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*Review Article*

# Preventive Strategies against Bleeding due to Nonvitamin K Antagonist Oral Anticoagulants

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Dabigatran etexilate (DE), rivaroxaban, and apixaban are nonvitamin K antagonist oral anticoagulants (NOACs) that have been compared in clinical trials with existing anticoagulants (warfarin and enoxaparin) in several indications for the prevention and treatment of thrombotic events. All NOACs presented bleeding events despite a careful selection and control of patients. Compared with warfarin, NOACs had a decreased risk of intracranial hemorrhage, and apixaban and DE (110 mg BID) had a decreased risk of major bleeding from any site. Rivaroxaban and DE showed an increased risk of major gastrointestinal bleeding compared with warfarin. Developing strategies to minimize the risk of bleeding is essential, as major bleedings are reported in clinical practice and specific antidotes are currently not available. In this paper, the following preventive approaches are reviewed: improvement of appropriate prescription, identification of modifiable bleeding risk factors, tailoring NOAC's dose, dealing with a missed dose as well as adhesion to switching, bridging and anesthetic procedures.

## 1. Introduction

Nonvitamin K antagonist oral anticoagulants (NOACs) [1] have been approved by the European Commission, as an alternative to vitamin K antagonists (VKAs) and parenteral anticoagulants, for the following indications: prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee surgery (apixaban [2–4], dabigatran etexilate (DE) [5–7], and rivaroxaban [8–11]), prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) (apixaban [12], DE [13], and rivaroxaban [14]), treatment and secondary prevention of

deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (rivaroxaban and DE [15, 16]), and prevention of atherothrombotic events after an acute coronary syndrome with elevated cardiac biomarkers, combined with a single or dual antiplatelet therapy (acetylsalicylic acid alone or associated with clopidogrel or ticlopidine) (rivaroxaban [17, 18]). In NVAF trials, NOACs proved to be either superior or noninferior to warfarin for the prevention of stroke and systemic embolus [12–14]. Several guidelines (European Society of Cardiology, American College of Chest Physicians, and Canadian Cardiovascular Society) recommend NOACs as broadly preferable to VKAs in most patients with NVAF. This will lead to a wider use of NOACs in the future.

Compared with warfarin, the NOACs showed less risk of intracranial hemorrhage, and apixaban and DE (110 mg bid) showed less risk of major bleeding from any site [12–14]. Unfortunately, rivaroxaban and DE had an increased risk of gastrointestinal (GI) bleeding compared with warfarin. Apixaban was associated with fewer GI bleeding compared with warfarin, but it was not statistically significant [19].

Bleeding events were reported despite a regular monitoring of adverse events, a strong medication adherence and a careful selection of patients in the pivotal clinical trials (exclusion of patients with assumed poor compliance, bleeding risks, renal insufficiency, etc.). Extension of adverse events into clinical practice is currently under research and postmarketing registers, like the GLORIA-AF registry, are recruiting [20, 21].

The aim of this review is to highlight the bleeding risks with NOACs in the clinical practice and to broach different prevention strategies to minimize these adverse events.

## 2. NOACs and Major Bleeding

Large randomized controlled trials (RCT) allowing head-to-head comparison between NOACs are not available. Only indirect comparison on bleeding can be proposed since the three pivotal NOAC trials contain a common comparator (i.e., adjusted-dose warfarin). Even so there are limits in the conclusiveness of such comparisons, like differences in the study populations (differences in reporting age, renal function, exclusion criteria, and additional risk factors), in the definition of adverse events, in study protocols (open or double-blind design) and in time in therapeutic range (TTR) of the international normalized ratio (INR) values among these RCTs. In the three pivotal trials comparing NOACs with warfarin, evidence of the validation of the stated INR was not provided. This makes cross-trial comparisons difficult [30–32].

Few data exist regarding the safety of NOACs in clinical practice, and the available information reflects the limitations of post-authorization studies, such as reporting bias. Recent evidence provides contradiction to earlier safety reports that suggested that the major bleeding rates in patients receiving NOACs in clinical practice did not exceed the rates reported in the pivotal trials [21, 33].

McConeghy et al. evaluated DE adverse event reports with a reported bleeding event and/or reported fataloutcome compared with warfarin [34]. This retrospective analysis of the FDA Adverse Event Reporting System (FAERS) database suggested increased odds of bleed-related mortality in clinical practice with dabigatran compared with the clinical trials [34].

The bleeding reports were driven by patients who were older, renally impaired, acutely injured, and had low body weight. These patients were underrepresented in the RELY trial and may have higher risks of dabigatran-induced bleeding. Furthermore, reports from FAERS showed underreporting bias [34].

For rivaroxaban, the following clinical characteristics were associated with an increased risk for major GI bleeding [32]: concurrent aspirin or nonsteroidal anti-inflammatory drugs (NSAID) use, prior vitamin K antagonist use, decreased creatinine clearance, prior stroke, transient ischemic attack or systemic embolization, sleep apnea, cigarette smoking, chronic obstructive pulmonary disease, male gender, patient treated with histamine-2 receptor antagonist or proton pump inhibitor (PPI), and prior upper and lower GI bleeding. Most of these characteristics were also associated with an increased risk of major GI bleeding in patients treated with warfarin [32].

Concerning apixaban, Hylek et al. recently analyzed the bleeding events of all patients who received at least one dose of a study drug in the ARISTOTLE trial. All major bleedings (defined by the criteria of the International Society on Thrombosis and Haemostasis (ISTH)) that appear from the time of the first dose until 2 days after the last dose was received were included [19]. Apixaban, compared with warfarin, was associated with a 31% reduction of first major bleeding and with half of the death within 30 days following a major hemorrhage. Independent factors associated with first major hemorrhage were: older age, prior hemorrhage, prior stroke or transient ischemic attack (TIA), diabetes, lower creatinine clearance, and decreased hematocrit. Female gender and liver disease were more associated with apixaban randomization, compared with warfarin. A subgroup analysis showed that patients with renal dysfunction and low body weight had a greater reduction in bleeding with apixaban versus warfarin than in patients with normal renal function and higher body weight.

The use of aspirin and nonsteroidal anti-inflammatory drugs (NSAID) with apixaban increased independently the risk of major bleeding by around 30% [19].

Based on the RE-LY trial, DE 150 mg BID, combined with a single or dual antiplatelet therapy, increased the rate of extracranial bleeding [35].

A brief summary of NOAC's pharmacology is available in Table 1 [22–25].

## 3. Prevention of Major Bleeding in Patients Receiving NOACs

The following preventive strategies are achievable to reduce the incidence rate of NOAC-related major bleeding:

Table 1: Summary of pharmacokinetic properties of nonvitamin K antagonist oral anticoagulants (NOACs) [22–25].

| | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|
| Target | Factor lla | Factor Xa | Factor Xa |
| Prodrug | Yes | No | No |
| Tmax (h) | 1.5–3.0 | 2.0–4.0 | 3.0–4.0 |
| Distribution volume (L) | 60–70 | ±50 | 23 |
| Half-life (h) | 11: healthy individuals<br>12-13: elderly | 5–9: healthy individuals<br>11–13: elderly | 8–15: healthy individuals |
| Bioavailability | 3–7%<br>pH sensitive | 80–100%: 10 mg<br>66%: 15–20 mg under fasting conditions | ±50% |
| Protein binding | 35% | >90% | 87% |
| Metabolism | Conjugation | CYP-dependent and independent mechanism | CYP-dependent mechanism |
| Active metabolites | Yes glucuronide conjugates | No | No |
| Elimination | 80% renal<br>20% bile (glucuronide conjugation) | 33% unchanged via the kidney<br>66% metabolized in the liver into inactive metabolites then eliminated via the kidney or the colon in an approximate 50% ratio | 25% renal<br>75% through the liver while the residue is excreted by the hepatobiliary route in the feces |
| Effects of food | Tmax delayed;<br>Cmax and AUC unchanged | Tmax delayed;<br>Cmax and AUC increased (76% and 30–40%, respectively) | Tmax delayed;<br>Cmax and AUC unchanged |
| CYP substrate | No | CYP3A4, CYP2J2 | CYP3A4 |
| P-gp substrate | DE: yes | Yes | Yes |

(1) improving appropriate prescription,

(2) identifying modifiable bleeding risk factors,

(3) improving individual benefit-risk by tailoring NOACs dose,

(4) dealing with a missed dose,

(5) adhering to switching procedures,

(6) adhering to bridging procedures,

(7) adhering to anesthetic recommendations.

### 3.1. Improving Appropriate Prescription

*3.1.1. Off-Label Use or Misuse.* The off-label use or misuse of NOACs means a use outside an appropriate indication or at inappropriate doses. For example the off label uses of DE are: age >80 years, patients with liver or kidney disease, with previous bleeding, with previous ischemic heart disease or severe renal impairment, patients with a $CHADS_2$ score of 0 and patients with coadministration of systemic ketoconazole, cyclosporine, itraconazole, tacrolimus, dronedarone and aspirin [36–41].

Misuse is frequent (between 8.0 and 43.5%) and can induce supratherapeutic anticoagulation with a potential risk of severe or even fatal bleeding [36–38]. A lack of consensus in NVAF's definition and the complexity of dose regimens for different indications and populations (as illustrated in Table 2) can lead to inadequate prescriptions.

Because of an increased risk of bleeding, NOACs should be used with caution if a concomitant use of antiplatelet agents is indicated [42–44], and NSAIDs should be avoided if possible.

*3.1.2. Renal Function.* Several cases of severe bleedings (often leading to death) have been reported in older patients under DE [45]. Renal failure was the most recurrent risk factor associated with bleedings in these elderly patients and should therefore be reassessed during the treatment if clinically indicated (fluctuating renal function, diuretic use, and hypovolemia).

In clinical trials of DE and rivaroxaban for NVAF, drug eligibility and dosing were determined by using the Cockcroft-Gault equation to estimate creatinine clearance ($Cr_{Cl}$), a measure of renal function. The modification of diet in renal disease (MDRD) equation (used to estimate glomerular filtration rate (eGFR)) leads, in low GFR values, to a surestimated renal function in comparison with the Cockcroft-Gault equation [46, 47]. Thus, by using the MDRD equation, many elderly patients with AF would either become incorrectly eligible for these drugs or would receive higher doses than required. Regulatory authorities and drug companies recommend therefore the use of the Cockcroft-Gault equation instead of the MDRD-derived eGFR to calculate

Table 2: Indication and dose regimens of Dabigatran etexilate, Rivaroxaban, and Apixaban [2–18].

| | Dabigatran etexilate | Rivaroxaban | Apixaban |
|---|---|---|---|
| VTE Prophylaxis | 220 mg/day (2 capsules of 110 mg OD) or 150 mg/day (2 capsules of 75 mg OD) → if $Cr_{Cl}$ 30–50 mL/min, if >75 ys, if verapamil, amiodarone and quinidine THR: 28–35 days TKR: 10 days | 10 mg/day (1 tablet of 10 mg OD) THR: 5 weeks TKR: 2 weeks | 5 mg/day (1 tablet of 2.5 mg BID) THR: 32–38 days TKR: 10 days |
| Nonvalvular atrial fibrillation | 300 mg/day (1 capsule of 150 mg BID) 220 mg/day (EU) (1 capsule of 110 mg BID) → if >80 ys or verapamil 150 mg/day (US) (1 capsule of 75 mg BID) → if $Cr_{Cl}$ between 15–30 mL/min | 20 mg/day (1 tablet of 20 mg OD) 15 mg/day (1 tablet of 15 mg OD) → if $Cr_{Cl}$ between 15–49 mL/min | 10 mg/day (1 tablet of 5 mg BID) 5 mg/day (1 tablet of 2.5 mg BID) → if at least 2 of the following conditions: ≥80 ys, ≤60 kg or serum creatinine ≥1.5 mg/dL; or if $Cr_{Cl}$ 15–29 mL/min |
| VTE treatment | Adopted indication by the CHMP on 25th April 2014 (EU) 300 mg/day (US) (1 capsule of 150 mg BID) after 5–10 days of parenteral anticoagulation | Treatment phase: 30 mg/day (1 tablet of 15 mg BID) for 21 days Secondary prevention: 20 mg/day (1 tablet of 20 mg OD) 15 mg/day (1 tablet of 15 mg OD) → if $Cr_{Cl}$ between 15-49 mL/min and the risk of bleeding outweighs the risk of recurrent DVT or PE | × |
| Prevention of atherothrombotic events after ACS with elevated cardiac biomarkers | × | 5 mg/day (1 tablet of 2.5 mg BID) in association with ASA (75–100 mg) alone or ASA + clopidogrel (75 mg) | × |

×Off-label; BID: twice daily; $Cr_{Cl}$: creatinine clearance; DVT: Deep-vein thrombosis; OD: once daily; PE: pulmonary embolism; THR: total hip replacement; and TKR: total knee replacement; vte: venous thromboembolism; CHMP: committee for medecinal products for human use.

eligibility for NOACs and adapted dose for elderly patients with AF.

*3.1.3. Bioavailability.* By opening DE capsules, the bioavailability reaches 75% and increases highly the bleeding risk [43]. Therefore, gastrostomies and jejunostomies are not advised with DE.

For rivaroxaban, Moore et al. studied its relative bioavailability when administered as a whole tablet orally or as a crushed tablet mixed with applesauce or water suspension through a nasogastric tube (NGT) or a gastrostomy. There was no difference in both pharmacokinetics, so that they concluded to a safe administration for rivaroxaban through a NGT or gastrostomy [48].

To the best of our knowledge, there is currently no data available for apixaban.

*3.1.4. Patient with Low Body Weight.* Despite recent data suggesting that the clearance of anticoagulants increases with weight, the optimal dosing strategies for most anticoagulants remain unknown [49]. This uncertainty is mainly relevant for anticoagulants with fixed-dosing regimen such as NOACs, in contrast to anticoagulants for which efficacy monitoring is routinely required (i.e., VKAs).

In the RE-LY study, the overall mean weight of patient was 82.6 kg (ranging from 32 to 222 kg) with 17.1% of patients weighing above 100 kg. A tendency of increasing *dabigatran* concentrations with decreasing body weight was found [49]. There is very limited clinical experience in patients with a body weight <50 kg. In this population, no dose adjustment is advised but a close clinical surveillance is recommended by the different authorities [43, 50].

A study with 48 healthy participants assessed the influence of extremes of body weight (≤50 kg and >120 kg) on

the pharmacokinetics (PK) of *rivaroxaban* 10 mg OD as compared with normally weighted patients (80 kg). The results show that the $C_{max}$ of rivaroxaban was increased by 24% in subjects weighing ≤50 kg while the area under the curve (AUC) was unaffected (difference is <25%) by body weight. The 24% increase in $C_{max}$ in patients with low body weight resulted in a small (15%) increase in prolongation of prothrombin time (PT), which was not considered as clinically relevant [51]. However, this was performed with STA Neoplastin CI+, a reagent with a moderate sensitivity to rivaroxaban. In a population pharmacokinetic/pharmacodynamics (PK-PD) modeling study, there was a clear increase in the volume of distribution interrelated with weight and probably due to secondary increase of body volume [52]. Based on these findings, a higher exposure to rivaroxaban could be expected in patients with low body weight and, consequently, a higher risk of bleeding with a standard dose. However, these preliminary data need confirmations in larger studies. Similarly to dabigatran, no dose adjustment is currently proposed by the European and American agencies in patients with extreme body weight (<50 kg or >120 kg) [42].

*Apixaban* has also been evaluated in patients with extreme body weight. A 30% and 20% increase in $C_{max}$ and AUC, respectively, has been seen in patients weighing <50 kg [53]. These modifications were considered as modest and unlikely to be clinically meaningful. However, further evaluation of clinical data is warranted. Since the body weight seems to have a modest effect on apixaban exposure, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend dose adjustment in patients weighing <60 kg (2.5 mg BID instead of 5 mg BID) in the presence of additional risk factors, namely, age ≥80 years or serum creatinine >1.5 mg/dL [54, 55].

*3.1.5. Patients with Impaired Hepatic Function.* Hepatic impairment may alter the pharmacokinetics of drugs that are metabolized by the liver, such as rivaroxaban and apixaban [56]. Data on the use of NOACs in hepatic impairment are scarce and mainly restricted to single-dose studies in a limited number of subjects with mild or moderate hepatic impairment. In addition, patients with elevated liver enzymes and/or bilirubin levels were excluded from clinical trials. The manufacturer's recommendations for rivaroxaban, apixaban, and DE regarding impaired hepatic function are based on both Child-Pugh classification and liver-related exclusion criteria applied in clinical trials [57].

Stangier et al. found no influence of moderate hepatic impairment on pharmacokinetic, pharmacodynamics and safety profile of DE following administration of a single 150 mg dose in 24 subjects [56]. However, patients with elevated liver enzymes above 2 times the upper limit of normal (ULN) were excluded from clinical trials [43]. The Summary of Product Characteristics of the European Commission (EU-SmPC) contraindicates the use of DE in patients with hepatic impairment or liver disease expected to have any impact on survival [43].

In contrast to dabigatran, liver metabolism is an important route of elimination for FXa inhibitors. Approximately two-thirds of the administered *rivaroxaban* dose is metabolized by the liver via CYP3A4, 2J2, and CYP-independent mechanisms to inactive metabolites [42]. The AUC following administration of a single dose of rivaroxaban 10 mg was increased by 2.27-fold in patients with moderately impaired liver function (Child-Pugh B). Moderate but not mild hepatic impairment reduced total body clearance of rivaroxaban and led to pharmacodynamics effects [58]. Therefore, EMA contraindicates its use in case of hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

*Apixaban* undergoes liver metabolism mainly via CYP3A4/5, but other isoenzymes are also involved [44]. Data on the use of apixaban in patients with moderate hepatic impairment (Child Pugh B) show that AUC increased slightly by 1.09-fold when a 5 mg single dose was administered [59]. Apixaban should be used with caution in patients with elevated liver enzymes (ALT/AST > 2 × ULN) or total bilirubin ≥ 1.5 × ULN because those were excluded from clinical trials. The EMA recommends to perform liver function test prior to initiating apixaban and to use it with caution in patients with moderate and severe hepatic impairment. Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk [44].

In conclusion, limited data indicate that the PK and PD of NOACs such as rivaroxaban or apixaban can be modified in moderate hepatic impairment, in contrast to dabigatran. Further evaluations are needed to better support clinicians in their decision process. Evaluations of liver function are recommended before prescribing NOACs and regularly during treatment in patients with possible liver impairment.

*3.1.6. Drug Interactions.* In addition to these specific populations, NOACs have also drug interactions with P-glycoprotein substrates or CYP3A4 inhibitors that may highly increase their plasma concentrations and hence bleeding risks. Table 3 summarizes drug-drug interactions reported in the literature as well as recommendations for dose adaptation and contraindications for the EU-SmPC and FDA prescribing guidelines [26–28].

*3.2. Identifying Modifiable Bleeding Risk Factors.* Identification of modifiable and nonmodifiable bleeding risk factors will help to ascertain and manage the risk of major bleeding. This can be performed before NOAC's initiation using validated bleeding scores like the International Society of Thrombosis and Hemostasis bleeding assessment tool [60]. The HAS-BLED score is a tool designed for assessing bleeding risks during anticoagulation. Despite debate in the literature on its ability to predict any clinically relevant bleeding, it may be useful for this purpose [61, 62]. For example, a HAS-BLED score ≥3 indicates high risk for hemorrhage and suggests that modifiable risk factors affecting bleeding should be reviewed and corrected (e.g., blood pressure, hepatic/renal function, INR, antiplatelet agents, NSAIDs, alcohol ingestion, and selective serotonin reuptake inhibitors (SSRI)).

Table 3: Summary of drug-drug interactions provided in the literature. When available, recommendations for dose adaptation or contraindications by the competent authorities are provided [26–28].

| Molecule | Mechanism | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|---|
| | | Antiarrhythmics | | |
| Dronedarone | P-gp and CYP 3A4 inhibitor | AUC: +114% (400 mg: single dose)* | Minor effect (use with caution if CrCl 15–50 mL/min)*** | No data yet |
| | | AUC: +136% (400 mg: multiple doses) | | |
| Quinidine | P-gp competition | AUC: +53% (1,000 mg: single dose)** | Minor effect (use with caution if CrCl 15–50 mL/min) | No data yet |
| Verapamil | P-gp competition and weak CYP 3A4 inhibitor | AUC: +18% (120 mg IR: single dose taken 2 h after DE intake)** | Minor effect (use with caution if CrCl 15–50 mL/min) | No data yet |
| | | AUC: +143% (120 mg IR: single dose, 1 h before DE intake)** | | |
| | | Cmax: +12% (120 mg IR: single dose taken 2 h after DE intake)** | | |
| | | Cmax: +179% (120 mg IR: single dose, 1 h before DE intake)** | | |
| Amiodarone | P-gp competition | AUC: +58% (600 mg: single dose)** | Minor effect (use with caution if CrCl 15–50 mL/min) | No clinically relevant effect |
| Diltiazem | P-gp and CYP 3A4 inhibitor | No effect | Minor effect (use with caution if CrCl 15–50 mL/min) | AUC: +40% |
| | | Antianginal/antihypertensive drugs | | |
| Ranolazine | P-gp and CYP 3A4 inhibitor | No data yet | Minor effect (use with caution if CrCl 15–50 mL/min) | No data yet |
| Felodipine | P-gp and CYP 3A4 inhibitor | No data yet | Minor effect (use with caution if CrCl 15–50 mL/min) | No data yet |
| | | Anti-inflammatory | | |
| Naproxen | P-gp competition | No data yet | AUC: +10% (500 mg) | AUC: +50% |
| | | Antihypercholesterolemiant | | |
| Atorvastatin | P-gp and CYP 3A4 substrate | AUC: +18% | No effect | No PK data yet |
| | | Antimycotic | | |
| Ketoconazole | P-gp and CYP 3A4 inhibitor | AUC: +138% (400 mg: single dose)* | Cmax: +72% (400 mg: single dose) | Cmax: +62% (400 mg od) |
| | | AUC: +153% (400 mg: multiple doses) | AUC: +158% (400 mg: single dose) | AUC: +100% (400 mg od) |
| Itraconazole | P-gp and CYP 3A4 inhibitor | No data yet* | No data yet, but similar results than ketoconazole are expected | No data yet, but similar results than ketoconazole are expected |
| Voriconazole | P-gp and CYP 3A4 inhibitor | No data yet | | |
| Posaconazole | P-gp and CYP 3A4 inhibitor | No data yet*** | No data yet | |
| Fluconazole | CYP 3A4 inhibitor | No data yet Supposed no effect | Cmax: +28% | No data yet |
| | | | AUC: +42% | |

Table 3: Continued.

| Molecule | Mechanism | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|---|
| | | Antibacterial | | |
| Clarithromycin | P-gp and CYP 3A4 inhibitor | Cmax: +49%<br>AUC: +60% | AUC: +54% (500 mg bid) | No data yet |
| Azithromycin | P-gp and CYP 3A4 inhibitor | No data yet | Minor effect (use with caution if CrCl 15–50 mL/min) | No data yet |
| Erythromycin | P-gp and CYP 3A4 inhibitor | No data yet | AUC: +34% (500 mg tid) | No data yet |
| | | Protease inhibitors | | |
| Ritonavir | P-gp and CYP 3A4 inhibitor | No data yet*** | Cmax: +55% (600 mg bid)<br>AUC: +153% (600 mg bid) | No PK data but strong increase |
| | | Immunosuppressor | | |
| Cyclosporine | P-gp competition | No data yet* | AUC: +50% | No data yet |
| Tacrolimus | P-gp competition | No data yet* | AUC: +50% | No data yet |

*The FDA recommends reducing the dabigatran etexilate at 75 mg bid for stroke prevention in NVAF. No recommendations are given by the FDA for cyclosporine, tacrolimus, and itraconazole.
**The EMA contraindicates concomitant treatment with these drugs. EMA recommends dose reduction from 220 mg od to 150 mg od in major orthopedic surgery and from 150 mg bid to 110 mg bid in stroke prevention in patients with NVAF. No dose recommendation is provided by the FDA.
***Not recommended by the EMA.

The EMA has introduced new contraindications for all NOACs since September 2013. This statement mentions that a screening of injuries and sicknesses that may lead to major bleeding is required before starting NOAC therapies. This can be a current or recent gastrointestinal bleeding, suspected or known esophageal varicose veins, any malignancy with high bleeding risks (e.g., colon cancer), recent cerebral, spine or ophthalmic injuries, recent intracranial hemorrhage, arteriovenous malformations, vascular aneurysm, or major intraspinal and intracranial vascular anomalies [32].

Careful attention must be directed to renal protective strategies for patients under DE. These patients should know that concurrent medications (e.g., NSAIDs) or clinical comorbidities (e.g., dehydration) can deteriorate their renal function, and, as consequence, increase and prolong dabigatran anticoagulant effect [32].

### 3.3. Improving Individual Benefit-Risk by Tailoring NOAC's Dose

*3.3.1. Why?* A reanalysis of the RE-LY study has shown that bleeding outcomes were correlated with dabigatran plasma concentrations [63]. Demographic characteristics (mainly age and previous stroke) played the strongest role in determining risk of clinical events. In addition, the authors concluded that for patients at highest risk for events, such as the very elderly and/or those with poor renal function, an adjustment of dabigatran dose to optimize exposure might improve benefit-risk ratio if they are at either extreme of the concentration range.

The EU-SmPC mentions that exceeding the 90th percentile of NOAC's trough level is considered to be associated with an increased risk of bleeding. For example, patients treated with 150 mg dabigatran BID for stroke prevention in NVAF have a 90th percentile of dabigatran plasma concentrations measured at trough (10–16 hours (h) after the previous dose) about 200 ng/mL [43].

Moreover, estimation of plasma drug concentrations can also be interesting to identify high responders which are at risk of bleeding [64]. Pharmacokinetic studies showed that dabigatran has considerable variation in plasma drug concentrations [65]. Most patients will obtain an adequate plasma level when given a fixed dose. But a measurable proportion will either achieve an insufficient or a supratherapeutic drug level [66–68]. Furthermore, medication adherence is not better than 50% in unmonitored conditions [64, 69], meaning that losing track of the patients during long-term (often life-long) treatment can be worrying. For these reasons, searching for the optimal dose in patients at risk of supra- or infratherapeutic plasma level can improve the efficacy and safety of NOACs. In addition, without a structured organization, there will be no routine check on side effects, tolerance, and adherence [64, 69].

*3.3.2. When?* To prevent massive bleeding, biological monitoring would be valuable in the following situations [64, 68, 70, 71]:

(i) before urgent surgery or procedure (with the last administration in the last 24 h, or more, if $Cr_{Cl}$ < 50 mL/min),

(ii) before fibrinolytic therapy of acute ischemic stroke,

(iii) for bridging therapy,

(iv) for patients with multiple risk factors for NOAC's accumulation (i.e., patients older than 75 years, drug-drug interactions as with frequently used medication like amiodarone and verapamil, extreme body weight (<50–60 kg and >110–120 kg), hepatic impairment, and renal impairment),

(v) for patients with renal impairment (progressive decrease of renal function, acute decrease due to dehydration, antibiotics administration, etc.),

(vi) in complex management of dual or triple antithrombotic therapies (e.g., patients with AF undergoing percutaneous coronary intervention or dual platelet inhibitors added to NOACs).

*3.3.3. How?* NOACs affect all routine coagulation assays [72]. The maximum effect of NOAC on clotting tests occurs at the same time as their maximal plasma concentrations (Table 1).

Therefore, it is essential to know the timing of NOAC's administration and the timing of blood sampling when interpreting results of a coagulation assay in a NOAC treated patient.

For example, coagulation assay results will differ if blood samples are taken 2 hours after DE intake (peak level) compared with blood sampling 12 hours after ingestion of the same dose. A French group (GIHP: Groupe d'Intérêt en Hémostase Périopératoire) proposed the following cut-off for the perioperative management of DE and rivaroxaban (Table 4): <30 ng/mL: the operation may take place; between 30 and 200 ng/mL: therapeutic zone; between 200 and 400 ng/mL: minor hemorrhagic risk; >400 ng/mL: major hemorrhagic risk [29].

For apixaban, there is no data regarding the plasma trough or max level versus bleeding or recurrence of thrombosis. Pharmacokinetic studies revealed that apixaban plasma concentrations varied modestly between peak and trough and were mainly comprised within the range of 100–300 ng/mL [73].

The recent recommendation of the International Society of Thrombosis and Hemostasis (ISTH) mentions that the activated partial thromboplastin time (aPTT) and prothrombin time (PT) can be used in emergency situations to determine the relative intensity of anticoagulation due to DE and rivaroxaban, respectively [72]. However, aPTT and PT should not be used to quantify the drug plasma concentration. Further studies are required to determine the relative sensitivity of aPTT and PT reagents in order to give more specific recommendations. In addition, aPTT and PT are global assays which are not reflecting peripheral concentrations of NOACs, especially at high plasma concentrations [72].

PT is not sensitive enough to estimate apixaban plasma concentrations. Furthermore, depending on the reagent, it may be normal with apixaban therapeutic concentration. Even for the most sensitive reagents, it may only inform the clinician if the patient is taking the drug.

Table 4: Perioperative management of NOACs (dabigatran and rivaroxaban)—proposal for recommendations from the GIHP (Groupe d'Intérêt en Hémostase Périopératoire) [29].

| Measured concentration | Recommendations |
|---|---|
| <30 ng/mL | Operate |
| 30–200 ng/mL | (i) Wait up to 12 h and obtain new dosage or (if time is not compatible with emergency)<br>(ii) Operate, if abnormal bleeding: antagonise the anticoagulant effect |
| 200–400 ng/mL | (i) Wait up to 12 h and obtain new dosage or (if time is not compatible with emergency)<br>(ii) Maximise delay surgery<br>(iii) Discuss hemodialysis, especially if $Cr_{cL}$ <50 mL/min (with dabigatran only)<br>(iv) Operate, if abnormal bleeding: antagonise |
| >400 ng/mL | Overdose major haemorrhagic risk<br>Discuss haemodialysis before surgery (with dabigatran only) |

As thrombin time (TT) is too sensitive to dabigatran [74], it is advisable to use a calibrated diluted thrombin time (dTT) with dabigatran standards to estimate dabigatran plasma concentration [74]. Therefore, Hemoclot thrombin inhibitor (HTI) is a rapid, linear, standardized, and calibrated assay which determines precisely plasma concentrations of dabigatran [74].

Chromogenic anti-Xa assays are recommended to accurately estimate rivaroxaban and apixaban plasma concentrations higher than 30 ng/mL [75, 76].

*3.4. Dealing with a Missed Dose.* To minimize the risk of bleeding, keep in mind that patients on DE for NVAF or on rivaroxaban for NVAF and VTE prevention should *never* take a double dose at the same time. If the missed dose is within 6 hours for dabigatran and within 12 hours for rivaroxaban, patients should take the forgotten capsule immediately. Otherwise, if the time is exceeded, they should just go on with the treatment without taking any capsule.

The only exception concerns VTE treatment with rivaroxaban, where patients may take simultaneously 2 tablets of 15 mg to ensure a total daily dose of 30 mg.

For apixaban, there is no time schedule. Patients should just take the forgotten capsule immediately and go on with the treatment [26].

*3.5. Adherence to Switching Procedures.* To avoid hypercoagulability during a switching procedure, it is important to consider NOAC's pharmacokinetics and patient comorbidities.

When VKAs are switched to NOACs, VKAs should be discontinued and NOACs should be started as soon as the INR is lower than 2 [77].

Inversely, if DE is switched to VKAs, physicians need to consider the renal function before starting VKAs. Creatinine

clearance ($Cr_{Cl}$) influences the delay of VKA's introduction, which in this case, precedes dabigatran arrest (from 3 days to 1 day, if $Cr_{Cl}$ is over 50 mL/min, between 30 and 50 mL/min or between 15 and 30 mL/min, resp.). NOACs interfere with an elevated INR, so that a better reflect of VKA on the INR will appear only after 2 days of NOAC's arrest [77].

To switch from NOACs to parenteral anticoagulants, these last ones should be started when the next dose of NOACs is due [77]. Inversely, NOACs should be started at the same time or up to 2 hours before the next parenteral anticoagulant dose. For intravenous unfractionated heparin, NOACs should be started at the time of discontinuation of the infusion.

*3.6. Adherence to Bridging Procedures.* The aim of bridging procedures is to avoid thromboembolic events in patients at high risk during the perioperative period.

Unfortunately, there is a lack of consensus regarding the different bridging procedures. These differences between national recommendations make safety studies difficult [78–82].

Only one prospective study has recently evaluated the peri-interventional NOAC management in unselected patients from daily care [83]. Outcomes and bleeding risks were compared for different types of procedure (minimal, minor, or major) in patients under NOACs. In 22% of the patients, NOACs were not interrupted, and in 30%, the gap in NOAC's intake was bridged with heparin. The rest of the patients underwent an interruption of NOACs of maximal 3 perioperative days. Major procedures had the highest cardiovascular and major bleeding complications. Interestingly, the bridging therapy did not reduce cardiovascular events but led to higher rates of major bleeding complications compared with no bridging. But these bleedings were similar to VKA patients who had bridging therapy before invasive procedures.

However, a selection bias resulted from a more frequent use of bridging therapy in severe procedure (most physicians anticipated the increased cardiovascular risk in patients undergoing major procedure). This can explain why cardiovascular and bleeding events were more frequent in major procedures [83].

They concluded that a continuation or short interruption of NOACs is safe for most invasive procedures and that patients with cardiovascular risks undergoing major procedure may benefit from bridging therapy, with as a consequence a higher bleeding risk. As the bridging therapy with heparin does not reduce the risk of cardiovascular events, a benefit-risk evaluation is needed to target the appropriate candidates who could benefit from it.

NOACs are sometimes interrupted perioperatively without bridging procedure. In this case, a postoperative resumption balanced between bleeding and thromboembolic risk needs to be defined. Spyropoulos and Douketis proposed a management based on studies assessing DE as thromboprophylaxis after orthopedic surgery and on the RELY trial. These authors suggest that NOACs should be resumed 24 hours after low bleeding risk surgery and 48–72 hours after high bleeding risk surgery. In patients with high thrombotic risk, consider a reduced dose of NOACs on the evening after surgery (DE) and on the first postoperative day (DE, rivaroxaban, and apixaban). Further studies are necessary to validate the safety of this approach [82].

*3.7. Adherence to Anesthetic Recommendations.* Anesthesia recommendations are available to decrease bleeding risks during perioperative procedures (e.g., regional anesthesia), especially in neuraxial anesthesia, which has potential risk of spinal hematoma [71, 84, 85].

Extreme caution is recommended with neuraxial blockade for rivaroxaban and apixaban. For DE, the manufacturer advise against its use [84].

For regional nerve blockade, ultrasound is a valuable tool to optimize catheter placement and decrease accidental vascular puncture [86].

Postprocedure anticoagulation (e.g., after removing indwelling catheter) should be restarted after 8 hours minus the time to reach maximum activity ($T_{max}$) (8 hours equal to the time to establish a stable clot) [87].

## 4. Absence of Antidote

The absence of antidote for NOACs emphasizes the importance of implementing strategies to prevent massive bleeding.

NOACs have a relatively short half-life, so that stopping the drug in patients without altered renal or liver function could be already valuable to eliminate it.

In large randomized controlled trial (RCT), the number of fatal bleedings was similar between NOACs and warfarin groups, despite absence of antidote for NOACs [12–14]. Strategies against life-threatening bleedings under NOACs are needed in any cases. Currently, there is no high-quality evidence in the clinical management of severe bleedings under NOACs but rather experience-related management. Animals and *in vitro* studies are guiding treatment approaches. The discussed effectiveness of nonspecific reversal therapies must be counterbalanced with their increased thrombotic risk [88–90].

A recent paper has presented the management and outcome of major bleeding during treatment with DE or warfarin [91].

Dickneite and Hoffman [92] reviewed the currently available data of PCC's use in reversing NOAC's anticoagulant effects. Because of different study models, the results are not entirely consistent. Some studies used 3F-PCCs, which contain high concentrations of coagulation factors II, IX and X and low and/or variable amounts of FVII. Other studies used 4F-PCCs, which additionally contain high levels of FVII. Due to their ability to raise the levels of these factors and consequently enhance thrombin generation in *in vitro* models, their utility to overcome the anticoagulant effects of FIIa and FXa inhibitors is plausible. But using PCCs to attempt to overcome the effect of an inhibitor is more complicated than simply replacing factors that are deficient. For example, the still present dabigatran will continue to

inhibit thrombin activity, even if PCCs are supplied and lead to thrombin formation.

Effectiveness and appropriate doses of PCCs still need to be established, especially when there appear variations in the ability of different PCCs to reverse NOAC's anticoagulant effects [92].

Only one of the available 4F-PCCs is able to reverse anticoagulation due to dabigatran and rivaroxaban. The others are more selective for dabigatran or rivaroxaban. These differences can be due to the wide variation in the amount of factors II, VII, IX and X, of antithrombotic proteins (proteins C and S) and also of anticoagulants, such as heparin and antithrombin, among the different PCCs. For the 3F-PCCs, two of them were able to normalize increased bleeding time following dabigatran administration, but the effect was short-lasting in comparison with 4F-PCC. This can be explained by the smaller amount of FVII in 3F-PCCs and its short half-life compared with the other factors. Activated PCCs seem to enhance more the parameters of thrombin generation to supratherapeutic levels than nonactivated PCCs, but it may be consequently at greater risk of thrombosis. Thrombin generation appears to have the best predictive value in the reversal of NOAC's anticoagulant effect.

Anyway, even if some PCCs seem promising in reversing anticoagulation due to NOACs, their effectiveness needs still to be studied in bleeding human patients [92].

Piccini et al. analyzed the management and outcomes of major bleeding events in patients treated with rivaroxaban versus warfarin, using data from the ROCKET AF trial [93]. Among high-risk patients with AF who experienced major bleeding, there was a reduction in fresh frozen plasma and PCC's use in the rivaroxaban group compared with the warfarin group [93].

Other alternatives exist to treat major bleedings in patients who do not respond to supportive measures. For dabigatran, due to its important renal excretion, hemodialysis can be proposed but with limited clinical experience [94–96]. Hemodialysis can also be discussed if a patient has renal insufficiency and needs an emergent surgery that cannot be delayed [29].

If NOAC's intake is recent, oral activated charcoal may also be effective [94].

Different specific antidotes are currently under evaluation. For DE, the antidote is a humanized selective and specific monoclonal antibody fragment (aDabi-Fab), which has no effect on other molecules. A recent study compared its *ex vivo* reversal effect with PCC, aPCC, and rFVIIa in a dabigatran anticoagulated liver trauma experimental model. Coagulation was assessed by thromboelastometry (TEM), global coagulation assays and diluted thrombin time. Interestingly, rFVIIa (90 and 180 microgrammes/kg) had no significant effect on coagulation parameters, but aDabi-Fab (60 and 120 mg/kg), PCC and aPCC (30 and 60 IU/kg) were effective in reducing the anticoagulation effects of dabigatran (TEM parameters and PT). In contrast, aDabi-Fab was the only reversal agent that normalized aPTT [97].

Andexanet alpha (PRT064445), a truncated form of enzymatically inactive factor Xa, is a universal reversal agent for all anti-Xa inhibitors. It reverses the inhibition of factor Xa dose-dependently, correcting the prolonged *ex vivo* clotting times due to anti-Xa inhibitors [98, 99].

Another antidote currently under research is aripazine (PER977), a small synthetic molecule that bounds several NOACs in animal studies, without significant adverse events. It reverses the anticoagulant activity of all clinically used NOACs in the rat-tail injury model and also in a human *ex vivo* model, using aPTT and anti-Xa analysis to measure its reversal effect [98, 99].

In the absence of specific antidotes, it is important to assess the degree of emergency and the patient characteristics (which type of NOAC, timing of the last dose, drugs interactions, comorbidities, site of bleeding, etc.) [100]. If possible, delay the surgery until the NOAC reaches trough concentration.

A hospital-wide policy for the management of NOAC's related bleedings should be easily accessible for every health worker involved in the patient's care.

## 5. Conclusions

NOACs are indisputably an important step forward in the field of anticoagulation. However, an inappropriate use can possibly lead to a higher risk of bleeding. This highlights the importance of strengthening education of health care professionals and patients, that is, with regard to dose adjustment, modalities of administration, choice of anticoagulant, and compliance guidance. Modifiable bleeding risk factors should also be screened and reviewed before initiation of NOACs. Individual benefit-risk might be improved in some clinical settings or patient subpopulations (patients at risk of supra- or infratherapeutic plasma level) by tailoring a dose following coagulation monitoring. Adherence to switching, bridging, resuming, and anesthetic recommendations is crucial to allow an optimal management of patient.

Anticoagulation with NOACs has still risks and requires strong adherence from the patient's side and careful supervision from the physician's side. Furthermore, since February 2012, the EMA has imposed the development of an education pack for patients and prescribers with regard to the safety and effectiveness of NOACs.

A well-structured organization will help to improve the control on side effects, tolerance, and adherence.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Authors' Contribution

Lessire Sarah, Dincq Anne-Sophie, Gourdin Maximilien, and Mullier François contributed equally.

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