual sites (splanchnic thrombosis, cerebral vein thrombosis, etc.) and in superficial thrombophlebitis. Moreover, for patients with VTE related to active cancer, LMWH remains the standard of care [22, 41].

Side effects

An obvious "side effect" of any anticoagulant drug is the increased bleeding tendency. Compared with VKAs, DOACs have an equivalent or even better safety profile in terms of their bleeding risk and in terms of patients' outcome in the event of bleeding [42]. The risk of intracranial bleeding, one of the most feared haemorrhagic complications of any anticoagulant, has consistently been shown to be lower with DOACs than with VKAs. Of note, DOACs tend to be associated with a modest but significantly higher risk of gastrointestinal bleeding [43] and of abnormal uterine bleeding [44].

General side effects are reported in all DOACs (nausea, hypersensitivity, etc.). Dabigatran is associated with significant dyspepsia (around 10% of patients) and abdominal pain (1–10% of patients) related to its formulation with tartaric acid. FXa inhibitors are associated with a higher incidence of rash and prurigo (1–10%) and increased transaminase levels (0.1–1%), although this latter finding was less frequent than with standard treatment (enoxaparin plus warfarin or warfarin alone) in clinical studies. Cases of acute liver failure have been declared in pharmacovigilance reports for every individual DOAC, but most patients had concomitant drugs or diseases [45].

Clinically significant interactions

One of the major obvious advantages of DOACs over VKAs is the markedly decreased frequency of potential drug-drug interactions. So, are there any drugs that should not be used in association with DOACs? Referring to the metabolic pathways discussed above, strong inhibitors or inducers of P-gp and CYP3A4 are of concern in association with DOACs. Of note, many drugs that affect CYP3A4 function also affect P-gp [46]. Moderate or weak inducers or inhibitors of cytochromes or P-gp may theoretically also influence concentrations of DOACs, but because of the wide therapeutic range of DOACs, such interactions do not seem to be clinically relevant.

In clinical practice, dabigatran should not be prescribed in combination with drugs that are strong inhibitors or inducers of the P-gp transporter (such as quinidine, ketoconazole, among others), but also avoided in combination with other drugs that have a significant impact on P-gp function (table 3). FXa inhibitors should not be prescribed in combination with drugs that are strong inhibitors or inducers of the P-gp and CYP3A4 (table 3) and preferably avoided in combination with moderate inhibitors of CYP3A4. Of note, less than 10% of edoxaban seems to be metabolized through CYP3A4. Because of the acid microenvironment needed for dabigatran absorption, proton-pump inhibitors should preferably not be taken at the same hour of the day as dabigatran.

Biological monitoring and influence on coagulation assays

Dosing of DOACs may differ according to the indication and renal clearance as evaluated with the C-G formula. Therefore, a recent creatinine measurement should be available before prescribing a DOAC. As for all anticoagulants, haemoglobin, haematocrit and coagulation parameters (prothrombin time, activated partial thromboplastin time [aPTT] and fibrinogen) should be performed. Finally,

liver function tests may be indicated before prescribing a DOAC in some patients if a liver failure is suspected.

During the follow-up of patients treated with DOACs, haemoglobin and creatinine levels should be measured at least once a year, and more often in patients at risk of renal failure such as elderly patients or those with nephrotoxic medications. The creatinine level should also be measured in the event of an acute illness that could alter renal function (acute infection, diarrhoea, dehydration, etc.). There is no need to quantify DOACs on a routine basis. Indeed, there is no "therapeutic range" for DOACs, and dosing should not be adapted to any coagulation parameter. Coagulation parameters may be influenced by DOACs, depending on the reagents used. Coagulation tests such as prothrombin time or aPTT may therefore differ according to the laboratory. Several other coagulation assays are influenced by DOACs, such as thrombophilia screening tests (activity of antithrombin, protein C, protein S or lupus anticoagulant, for example). Of note, genetic testing and antigenic assays are not influenced by DOACs (table 4).

Bleeding events

Since DOACs have a short half-life, time is an efficient way to eliminate the anticoagulant effect and most mild or moderate bleeding events can be managed with local treatment and skipping one or more doses, if necessary. When a major bleed occurs, optimal management remains uncertain [47]. Most studies of DOAC reversal agents were performed in healthy volunteers using laboratory coagulation endpoints, or in animal models. Moreover, the available data are mostly related to rivaroxaban and dabigatran, with few data regarding apixaban and edoxaban. Thus, recommendations regarding bleeding management result more from experts' opinions than from clinical experience. For example, the European Heart Rhythm Association [38] provided an updated guidance that may help the practitioner in managing bleeding events in patients treated with DOACs. Oral activated charcoal may be considered within the first 6 hours after ingestion of the DOAC. Haemodialysis is effective for the removal of dabigatran, but not to remove the other DOACs. When a life-threatening bleed occurs, nonspecific agents such as prothrombinic complex concentrate (PCC, 25–50 U/Kg) or activated PCC (30–50 U/Kg) should be considered in addition to the standard protocol of massive bleeding management.

Nevertheless, use of these latter agents remains relatively rare [48], and the outcome of major bleeding in patients treated with DOACs does not differ from that of those treated with VKA [49, 50], probably because of the short

Table 3: Clinically relevant drug-drug interactions with oral FXa inhibitors (A) and oral FIIa inhibitor (B).

A. Significant interactions with FXa inhibitors rivaroxaban, apixaban, edoxaban*		
Recommendation	CYP3A4/P-gp inhibitors ↑ AUC	CYP3A4 inducers ↓ AUC
	Strong	Strong
Association contraindicated	Antifungal treatment (ketoconazole, itraconazole, voriconazole, posaconazole) HIV protease inhibitors (ritonavir)	Rifampicin Phenytoin, carbamazepine St. John's wort
	Strong / moderate	
Avoid association	Clarithromycin	
No clear recommendation	Erythromycin Diltiazem	
B. Significant interactions with FIIa inhibitor dabigatran*		
Recommendation	P-gp inhibitors ↑ AUC	P-gp inducers ↓ AUC
Association contraindicated	Quinidine Antifungal treatment (ketoconazole, itraconazole) Immunosuppressive drugs (ciclosporin, tacrolimus)	
Avoid association	Amiodarone Verapamil Ritonavir Clarithromycin	Rifampicin Phenytoin, carbamazepine St. John's wort

AUC = area under the plasma concentration-time curve; HIV = human immunodeficiency virus; P-gp = P-glycoprotein
* Lists are not exhaustive. Check for potential interactions with any individual concomitant medication.

Table 4: Effect of direct oral anticoagulants on routine haemostasis assays and thrombophilia screening.

Assay	Rivaroxaban, apixaban, edoxaban	Dabigatran
aPTT	↑	↑
Prothrombin time	↓	↓
Fibrinogen	↔	↓
Thrombin time	↔	↓
Anti-Xa activity	↑	↔
Anti-IIa activity	↔	↑
Genetic analysis	Possible	
Antithrombin, proteins C and S (activity)	Not possible (false negative)	
Lupus anticoagulant	Not possible (false positive)	
Anticardiolipin and anti-B2GP1 antibodies	Possible	

aPPT = activated partial thromboplastin time; B2GP1 = β2 glcoprotein-1

half-lives of DOACs and their wide therapeutic windows. The necessity for specific antidotes is therefore questionable [51, 52], but the general consensus is still in favour of their development. Indeed, the possibility to rapidly antagonise the effect of DOACs may probably be beneficial in some instances and is certainly reassuring for the long-term prescription of these compounds [53].

Idarucizumab (Praxbind®, Boehringer Ingelheim), a humanised mouse antibody fragment that specifically targets dabigatran, is the first specific antidote that will be available in 2016. Clinical data show that idarucizumab rapidly normalises coagulation times in a few minutes, with a clinically significant effect on haemostasis in patients undergoing urgent surgery [54].

Andexanet alpha (Annexa®, Portola Pharmaceuticals) is a recombinant protein similar to factor Xa without any procoagulant activity but with a strong affinity for factor Xa inhibitors [55]. Preliminary data in healthy volunteers taking apixaban or rivaroxaban show a rapid and effective biological effect [56]. This compound may also reverse the effect of other anticoagulant drugs with anti-Xa activity such as fondaparinux [55]. Adexanet alpha should become available by the end of 2017.

Finally, ciraparantag (PER977) is a compound that binds directly to several anticoagulants such as unfractionated heparin, LMWH and DOACs (anti-FXa and anti-FIIa), removing them or preventing them from binding to their respective targets [53]. Thus, ciraparantag could be considered as a potential universal antidote for several different classes of anticoagulant drugs [53]. Phase III trials are, however, still needed.

Association with antiplatelet drugs

The combination of antiplatelet drugs and anticoagulation is associated with an increased bleeding risk. Subgroup analyses of phase III trials show that when antiplatelet agents are combined with anticoagulation, the bleeding risk increases by roughly 60%, regardless of the anticoagulant treatment (VKA or DOAC) [57–59]. These data relate mostly to aspirin and/or clopidogrel and clinical experience with next-generation anti-P2Y12 inhibitors such as prasugrel or ticagrelor in addition to DOACs is scarce. Therefore, when antiplatelet therapy is indicated, we suggest using aspirin and/or clopidogrel in addition to DOACs. Of note, use of antiplatelet drugs in addition to anticoagulation should be restricted to patients with recent stent placement and/or an acute coronary syndrome, and may be stopped after 1 year of treatment in most instances [60].

Perioperative management

Characteristics of DOACs prompt different management in the perioperative setting compared with that of patients treated with VKA.

First, the onset of action of DOACs is fast (around 2 hours), and their half-life is shorter than VKAs and similar to LMWH. Therefore, bridging with heparin should be exceptional and restricted to patients with a high thrombotic risk such as those with venous thrombotic event (<3 months) or atrial fibrillation with recent stroke or transient ischaemic attack (<3 months) undergoing a high bleeding risk procedure. Second, the elimination of DOACs depends on renal function, especially for dabigatran (>80%). The evaluation of renal clearance is therefore of utmost importance for determining the appropriate delay between the last dose and the intervention.

Table 5 details the perioperative management of DOACs according to bleeding risk and renal clearance. A low bleeding risk intervention is defined as an invasive procedure that would be feasible in patients treated with VKA with an INR between 2.0 and 3.0, such as tooth extraction, cataract operation, pacemaker implantation or colonoscopy. High bleeding risk procedures are all other invasive interventions. Of note, neuraxial anaesthesia is also considered a high bleeding risk procedure.

Conclusion

DOACs represent a major step forward in the management of patients with VTE disease and atrial fibrillation. After the promising results of phase III trials, growing post-marketing clinical experience has been acquired over the last few years with rather reassuring data regarding "real life" patients [48]. Subgroup meta-analyses do not raise any red flag for fragile patients such as elderly patients [61] or patients with mild renal insufficiency [62, 63]. However, particular caution should still apply to these patients, especially if they present cumulative risk factors associated with an increased pharmacodynamic profile such as impaired renal function, low body weight and drug-drug interaction. Moreover, for an efficient and safe use of DOACs, the right dosing of each drug for each indication, the situations requiring dose adjustments and the restrictions of use should be strictly respected. Several issues still remain open such as the possibility to use DOACs in patients with antiphospholipid syndrome or for VTE treatment in cancer patients. No doubt that these issues will find answers, and the use of DOACs will evolve in the near future.

Table 5: Perioperative management with direct oral anticoagulants according to bleeding risk and renal function.

	Low bleeding risk	High bleeding risk		
Before the procedure	No drug intake the day before (D-1, evening only) and the morning (D0) of the procedure*	Apixaban, rivaroxaban Edoxaban	Last dose* D-3†	
		Dabigatran	ClCr >80 ml/min	Last dose* D-3
			ClCr 50–80 ml/min	Last dose* D-4
			ClCr <50 ml/min	Last dose* D-5
After the procedure	Resume in the evening of the procedure or the morning after (at least 6 h after procedure)	Resume a prophylactic dose at least 6 h after the procedure and a therapeutic dose as soon as possible		

ClCr = creatinine clearance (Cockcroft-Gault)
* Whatever the dosing and posology (once or twice a day).
† In some instances, a last dose on D-2 may be considered.

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