



Anticoagulation therapy in France: state-of-the-art in 2020

Georges Jourdi^{1,2}, Alexandre Mansour³, Caroline Vayne^{4,5}, Alexandre Godon⁶, Charles Tacquard⁷, Virginie Siguret^{1,8}, Pierre Albaladejo^{9,10}, Yves Gruel^{4,5}, Isabelle Gouin-Thibault^{11,12}, French Study Group on Hemostasis and Thrombosis (GFHT) & French Working group on perioperative hemostasis (GIHP)

¹Université de Paris, Innovative Therapies in Hemostasis, INSERM, Paris, France; ²Service d'Hématologie Biologique, AP-HP, Cochin Hospital, Paris, France; ³Department of Anaesthesiology and Critical Care, Rennes University Hospital, CIC-Inserm1414, Rennes, France; ⁴Service d'Hématologie Hémostase, Hôpital Trousseau, CHRU de Tours, Tours, France; ⁵EA 7501, Université François Rabelais, Tours, France; ⁶Department of Anaesthesiology and Critical Care, Grenoble Alpes University Hospital, Grenoble, France; ⁷Department of Anesthesia and Intensive Care, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; ⁸Service d'Hématologie Biologique, AP-HP, Lariboisière Hospital, Paris, France; ⁹Department of Anaesthesiology and Critical Care, Grenoble Alpes University Hospital, Grenoble, France; ¹⁰ThEMAS, TIMC, UMR CNRS 5525, Université Grenoble-Alpes, Grenoble, France; ¹¹University of Rennes 1, CIC-Inserm1414, Rennes, France; ¹²Laboratory of Hematology, Rennes University Hospital, Rennes, France

Contributions: (I) Conception and design: G Jourdi, I Gouin-Thibault; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: G Jourdi, I Gouin-Thibault; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Isabelle Gouin-Thibault. University of Rennes 1, CIC-Inserm1414, Rennes, France; Laboratory of Hematology, Rennes University Hospital, Rennes, France. Email: isabelle.gouin@chu-rennes.fr.

Abstract: More than 10 years after the marketing of direct oral anticoagulants (DOAC) in France, significant changes were brought to anticoagulant therapeutic and prophylactic strategies. Today, health professionals need to be aware of the benefit-risk profiles of DOAC as well as of heparin derivatives and vitamin K antagonists (VKA) in order to deal properly with these drugs making therefore sure that the right patient gets the right anticoagulant therapy at the right time. In this review, we briefly go over the anticoagulant drugs available in France in 2020 and briefly outline different management strategies and suggestions of national expert groups.

Keywords: Direct oral anticoagulants (DOAC); vitamin K antagonists (VKA); heparin derivatives; anticoagulant therapy; France

Received: 08 October 2019; Accepted: 14 February 2020; Published: 25 March 2020.

doi: 10.21037/aob.2020.02.04

View this article at: <http://dx.doi.org/10.21037/aob.2020.02.04>

Introduction

Anticoagulant drugs are mainly prescribed for treatment and prevention of venous thromboembolism (VTE) and for stroke and systemic embolism prevention in non-valvular atrial fibrillation (NVAf) patients. Prevalence of NVAf in France is estimated between 1% to 2% of the general population (1), and increases with aging from less than 1% in people below 60 years of age to at least 8% in those above 80 years (2). As well, the incidence and the burden of VTE, which includes pulmonary embolism and deep vein thrombosis are important and increase with age. The

incidence of VTE in the French population was estimated at 184 per 100,000 subjects in 2011 with a mortality rate of 6.2% over a 12-month follow-up (3). Consequently, the number of patients receiving anticoagulant therapy per year is considerable in France, as worldwide, and has a substantial impact on the overall cost of health care. Anticoagulated French patients were estimated above 3 million in 2013 (4). We hence propose in this review to go over the available anticoagulant drugs, their indications and doses, their monitoring strategies, their perioperative management as well as their reversal as proposed by French expert groups.

Anticoagulant drugs: availability and indications

Heparin derivatives

Unfractionated heparin (UFH) is marketed in France as sodium (Heparin sodium Panpharma since March 1977 and Heparin Choay since December 1986) or calcium (Heparin calcium Panpharma since February 1978) salts. UFH is administered either by a continuous intravenous (IV) infusion or subcutaneously (SC) every 8 or 12 hours, respectively. Four low molecular weight heparin (LMWH) compounds are commercialized in France: enoxaparin (Lovenox[®] since April 1987 and Crusia[®] since July 2017), tinzaparin (Innohep[®] since October 1991), dalteparin (Fragmine[®] since December 1987) and nadroparin (Fraxiparine[®] since March 1985 and Fraxodi[®] since May 1998). Heparin derivatives are indicated for treatment of acute phase VTE, extra-cerebral arterial embolisms, acute coronary syndromes (ACS), hemodialysis and VTE prevention. UFH remains the anticoagulant of choice during cardiothoracic surgery with extracorporeal circulation and in case of extracorporeal membrane oxygenation. In most indications, a bolus of 80 IU/kg or 5,000 IU UFH is recommended before administration of IV or SC UFH. The bolus is then followed by an initial dose of 18 IU/kg/h (IV) or 500 IU/kg/24 h in 2 to 3 injections per day (SC) (5). UFH doses are then adjusted preferably according to anti-Xa activity (see below).

LMWH are used either twice daily (100 IU/kg enoxaparin or dalteparin, 85 IU/kg nadroparin) or once daily (171 IU/kg nadroparin, 175 IU/kg tinzaparin, 150 IU/kg enoxaparin).

In 2002, the French authorities issued a contraindication to the use of curative dose of LMWH in patients with severe renal impairment defined as a creatinine clearance (CrCl) calculated using Cockcroft and Gault formula, <30 mL/min. In 2017, modifications of the summaries of product characteristics (SmpC) of enoxaparin and tinzaparin have been proposed (6): enoxaparin may be used in patients with CrCl between 15 and 30 mL/min with dose reduction; full dose tinzaparin may be used in patients with CrCl between 20 and 30 mL/min, with peak anti-Xa measurement to detect accumulation (target anti-Xa: 0.5 to 1.5 IU/mL). Enoxaparin (4,000 IU od), dalteparin (5,000 IU od) and tinzaparin (4,500 IU od) are also prescribed for VTE prevention in medical ill patients. All the 4 available LMWH compounds are prescribed for VTE prevention following surgeries with doses depending on the surgery and the patient's VTE risk (7).

Vitamin K antagonists (VKA)

Three VKA, two coumarin (warfarin and acenocoumarol) and one indane-dione (fludione) derivatives are currently commercialized in France. Warfarin (Coumadine[®]) is available in 2 and 5 mg tablets. Acenocoumarol (Sintrom[®] and Minisintrom[®]) is available in 4 and 1 mg tablets, respectively. Fludione (Previscan[®]) is available in 20 mg tablet in France (8). Outside France, fludione exists only in Luxembourg and Switzerland. Fludione is the most prescribed VKA in France since decades, but in February 2019, the French National Authority for Health prohibited the prescription of fludione in VKA naïve patients due to the risk of immuno-allergic, nephro- and hepato-toxic side effects during the first 6 months of its administration (9). VKA were until recently the primary cause of hospitalization due to drug adverse events in France, inducing about 5,000 deaths per year due to bleedings (10). Since the commercialization of direct oral anticoagulants (DOAC), the prevalence of VKA treatment has been continuously decreasing (11). Indeed, a recent repeated cross-sectional study conducted between 2011 and 2016 revealed a steady decrease in VKA use from 56.6% to 40.8% of all NVAf included patients (12). French patients treated with VKA were estimated around 928,772 in the beginning of October 2016 (11) with 82% receiving fludione, 13% warfarin and 5% acenocoumarol. Among all oral anticoagulant new users in 2016, 33.7% were prescribed a VKA according to Maura *et al.* (12). Thus in 2016, VKA remained in France the most prescribed oral anticoagulant for NVAf patients aged above 75 years and for those with a history of arterial thrombotic events or with a high hemorrhagic risk (12). This was also the case for patients included in the non-interventional cross-sectional multicenter French study of routine clinical practice (PAROS study; published in 2019) in which VKA therapy was more common than DOAC among patients with higher bleeding risk and/or worse renal function (13).

French authorities recommended coumarin derivatives or DOAC as first-line anticoagulant drugs for stroke and systemic embolism prevention in patients with NVAf, while DOAC were recommended over VKA in eligible patients by the European Society of Cardiology (14). Noticeably, VKA remain the unique oral anticoagulants recommended in atrial fibrillation (AF) patients with mechanical heart valves in France (8).

Table 1 Current DOAC indications and doses in France (8)

Indications	Dabigatran etexilate (Pradaxa [®])	Rivaroxaban (Xarelto [®])	Apixaban (Eliquis [®])
Presentation	75, 110 & 150 mg; capsules	10, 15 & 20 mg; tablets	2.5 & 5 mg; tablets
VTE prevention following THRS or TKRS	220 mg od; 150 mg od*; THRS 28–35 days; TKRS 10 days; reimbursable at 30%; since March 2008	10 mg od; THRS 35 days; TKRS 14 days; reimbursable at 65%; since September 2008	2.5 mg bid; THRS 32–38 days; TKRS 10–14 days; reimbursable at 65%; since May 2011
VTE treatment and prevention	150 mg bid; 110 mg bid [†] ; not reimbursable; since June 2014	15 mg bid for 3 weeks then 20 mg od; reimbursable at 65%; since November 2012	10 mg bid for 7 days then 5 mg bid; reimbursable at 65%; since July 2014
Stroke and systemic embolism prevention in NVAF patients [§]	150 mg bid; 110 mg bid [†] ; reimbursable at 30%; since August 2011	20 mg od; 15 mg od [‡] ; reimbursable at 65%; since December 2011	5 mg bid; 2.5 mg bid [‡] ; reimbursable at 65%; since November 2012

[§], with at least one additional risk factor: previous stroke or transient ischemic attack, age ≥ 75 years, diabetes, arterial hypertension or symptomatic heart failure; *, if CrCl 30–50 mL/min, age ≥ 75 years or P-glycoprotein inhibitors; [†], if age ≥ 80 years or verapamil treatment; [‡], if CrCl 30–49 mL/min; ^{††}, if at least 2 criteria: age ≥ 80 years, weight ≤ 60 kg and/or plasma creatinine ≥ 133 μ M. bid, bis in die—twice daily; DOAC, direct oral anticoagulants; NVAF, non-valvular atrial fibrillation; od, omne in die—once daily; TKRS, total knee replacement surgery; THRS, total hip replacement surgery; VTE, venous thromboembolism.

DOAC

Three DOAC, one thrombin (dabigatran) and two factor Xa inhibitors (xabans: rivaroxaban and apixaban) are currently commercialized in France. DOAC doses and indications are summarized in *Table 1*. Rivaroxaban 2.5 mg bid was approved by the European Medicines Agency (EMA) and the French National Agency for Medicines and Health Products Safety (ANSM) in association with aspirin and clopidogrel (P2Y12 inhibitor) for treatment of ACS in patients with low hemorrhagic risk and no previous stroke or transient ischemic attack; however its usage remains very limited in France for this indication (15).

A high-dimensional propensity score-matched cohort study of the French national healthcare system database followed up new users of dabigatran, rivaroxaban or VKA in NVAF patients in 2013. It revealed that dabigatran and rivaroxaban were at least as effective and safe as VKA (16). Proportion of DOAC prescription among other anticoagulant drugs continuously increased in France from the last trimester of 2012 to the third trimester of 2016 (11).

Based on the French National Health Insurance System database, a recent retrospective population-based cohort study comprising 814,446 NVAF adult patients revealed that by the end of 2015, 61% of patients received DOAC as initial anticoagulant treatment among which 46.0% were on apixaban, 42.5% on rivaroxaban and 11.5% on

dabigatran. Patients receiving apixaban were older and had more comorbidities such as high blood pressure and heart or renal failure than those receiving other DOAC (17). DOAC initiators were younger and healthier compared to VKA initiators. DOAC were more frequently prescribed by cardiologists whereas general practitioners still prescribed VKA more frequently as initial anticoagulant therapy for NVAF (17). A second population-based cohort study revealed that in 2016, among 1.1 million NVAF French patients, 66% were receiving DOAC. Among 192,851 anticoagulant initiators in 2015–2016, DOAC were initiated in 66.3% of cases. Reduced doses were prescribed in 40% of DOAC new users, even though it was not always justified. Inappropriate use was identified in many situations such as concomitant intake of drugs that potentiate the hemorrhagic risk in 33% of the cases or DOAC underdosing, despite that the reduced doses of dabigatran (75 mg) and rivaroxaban (10 mg) are not approved in NVAF patients in Europe (12). As shown in the study of Huiart *et al.* (17), patients receiving apixaban were also older and had more comorbidities than rivaroxaban- and dabigatran-treated patients in the present one (12). The PAROS cross-sectional multicenter French study of routine clinical practice conducted between January and August 2016 revealed that among 2,027 included patients, 84.8% received DOAC (apixaban was initiated in 38.6% of the cases, rivaroxaban in 36.2% and dabigatran in 10%) and 15.1% VKA (13). Seventy-

nine percent of patients treated with apixaban had doses consistent with the summaries of product characteristics (SmpC); underdosing was the most frequent inconsistency, mainly observed in elderly patients despite normal weight and renal function (13). As in the study of Maura *et al.* (12), apixaban was more common among older patients with a higher bleeding risk and decreased renal function than rivaroxaban and dabigatran (13). The NAXOS study, a nationwide observational retrospective study of a cohort generated from the French national healthcare insurance database, will provide new routine clinical practice data on the effectiveness and safety profiles of apixaban *vs.* other DOAC and VKA (18).

Recently, an observational study assessed the initial anticoagulant treatment patterns at baseline (± 30 days of diagnosis) in patients with objectively confirmed VTE included in the prospective international non-interventional Global Anticoagulant Registry in the Field (GARFIELD)-VTE. It revealed that more than half of the patients (52.2%) in Europe were given DOAC (19). Six hundred and one French patients were included among which 59.4% received DOAC either alone or after parenteral therapy (19). A prospective monocentric observational study of DOAC patients admitted to emergency departments between August 2013 and April 2014 included 198 patients among which 68.7% were treated by rivaroxaban, 30.8% by dabigatran and 0.5% by apixaban. It showed that 25.8% of included patients suffered from DOAC side effects. Eighteen percent had hemorrhagic complications, 44.4% of which were categorized as major and 7.8% had thrombotic complications. In 16.2% of included patients, DOAC treatment was not consistent with the SmpC: of these, 22% were wrong initial indications and 78% were incorrect dosages (20).

In 2016, the ANSM published post-marketing data on dabigatran side effects reported by the Regional Pharmacovigilance Centers. In total, 1,624 notifications were recorded between December 2008 and August 2013, among which 49.4% were linked to hemorrhagic events (48.3% gastrointestinal, 11.7% muscular, 11% in the urinary tract, 9% cerebral and 8.3% epistaxis), 10.3% to arterial TE and 7% to VTE (21). Concerning rivaroxaban, 1,566 notifications were recorded during the same period, among which 52% were linked to hemorrhagic events (24% gastrointestinal, 11% neurologic, 8% in the urinary tract and 8% subcutaneous and muscular), 21% to TE and 6% to hematologic adverse events (21). Up till now, no post-marketing French data are available for apixaban.

Others

Other anticoagulants are available in France and have restricted indications. They are often delivered in hospital settings and/or are not widely available. They mainly include indirect (antithrombin mediated) FXa (fondaparinux; Arixtra[®] since March 2002) or FXa and thrombin (danaparoid; Orgaran[®] since July 1996) inhibitors, and direct thrombin inhibitors (argatroban; Arganova[®] since June 2011 and bivalirudine; Bivalirudine Accord since January 2018) all administered parenterally.

Danaparoid is given through IV or SC routes and is mainly indicated for prevention or treatment of thrombosis in type II heparin-induced thrombocytopenia (HIT). Argatroban is mainly indicated to treat type II HIT and bivalirudin is used parentally in the treatment of ST-segment elevation myocardial infarction (STEMI) patients having percutaneous coronary intervention.

Fondaparinux is given at fixed dose without any monitoring, and injected SC at a dose of 5 mg/24 h in <50 kg, 7.5 mg/24 h in 50–100 kg and 10 mg/24 h in >100 kg patients. The French Society of Vascular Medicine recommends fondaparinux 2.5 mg od for 45 days in case of initial or first recurrent isolated symptomatic superficial vein thrombosis with a thrombus over 5 cm long and located more than 3 cm from the saphenofemoral junction (22). A treatment for at least 3 months is suggested if it is located less than 3 cm from the saphenofemoral junction in the absence of any bleeding risk. For patients with CrCl of 20–30 mL/min, tinzaparin in replacement to fondaparinux is suggested at a prophylactic dose (22). Fondaparinux is also preferred to other anticoagulant drugs in Non-STEMI (NSTEMI) patients in association to aspirin and P2Y12 inhibitors as specified in the European Heart Rhythm Association guideline (23). Fondaparinux is contraindicated in patients with CrCl <30 mL/min (curative dose) and CrCl <20 mL/min (prophylactic dose).

Monitoring of anticoagulant therapy

Since the anticoagulation response to UFH greatly varies among patients, treatment at therapeutic dose should be regularly monitored and the dose adjusted using preferably a chromogenic anti-FXa assay with a target value between 0.30 and 0.70 IU/mL in most indications. If unavailable, an activated partial thromboplastin time (aPTT) assay may be used: aPTT therapeutic range at each institution should be adapted to the responsiveness of the reagent

and coagulometer used in order to correspond to plasma heparin levels of 0.3 to 0.7 IU/mL (24).

Monitoring of IV UFH is performed 6 h following the onset of treatment and 4 to 6 h following any dose change. In case of SC UFH treatment, monitoring is performed 6 or 4 h after injection when administered every 12 or 8 h, respectively. Platelet count should be measured two to three times a week from day 4 to day 14 of treatment, then once a week for 1 month if heparin therapy is continued in order to rule-out any HIT (25).

While monitoring is not recommended in patients treated with LMWH at therapeutic dose, anti-Xa measurement may be considered in special situations such as patients with renal failure or elderly ones in order to detect accumulation. Over-dosage is defined as peak anti-Xa >1.5 IU/mL (tinzaparin), ~>1.4 IU/mL (enoxaparin), >1.8 IU/mL (nadroparin od) (5). Platelet count should not be monitored with LMWH except in post-operative and post-traumatic context or in case of important comorbidities or recent treatment with UFH (during the last 6 months).

VKA treatment is monitored using prothrombin time with a result expressed as international normalized ratio (INR). The latter is comprised between 2.0 and 3.0 for most indications. In specific cases, INR values between 2.5 and 3.5 are targeted. The first INR value is determined following the third VKA intake, and the second determination is done 3 to 6 days thereafter. INR is determined afterwards at least weekly during initiation of anticoagulant therapy then at least monthly when anticoagulation is stable. Following every dose change, INR is controlled 3 days afterwards and repeated 1 to 2 times per week until stabilization. A safe and accurate warfarin initiation dosing algorithm specifically devoted to the elderly has been validated and is currently used (26,27). Noteworthy, anticoagulant clinics are poorly developed in France: general practitioners and cardiologists directly manage patients under VKA therapy. Point-of-care devices are available in France for INR rapid testing. The cost of these devices is covered by the French national health insurance only for patients with mechanical heart valve (28). INR testing is also mandatory for a reliable management of the switch from VKA to DOAC; here, DOACs can be started when INR is below 2 for apixaban and dabigatran and below 2.5 for rivaroxaban in case of VTE treatment or prevention or below 3 in NVAF patients (4,23). Inversely, when a switch from DOAC to VKA is performed, an overlapping of 3 days with dabigatran intake is required in patients with CrCl above 50 mL/min and of 2 days in those with CrCl between 30 and 50 mL/min.

As for xabans, they are concomitantly administered with VKA for 2 days, and then until INR is over 2.0. It is to mention that INR should be performed just before DOAC administration in order to limit their interference.

DOAC treatment does not require monitoring. However, specific anti-IIa and anti-Xa assays are commercialized and available to assess dabigatran and xabans plasma levels in specific situations such as urgent invasive procedures, hemorrhage or acute liver or renal failure. A French study performed in 30 laboratories using 4 dabigatran and 5 rivaroxaban/apixaban calibrated assays on 3 analyzers revealed an inter-laboratory coefficient of variation below 18% for concentrations above 100 ng/mL and higher for concentrations around 40 ng/mL. Therefore, calibrated DOAC assays commercialized allow reliable measurement of anticoagulant plasma concentrations with a relatively good between-laboratory agreement even though improvement of their performances is required especially for low concentrations assessment (29). Safety thresholds of anti-Xa and anti-IIa DOAC levels have been previously discussed in the literature. A threshold of 50 ng/mL has been proposed by the subcommittee on control of anticoagulation of the International Society on Thrombosis and Hemostasis (ISTH) and the French Working group on perioperative hemostasis (GIHP) to warrant antidote administration in case of serious bleeding in DOAC patients. As well a safety hemostatic threshold of 30 ng/mL is considered in case of high bleeding risk surgery (30,31). As for IV thrombolysis for acute ischemic stroke in patients on DOAC, joint propositions from the French Vascular Neurology Society and the French Study Group on Hemostasis and Thrombosis (GFHT) and based on DOAC concentrations were issued in 2018 (32).

Apart from anticoagulant effect monitoring, a structured follow-up of DOAC patients before initiation and at least annually are recommended by the European Heart Rhythm Association (23). Monitoring consists of assessing the hemoglobin level, platelets count, full coagulation panel and renal and hepatic functions. The recheck interval depends on patient comorbidities (23). Rechecking should be done yearly, every 6 months for patients above 75 years of age or every CrCl/10 months in renal insufficient patients. Switching between heparin derivatives and DOAC is relatively simple to manage. DOAC can be started when the next dose of LMWH or SC UFH is due or 2 to 4 h after IV UFH discontinuation. Inversely, UFH or LMWH can be initiated when the next DOAC dose is due (23). However, in this later case monitoring of UFH is complex due to the

Table 2 Management of VKA overdosage without bleeding based on the French guidelines (40)

INR measured value	INR target 2–3	INR target 2.5–4.5
INR <4	No intervention	No intervention
INR 4–6	Omit 1 dose	No intervention
INR 6–10	Stop VKA treatment; vitamin K 1–2 mg per os	Omit 1 dose; discuss vitamin K administration
INR >10	Stop VKA treatment; vitamin K 5 mg per os	Stop VKA treatment; hospitalization/discussion with a specialist

INR, international normalized ratio; VKA, vitamin K antagonists.

interference of xaban on UFH anti-Xa and conversely.

Fondaparinux presents little inter- and intra-subject variability therefore its monitoring is not required. Anticoagulant monitoring is generally not required in danaparoid patients except in particular cases such as renal failure, extreme body weight or old patients (>75 years). If performed, a specific anti-Xa assay is required with a target range comprised between 0.5 and 0.8 IU/mL (33). Treatment with argatroban is monitored by a specific chromogenic substrate assay or an aPTT assay with a target ratio between 1.5 and 3 times the control aPTT (34). Bivalirudin may be monitored by the activated clotting time if required.

Anticoagulants reversal agents and bleeding management

Despite its poor therapeutic index, protamine remains the unique commercialized antidote of heparin derivatives. Protamine induces hemodynamic side effects, increases histamine plasma concentration and has an anticoagulant activity; this explains why the dose of protamine is limited to 1 mg per 100 IU heparin and protamine-to-heparin ratio must not be above 1.1; otherwise bleeding risk would be significantly increased (32,35). Protamine completely neutralizes the thrombin-inhibitory activity of LMWH but only partially anti-Xa activity. Molecular size as well as the sulfonation degree makes it impossible to completely neutralize LMWH anticoagulant activity (36).

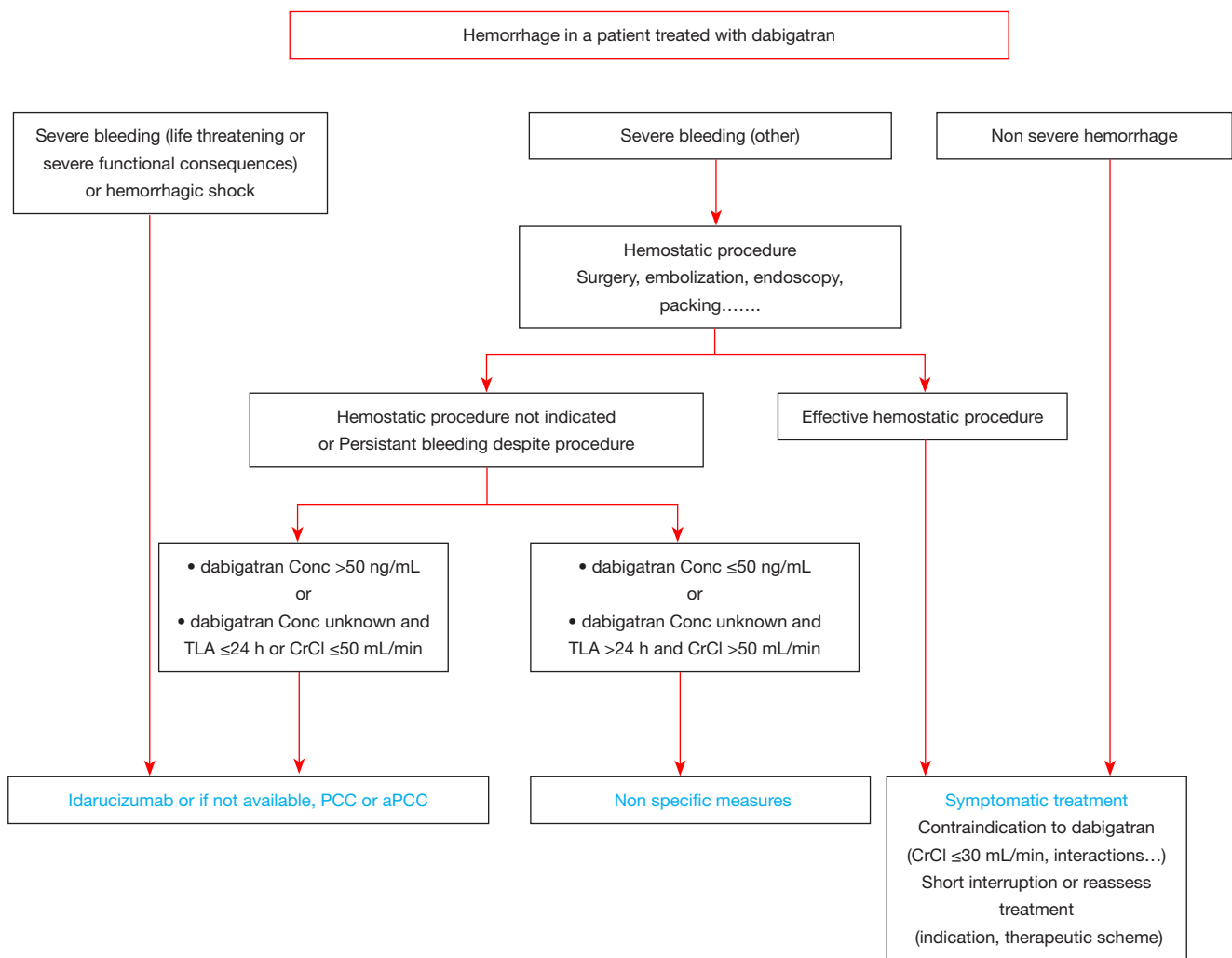
Major bleeding in patients while on VKA therapy is managed by co-administration of prothrombin complex concentrate (PCC, 25 IU/kg IV or dose based on INR if rapidly available) plus vitamin K (10 mg per os) in order to rapidly achieve an INR below 1.5 and maintain a normal coagulation profile. INR should be measured at least 30 min after the infusion (37). If INR remains above 1.5, a second dose of PCC should be administered and INR

is rechecked 6 h later (37). Indeed, the synthesis of new functional clotting factors by the liver following vitamin K administration in VKA patients requires at least 6 h and more likely 12 to 24 h to significantly lower the INR. The French prospective observational cohort EPAHK study showed that guideline-concordant VKA reversal with PCC and vitamin K within 8 hours after admission was associated with a significant decrease in 7-day mortality (38,39). According to the French guidelines, management of VKA over-dosage without bleeding is based on INR value and INR target range and is summarized in *Table 2* (40).

Bleeding during anticoagulant therapy remains a crucial issue with DOAC. Idarucizumab is available for dabigatran reversal since February 2016 in case of urgent surgery or life-threatening bleeding. Andexanet-alfa is not yet available in France, although in March 2019, the EMA human medicines committee (CHMP) recommended granting a conditional marketing authorization in the European Union for andexanet-alfa use in adult patients receiving xabans with life threatening or uncontrolled bleeding. Although these specific antidotes are available or imminent, they are very expensive in comparison to those of heparin derivatives and VKA.

Despite the lack of robust data, the European Heart Rhythm Association and the GIHP have proposed the use of activated PCC (aPCC; 30–50 IU/kg IV) or non-activated (PCC; 50 IU/kg IV) for life-threatening bleeding or when immediate hemostatic support is required in xaban-treated patients (23,41). These are also considered in patients under dabigatran when idarucizumab is not available especially since recent data from the French Pharmacovigilance database suggested that idarucizumab was not superior to aPCC or PCC in terms of fatality rate (17.6% *vs.* 18.6%) (42). The choice between PCC and aPCC depends on their availability, the clinical situation and the experience of the physicians (23).

A prospective multicenter observational cohort study in



[TLA, time since last administration; CrCl, creatinine clearance (Cockcroft and Gault); Conc, plasmatic concentration]

Figure 1 Proposed algorithm for hemorrhage management of patient receiving dabigatran or xaban (by extension) by the French Working Group on Perioperative Hemostasis. [Adapted with permission from Albaladejo *et al.* (41)]. PCC, prothrombin complex concentrate; CrCl, creatinine clearance; TLA, time since last administration.

France and Belgium of 732 patients with severe bleeding while treated with dabigatran (28%), rivaroxaban (64%) or apixaban (7.2%) was conducted between June 2013 and November 2015 on behalf of GIHP to describe the management strategies and outcomes. Thirty-seven percent of the bleeds were gastrointestinal bleedings and 24% intracranial. PCC or aPCC were administered in 38% of the cases and the mortality by day 30 was 14% (43). In patients with acute major bleeding associated with the use of a xaban and treated with andexanet-alfa, the mortality rate was of 14% within 30 days after enrollment; mortality rate was of 18.8% and 18.9% in patients treated with dabigatran

and receiving idarucizumab for uncontrolled bleeding or an urgent procedure, respectively (44,45). Recombinant FVIIa is no longer included in the French guidelines for DOAC management in context of bleeding or urgent invasive procedure owing to its uncertain benefit-risk balance.

The GIHP proposed in 2016 an algorithm for dabigatran management in patients with hemorrhagic events (*Figure 1*) (41). The management depends on the type and localization of bleeding and on DOAC concentration. This algorithm is also used by extension in xaban-treated patients. When idarucizumab is administered, it is recommended to measure dabigatran concentration before and 12 to 18 hours

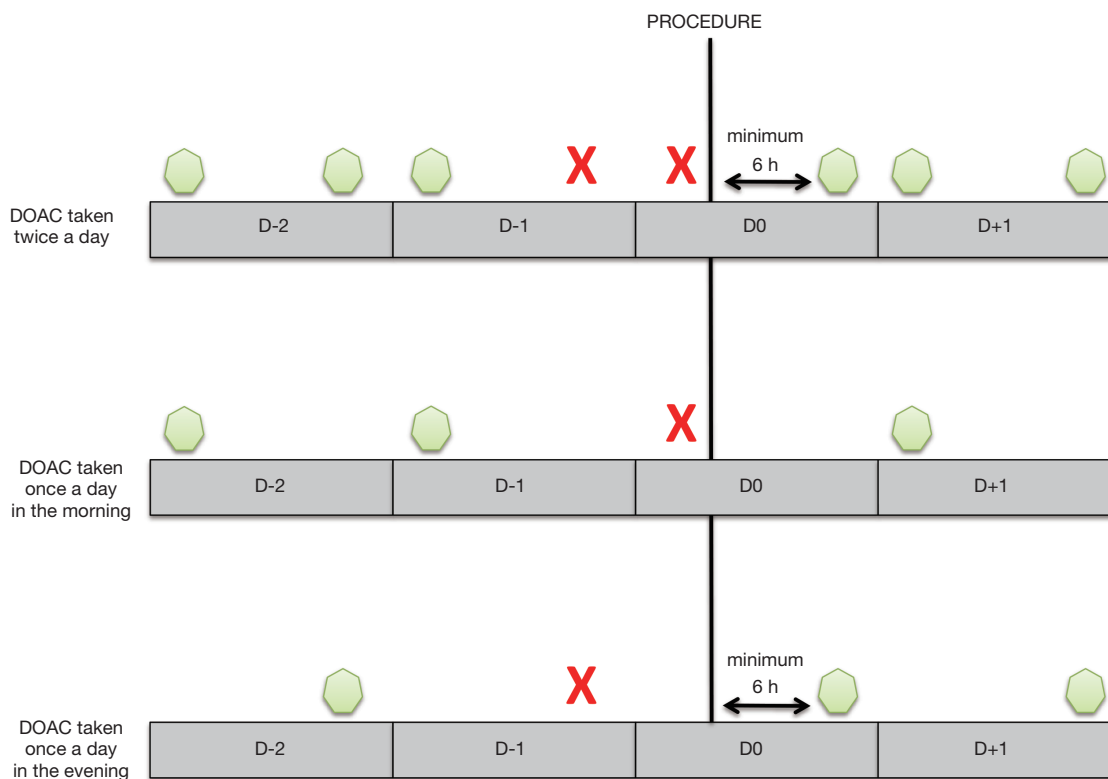


Figure 2 Proposed management of invasive elective procedure with low hemorrhagic risk in patient treated with DOAC by the French Working Group on Perioperative Hemostasis. [Adapted with permission from Albaladejo *et al.* (30)]. DOAC, direct oral anticoagulants.

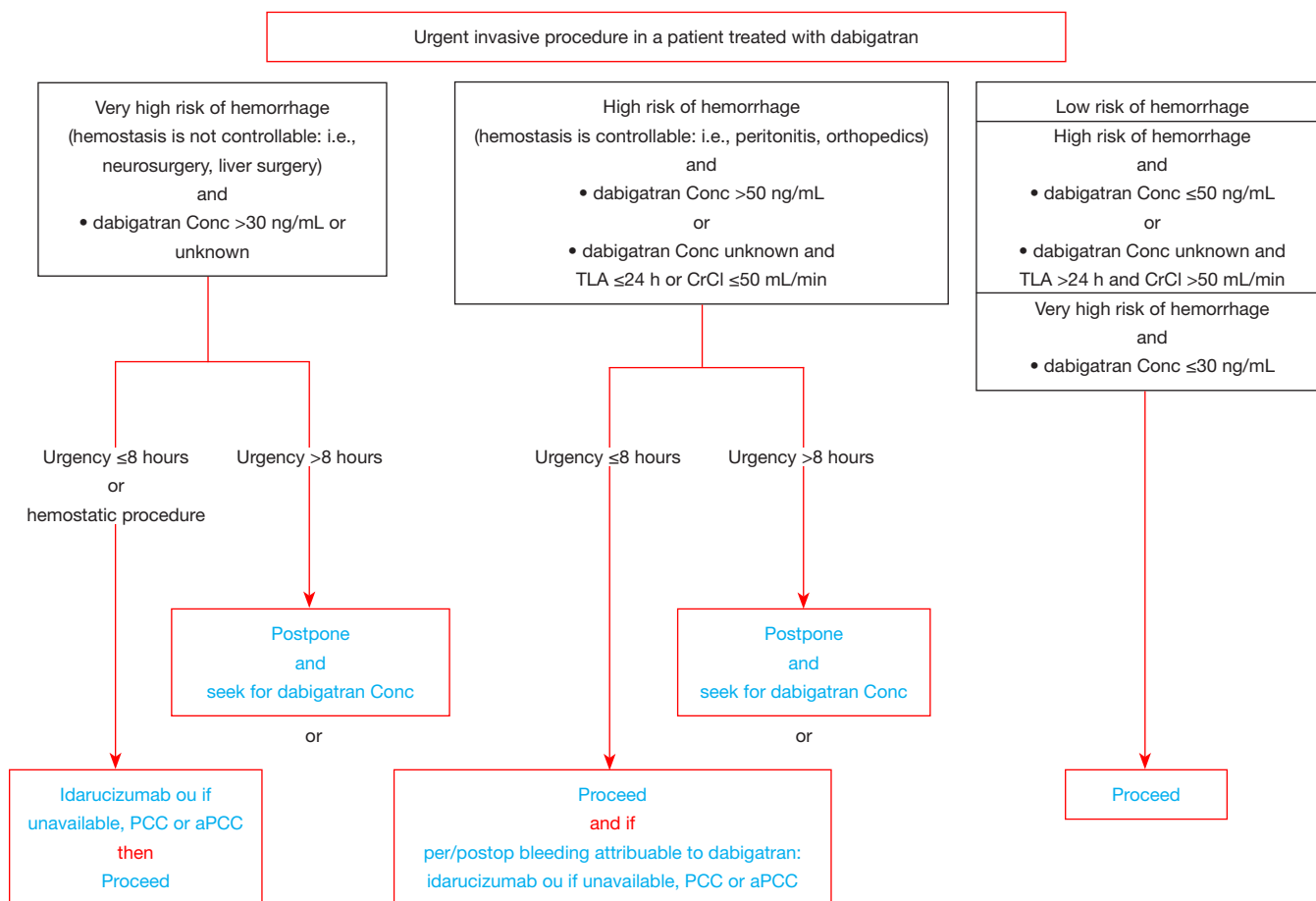
after in order to determine if a subsequent second dose of 5 g is needed (38).

Perioperative management of anticoagulant therapy

Every year, 10% to 15% of anticoagulant patients require urgent surgeries or invasive procedures (46). Elective invasive procedures with a high to moderate hemorrhagic risk require interruption of VKA therapy 5 days before without LMWH bridging. In patients with concomitant high thrombotic risk (patients with mechanical heart valves, a history of stroke or VTE in the preceding 3 months or more than 2 VTE with at least one idiopathic), perioperative bridging therapy is recommended. Therefore, LMWH is started 2 days following VKA stop and the last dose is given 24 hours before the procedure. If INR is still above the value for the procedure (cut-off of 1.5 or 1.3), 2.5 mg of vitamin K is given orally. In case of expedited surgery with high bleeding risk, 5 mg vitamin K with or without PCC is administered to reach an INR of <1.5 (<1.3 in

neurosurgery) (38). Procedures with a low risk of hemorrhage does not necessitate treatment discontinuation (38). When discontinued, VKA therapy should be resumed at least 6 hours after the end of the procedure. When necessary, LMWH is added to VKA 24 hours following interventions with low bleeding risk and 48 to 72 hours after those with high bleeding risk (47).

In case of elective surgery at low bleeding risk in patients on DOAC, the GIHP suggested that patients interrupt DOAC the night before irrespective of the type of drug and to resume therapy 6 hours or more after the end of the invasive procedure (*Figure 2*). For invasive procedures at high bleeding risk, it was suggested to interrupt rivaroxaban and apixaban 3 days before. Dabigatran should be interrupted according to the renal function, 4 and 5 days if CrCl is higher than 50 mL/min and between 30 and 50 mL/min, respectively. For invasive procedures at very high bleeding risk such as intracranial neurosurgery or neuraxial anesthesia, longer interruption times were suggested. Finally, bridging with parenteral anticoagulation and measurement of DOAC concentrations should no



(TLA, time since last administration; CrCl, creatinine clearance, Cockcroft and Gault; Conc, plasmatic concentration; PCC, non-activated PCC; aPCC, activated PCC)

Figure 3 Proposed algorithm by the French Working Group on Perioperative Hemostasis for management of urgent invasive procedure in patient treated with dabigatran or xaban (by extension). [Adapted with permission from Albaladejo *et al.* (41)]. PCC, prothrombin complex concentrate; CrCl, creatinine clearance; TLA, time since last administration.

longer routinely be used (30). The objective of the proposed management strategy is to ensure a minimal pre-procedural DOAC concentration (48). In case of urgent invasive procedure, algorithms for the management of dabigatran-treated patients are summarized in *Figures 3,4* (41). The same are used by extension in patients receiving xaban. Full dose (curative) can be reintroduced 24 to 72 hours following the procedures. If venous thromboprophylaxis is mandatory, heparin derivatives or fondaparinux can be administered at least 6 hours after the procedure. DOAC is thereafter reintroduced at least 12 hours following the last SC LMWH. In the PAUSE study, a standardized perioperative DOAC therapy interruption and resumption strategy for elective surgery in AF patients, based on DOAC pharmacokinetic properties, procedure-associated

bleeding risk, and CrCl levels without heparin bridging or coagulation function testing was evaluated. This strategy, very similar to those proposed by the GIHP (DOAC omitted for 1 day before a low-bleeding-risk procedure and 2 days before a high-bleeding-risk procedure) was associated with low rates of major bleeding and arterial TE (48,49).

Anticoagulation in specific population groups

Despite their improved ease of use compared to VKA and heparin derivatives, DOAC need to be managed cautiously in patients with particular clinical profile with regards to weight, renal and hepatic function, drug-drug interactions and risks of bleeding.

Until more data are available, obese patients are managed

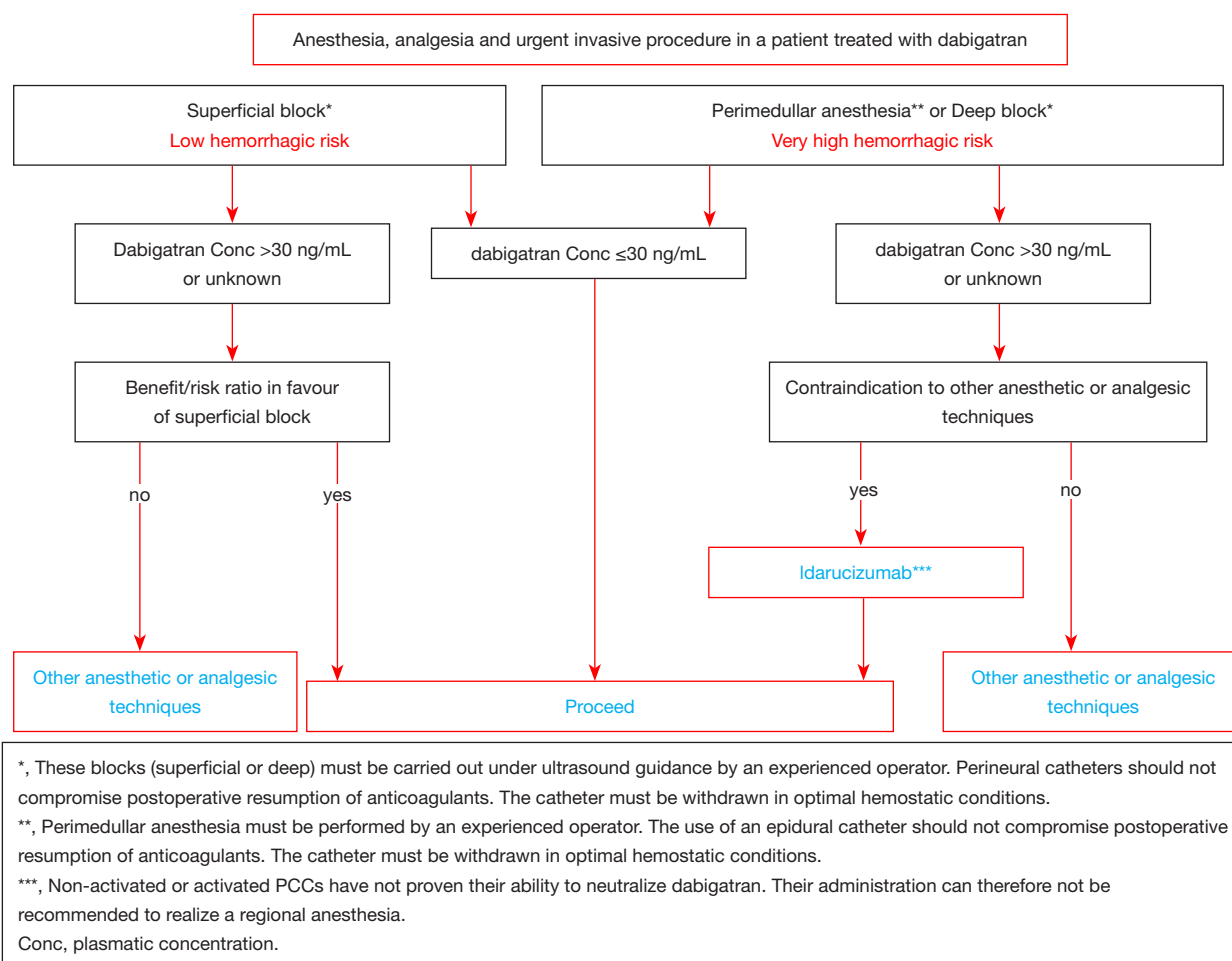


Figure 4 Proposed algorithm by the French Working Group on Perioperative Hemostasis for management of anesthesia and analgesia in patient treated with dabigatran or xaban (by extension). [Adapted with permission from Albaladejo *et al.* (41)].

according to the ISTH guidance statements which suggest not to use DOAC in patients with BMI >40 kg/m² or weight >120 kg and to check peak and trough drug-specific levels if DOAC are used in these patients and to change to VKA if the level is found to be below the expected range (50). Prospective studies of DOAC use after bariatric surgery are very limited and available information comes mostly from retrospective studies of small number of patients and numerous case reports. VKA is still preferred over DOAC in such patients as they can be monitored with the INR.

In case of severe renal failure (CrCl <30 mL/min) dabigatran is the unique DOAC contraindicated whereas in France as in all the European countries, xabans can be used with caution in patients with CrCl between 15 and 29 mL/min with the reduced dose regimen (23). In patients with end-stage chronic kidney disease (CrCl <15 mL/min)

or on dialysis, VKA (INR 2 to 3) are the unique recommended oral anticoagulant drug in France. Since June 2017, enoxaparin can be prescribed in patients with a CrCl ≥15 mL/min. All three DOAC are contraindicated in patients with hepatic disease associated with coagulopathy that results in a clinically relevant bleeding risk (23).

In patients with VTE associated to antiphospholipid antibody syndrome (APLS), VKA is the best option for long term treatment especially for triple positive APLS (positive lupus anticoagulant associated to positive anticardiolipin and anti-β₂-glycoprotein antibodies) as well as in APLS associated to arterial TE (51). An INR value of 2 to 3 is targeted. For patients with recurrent arterial or venous thrombosis despite adequate treatment, addition of low-dose aspirin, increase of INR target to 3 to 4 or switch to LMWH may be considered according to the updated guidelines

of the European League Against Rheumatism (52). In women with prior obstetric APLS, combination treatment with low-dose aspirin and prophylactic dose of LMWH during pregnancy is recommended (52). Oral anticoagulant treatment choice in simple positive venous APLS remained controversial since the evidence of DOAC efficacy and safety compared to VKA is limited by small samples and short follow-up retrospective studies (53). In contrast, the use of DOAC is now proposed in the management of patients with acute HIT, not only by the American Society of Hematology (54), but also more recently by the GIHP (25).

In pregnant women, the mainstay of anticoagulant treatment is LMWH with no need of monitoring. In breastfeeding mothers, warfarin is the recommended oral anticoagulant therapy that can be started 2 to 5 days post-partum. DOAC are contraindicated.

Optimal therapy of VTE in cancer patients is still uncertain. The French Society for Vascular Medicine suggests treatment with LMWH with no subsequent switch to any other anticoagulant drugs for patients with cancer in the absence of contraindication to LMWH (22). However, according to the 2018 guidelines of the ISTH and the 2019 guidelines of the International Initiative on Thrombosis and Cancer (ITAC) academic working group, DOAC can be used especially in patients with low bleeding risk, in the absence of drug-drug interactions with current systemic therapy, and of gastrointestinal cancers or cancers at risk of bleeding from genitourinary tract, bladder or nephrostomy tubes, or with duodenal ulcers, gastritis, esophagitis or colitis (55,56).

Conclusions

Both in France and worldwide, DOAC usage continues to grow-up as a replacement of VKA-heparin derivatives therapies. Further data are still needed to warrant favorable benefit-risk balance of DOAC compared to VKA in special populations and for management of DOAC in urgent situations.

Acknowledgments

None.

Footnote

Conflicts of Interest: Isabelle Gouin-Thibault and Virginie Siguret: Bristol-Myers Squibb/Pfizer, Bayer Healthcare

AG and Boehringer Ingelheim; Pierre Albaladejo: Bayer Healthcare AG, Bristol-Myers Squibb/Pfizer, Sanofi Aventis, Portola, Aspen; Yves Gruel: Bayer Healthcare AG, Sanofi Aventis, Aspen, LFB, Stago; The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aob.2020.02.04

Cite this article as: Jourdi G, Mansour A, Vayne C, Godon A, Tacquard C, Siguret V, Albaladejo P, Gruel Y, Gouin-Thibault I, French Study Group on Hemostasis and Thrombosis (GFHT) & French Working group on perioperative hemostasis (GIHP). Anticoagulation therapy in France: state-of-the-art in 2020. *Ann Blood* 2020;5:3.