Peri-operative management of anticoagulation and antiplatelet therapy in gastrointestinal surgery

S.-E. Degirmencu, A. Steib*

Service d’anesthésiologie et réanimation chirurgicale, Nouvel Hôpital Civil, 1, place de l’Hôpital, 67091 Strasbourg cedex, France

Summary Peri-operative management of the risks of hemorrhage and thrombosis related to gastrointestinal surgery tailored to patient characteristics are part of daily multidisciplinary practice tasks. The goal of this update is to discuss current practices concerning antithrombosis prophylaxis and the management of recently developed anticoagulants and antiplatelet agents. The duration of prophylaxis is 1 month for oncological surgery. The recommended doses in bariatric surgery are twice daily injections of low-molecular weight heparin without exceeding a total dose of 10,000 IU/day. Dual antiplatelet therapy is necessary for 6 weeks after placement of bare-metal stents, from 6—12 months for drug-eluting stents, and 12 months after an acute coronary artery syndrome. Abrupt discontinuation of antiplatelet therapy exposes the patient to an increased risk of thrombosis. Data are insufficient to make specific recommendations for antiplatelet therapy in gastrointestinal surgery. For major digestive surgery, prescription of daily aspirin should be discussed case by case. If discontinuation of treatment is absolutely necessary, this should be as short as possible (aspirin: 3 days, ticagrelor and clopidogrel: 5 days, prasugrel: 7 days). The modalities for elective management of new oral anticoagulants are similar to those for classical vitamin K antagonists (VKA) therapy, except that any overlapping with heparin administration must be avoided. In the emergency setting, an algorithm can be proposed depending on the drug, the available coagulation tests and the interval before performing surgery.

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Most operations performed in gastrointestinal surgery comprise a moderate to elevated risk of bleeding and/or thrombosis, depending on the procedure and patient characteristics. Pre-operative evaluation is essential to clearly identify these risks and adjust the peri-operative strategies meant to limit both the risks of bleeding and onset of venous or arterial thrombosis. These strategies include thromboprophylaxis but also

KEYWORDS
Gastrointestinal surgery; New direct oral anticoagulants; Antiplatelet agents; Emergency; Bleeding risk

* Corresponding author. Tel.: +33 3 69 55 10 91.
E-mail address: annick.steib@chru-strasbourg.fr (A. Steib).

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administration of long-term treatments (anticoagulants, antiplatelet agents) to prevent the risk of venous or arterial thrombosis. Measures should be discussed in a multidisciplinary fashion to establish consensual protocols based on the benefit/risk ratio. Expert recommendations or proposals published in this domain can help to make this decision. The goal of this update is to put these new hemostatic drugs into perspective according to the most recent data.

**Prevention of venous thromboembolism in gastrointestinal surgery**

Stratification of the risk of thrombosis in gastrointestinal surgery has led to the publication of recommendations by the French Society of Anesthesiologists and intensive care physicians (SFAR) in collaboration with the French Association for Surgery (AFC) for the prevention of venous thromboembolism (VTE) in 2005 [1]. These recommendations were updated in 2011 [2] according to the GRADE methodology. The formulation is binary: Grade 1 corresponds to either a positive (recommended +1) or negative (do not recommend −1) recommendation; Grade 2 corresponds to a positive (+2) or negative (−2) suggestion in the absence of pertinent data in the literature. Two chapters have been added for gastrointestinal surgery: one concerns oncological surgery focusing on the duration of prophylaxis, the other specifically concerns bariatric surgery with regard to dosage and the number of injections per day. These can be found in Tables 1 and 2.

**Oncological gastrointestinal surgery**

VTE is a frequent complication in patients with cancer, occurring in 4 to 20% of patients, and representing the second most common cause of death among patients hospitalized with cancer. The risk factors for thromboembolism are multiple [3]. They depend on patient characteristics (advanced age, co-morbidities, nutritional status, prior history of VTE, hereditary procoagulation disorders), the type of cancer (metastatic, gastro-pancreatic, renal, pulmonary), medical treatment (prolonged bed rest, active chemotherapy, hormonal therapy, pro-thrombotic drugs such as bevacizumab/thalidomide/lenalidomide), or surgery (oncological surgery). Several epidemiologic studies have clearly and objectively shown cancer to be an independent risk factor for thrombosis. White et al. [4] studied the risk factors for onset of VTE during the 3 months following surgery in 1,653,275 patients. The incidence was 0.8% [95% confidence interval (CI) = 0.7–0.8%] with approximately one third of the patients presenting with pulmonary embolism (PE). A prior history of VTE (OR = 6.2 [5.5–7.7]) and cancer (OR = 1.7 [1.6–1.8]) were found to be independent predictive factors of VTE. The RISTOS observational study [5], including 2373 patients undergoing operation for abdomino-pelvic cancer, showed a 2.3% incidence of VTE, 40% occurring 3 weeks post-operatively in patients who had undergone visceral surgery.

As concerns drug prophylaxis, one meta-analysis included 14 randomized studies comparing the prophylactic administration of LMWH vs. non-fractionated heparin (NFH) (2 or 3 injections/day) in patients undergoing surgery for abdomino-pelvic cancer; the study was unable to find any statistical significant differences between the two approaches [6] in terms of mortality, PE, symptomatic thrombosis or bleeding. LMWH is more effective than two daily subcutaneous injections of NFH on the incidence of VTE, but not when NFH is injected three times a day. The risk of immune-allergic thrombopenia (IAT) is however decreased with LMWH vs. NFH [7].

Fondaparinux (Arixtra®) was compared with mechanical thromboprophylaxis and LMWH in the prevention of thrombosis after abdominal surgery [8, 9]. The PEGASUS trial [8] showed that dalteparine 5000 IU/d was as effective as fondaparinux 2.5 mg/d administered during 7 to 10 days in patients at risk (70% oncological surgery). The APOLLO study [9] included patients over 40 years of age undergoing

<table>
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<tr>
<th>Table 1</th>
<th>Updated 2011 recommendations for thromboprophylaxis in gastrointestinal surgery [2].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical risk</td>
<td>Risk related to the patient</td>
</tr>
<tr>
<td>Weak</td>
<td>Non-major abdominal surgery: appendectomy, non-inflamed cholecystectomy, proctology, parietal surgery</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Extensive dissection or intra-operative bleeding</td>
</tr>
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<td>Operative duration abnormally prolonged</td>
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<td></td>
<td>Emergency</td>
</tr>
<tr>
<td>Elevated</td>
<td>Major abdominal surgery: liver, pancreas, colon, inflammatory bowel disease or gastrointestinal cancer</td>
</tr>
<tr>
<td></td>
<td>Bariatric surgery</td>
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</table>

IPC: intermittent pneumatic compression; LMWH: low-molecular weight heparin; IU: international units.

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abdominal surgery (40% oncological) lasting longer than 45 min and showed that there were fewer VTE events with fondaparinux 2.5 mg/d compared to mechanical prophylaxis. In both studies, the duration of administration of fondaparinux was short. Bleeding was not found to differ statistically significantly between the two groups. Nonetheless, several alerts were sent out by the French Agency for the Medical Safety of Health Products (AFSAPS) concerning this risk. Taking into account the long half-life (17h) and renal elimination, fondaparinux should be used with caution in the elderly, malnourished patient with decreased renal clearance, and injected no sooner than 6 hours after the end of surgery. The North-American recommendations, published in 2012 [10], proposed fondaparinux as a therapeutic alternative for patients at low risk of bleeding but who could receive neither LMWH nor NFH.

Use of mechanical prophylaxis (elastic stockings or intermittent pneumatic compression [IPC]) is effective in reducing the incidence of VTE events. One meta-analysis, published in 2005, showed that mechanical prophylaxis alone (30 studies) reduced the risk of venous thrombosis by 67% whatever the method used and independently of the surgical procedure performed [11]. Another recent meta-analysis showed that associating compression stockings with pharmacological or mechanical means reduced the incidence of deep venous thrombosis (DVT) and PE in general surgery [12]. The use of IPC in association with heparin in patients at high risk of thrombosis significantly reduced the incidence of PE and VTE compared to compression or pharmacologic prophylaxis alone. The evaluation included 11 studies, six of which were randomized, totaling 7431 patients [13]. This association was also suggested in the North-American recommendations published in 2012 for patients at high risk of thrombosis [10]. They suggested first-line use of IPC in preference to other means when the post-operative hemorrhagic risk was elevated until pharmacologic prophylaxis could be administered. This concerned major oncological surgery (hepatectomy, pancreatic and pelvic surgery).

The risk of TE events persists over several weeks after oncological abdominal surgery. One meta-analysis, comprising four randomized studies, has confirmed the benefits of prolonged (1 month) thromboprophylaxis with a significant decrease of more than 50% of TE events and more than 75% of proximal and symptomatic VTE after major surgery [14]. Injection of bemiparine after abdomino-pelvic surgery for cancer decreased the risk of major VTE without increasing the rate of hemorrhage-related complications in patients treated for 28 days vs. 8 days [15]. These data, strengthened by those of the PREOBS study [16], showed that prophylaxis for less than 4 weeks increases the risk of thrombosis by a factor of 7.85 in 2380 patients undergoing surgery for abdomino-pelvic surgery in France.

In sum, the propositions of the SFAR concur with those emanating from North America [2—10]: they recommend "high-risk" prophylactic anticoagulation for 1 month, irrespective of the type of abdomino-pelvic oncological surgery (grade 1+). Recent data remain without any answers. Thus, post-operative thrombocytosis is a possible risk factor for thrombosis after splenectomy. The use of antiplatelet agents has been proposed when the platelet count exceeds 1500 × 10^9/μL [17].

**Bariatric surgery**

Several studies have examined the risk of VTE after bariatric surgery. The incidence of VTE, however, differs greater between prospective and retrospective studies, posologies and drugs used, the number of included patients, and body mass index (BMI). One recent study including 4776 patients undergoing bariatric surgery (of which 3412 were gastric bypass procedures) showed that the independent factors for increased 30-day morbidity and mortality were antecedent of DVT or PE, sleep apnea syndrome, associated co-morbidities and a very high BMI [18]. Follow-up for 90 days of 73,921 patients undergoing bariatric surgery showed that the incidence of TE events was 0.42%, 73% of which occurred after discharge. These events occurred more often after bypass operations compared with gastric banding, after laparotomy compared with laparoscopy, in older patients, in patients with very elevated BMI, or with TE antecedent who had undergone vena cava filter insertion [19]. In all, bariatric surgery represents a high-risk surgery that warrants thromboprophylaxis (grade 1+).

Non-fractionated heparin (NFH), LMWH (enoxaparin, nadroparin, dalteparin and paparnarin) and fondaparinux have been used in a limited number of studies exploring the efficacy and clinical tolerance of these products in the obese. There are very few comparative data available: Enoxaparin 4000 IU injected twice daily reduced the incidence of TE events from 5.4% to 0.6% (P < 0.01) in 92 obese patients (BMI > 50 kg/m²) compared with twice daily administration of 3000 IU in 389 patients with identical BMI [20]. Conversely, no difference was observed in post-operative TE events when comparing two different regimens (5700 IU vs. 9500 IU) [21]. However, these clinical data, based on limited series of patients with an often-questionable methodology, do not allow establishment of any specific prophylactic policy. Therefore, the suggestion was to use LMWH (grade 2+).

The SFAR recommended "high-risk" prophylactic doses for bariatric surgery in 2005 (Table 2). Nonetheless, prescribing thromboprophylaxis in the obese raises several questions: is the efficacy of traditional strategies for

<table>
<thead>
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<th>Table 2: Administration modalities of heparin and low molecular weight heparin in gastrointestinal surgery [1].</th>
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<tr>
<td>Moderate risk (IU sc/d)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>UFH (Calciparine)</td>
</tr>
<tr>
<td>Nadroparin (Fraxiparine)</td>
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<tr>
<td>Enoxaparin (Lovenox)</td>
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<tr>
<td>Dalteparin (Fragmine)</td>
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<td>Tinzaparin (Innohep)</td>
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UFH: unfractioned heparin.
normal weight patients transposable to the obese? Can the same drugs be used? Do the doses have to be adapted to the real weight or to the ideal weight? Some studies have measured the anti-Factor Xa activity. Even though this measurement is not routinely recommended for follow-up of prophylaxis, it has supported the rationale. Thus, the comparison between two enoxaparin regimens (2 × 3000 vs. 2 × 4000 IU) injected in 19 and 33 patients, respectively (BMI 50 kg/m²), showed that 4000 IU allowed to obtain the desired target (0.2–0.6 IU/mL) in only 42% of patients after the third injection. The authors concluded that it was necessary to increase the doses [22]. A second study measured the anti-factor Xa activity obtained after injection of 2 × 4000 or 2 × 6000 IU of enoxaparin. After the third injection, the anti-Xa activity was still under the desired goal in 44% of patients treated with 4000 IU (n = 24) (0.18–0.44 IU/mL). All patients in the group treated with 6000 IU had an activity superior to 0.18 IU/mL but 57% were over-dosed (anti-Xa activity > 0.44 IU/mL). No bleeding occurred [23]. The third prospective study included 223 patients for whom the prophylaxis scheme was adapted to BMI (2 × 4000 IU enoxaparin when BMI < 50, 2 × 6000 IU when BMI > 50) and adjusted (±1000 IU) according to the anti-factor Xa activity measured at the time of the third dose (target 0.18–0.44 IU/mL). The goal was obtained in 74% of patients overall. The authors once again reported a 16.5% rate of overdoses for the posology of 6000 IU [24]. Parnaparin was used at the dose of 4250 IU vs. 6400 IU in two groups of 36 and 30 patients, respectively. Anti-factor Xa activity, measured on day 0, day 4 and day 6, 4 h after injection, did not show any correlation with BMI. The authors reported overdosing in 63% of patients in the group treated with 6400 IU (activity > 0.4 IU/mL) [25].

Thus, high dose regimens (6000 IU of enoxaparin, 6400 IU of parnaparine, 7500 IU of nadroparine) could lead to anti-Xa activity exceeding the upper limit of what is considered to be prophylactic and enter the therapeutic range in certain cases. However, the absence of correlation between the anti-Xa activity and BMI or bleeding does not allow any recommendation as concerns the adjustment of dosages in this manner. Because of this, it has been suggested to increase the daily doses without exceeding 10,000 IU anti-factor Xa/d (grade 2+) and to prescribe twice daily subcutaneous injections of LMWH (grade 2+).

Intermittent pneumatic compression (IPC) was used in most studies in association with pharmacological prophylaxis. In some studies, IPC alone was sufficient to prevent the onset of TE. It has been recommended to combine IPC with pharmacological prophylaxis (grade 2+), while inferior vena cava filters cannot be recommended (grade 1–). In most studies, prophylaxis started before the operation. The duration of prophylaxis as defined in the 2005 recommendations is 10 days for non-oncologic gastrointestinal surgery. For bariatric surgery, the arguments developed above seem to show that TE events occur at the time of discontinuation of treatment [18,19]. One study including 308 patients undergoing bariatric surgery has shown that extended prophylaxis (enoxaparin 4000 IU for 10 days after discharge) following in-hospital doses of 3000 IU BID reduced the incidence of TE events (4.5% → 0%) and bleeding (5.3% → 0.56%). Nonetheless, biased methodology (historical comparisons, more patients with higher risk factors in the group without extended prophylaxis) limits the pertinence of this study [26]. Dalteparin (5000 IU/d) was used post-operatively for 1 week after gastric banding and 3 weeks after gastric bypass in 735 patients. The authors did not observe any TE events or deaths and reported three instances of bleeding [27]. These results are insufficient to establish any formal recommendations for initiation (pre- or post-operative) or the optimal duration of prophylaxis. By analogy with gastrointestinal surgery, the minimal duration of 10 days post-operatively has been recommended (grade 1+).

**Ambulatory surgery**

The impact of ambulatory surgery and short-stay hospitalization has not been evaluated in gastrointestinal surgery [1]. The prescription of thromboprophylaxis depends on the procedure and patient characteristics, similar to traditional hospitalization. One cohort study [28] has shown that age over 40, uncontrollable cancer and duration of operation over 120 min were independent risk factors for the onset of TE events within 30 days of ambulatory surgery. Higher risk surgeries include orthopedic (arthroscopic) and peripheral vascular surgery [28].

**Management of patients treated with antiplatelet drugs**

Antiplatelet agents (APA) are prescribed as a primary prevention measure for diabetic patients with cardiovascular risk factors and for secondary prevention to prevent the risk of recurrent thrombosis in patients with coronary heart disease (stable, post-myocardial infarction, or after revascularization by stent or bypass), after transient ischemic or cerebrovascular accidents, in symptomatic lower-limb occlusive arterial disease, and in certain embolic/geneal heart disease settings.

**Pharmacology of long-term APA**

Aspirin is the most well-known and oldest agent used. Acetyl-salicylic acid acts irreversibly on the platelet COX-1 enzyme inhibiting its activity for 7–10 days (life-span of platelets). One dose of 75 mg is sufficient to totally inactivate this glycoprotein. Aspirin is prescribed at the dose of 75 or 160 mg per day.

Thienopyridines (ticlopidine, clopidogrel) are capable of inhibiting the ADP P2Y12 receptors of platelets. Clopidogrel (Plavix®) has a progressive action. This drug is more powerful than ticlopidine and associated with better tolerance, a reason for its emerging popularity. Maximal inhibition is obtained within a few days without the need for loading doses. The usual dosage is 75 mg per day.

Prasugrel (Effient®) is another new drug that also blocks the P2Y12 receptors irreversibly. This drug acts more quickly and more effectively than clopidogrel, but has a higher risk of bleeding incidents [29]. The usual dosage is 10 mg per day.

Ticagrelor (Brilique®) is a direct but reversible inhibitor of the P2Y12 receptor; it is absorbed rapidly and reaches its maximal concentration within 1.5 hours. Its half-life is 7 hours. This drug is more active than clopidogrel but with more undesirable effects [30]. The usual posology is 90 mg twice daily.

**Peri-operative management of APA for elective gastrointestinal surgery**

The French National Authority for Health (HAS) made recommendations concerning peri-operative management of APA in elective surgery in 2012. One specific chapter was devoted...
to each specialty. However, there are no recommendations dedicated to gastrointestinal surgery because of "lack of specific data" [31]. For primary prevention, APA is generally discontinued. For secondary prevention, the discussion is centered on the risk of bleeding if continued, vs. the risk of TE, if discontinued.

The risk of thrombosis depends on patient characteristics and the indications for APA treatment. Thus, a patient with a coronary stent or ongoing coronary artery disease is at high risk of thrombosis if APA treatment is untimely interrupted: 
• for bare-metal stents, dual therapy is recommended for 4 weeks. Elective surgery can be performed under aspirin alone, preferably after a delay of at least 6 weeks; 
• for drug-eluting stents, it is recommended not to discontinue APA treatment during the 6–12 months following stent insertion. Elective surgery can be performed under aspirin alone, after an interval of at least 6 months; 
• following myocardial infarction, dual therapy is recommended for 1 year.

In the case of discontinuation of dual therapy before the recommended date or discontinuation of APA irrespective of the interval, treatment should be restarted as soon as possible. The RECO study [32] clearly showed that, in a cohort of 1134 patients with coronary stents, interrupting APA treatment more than 5 days before surgery was an independent risk factor for the onset of heart or cerebrovascular thrombosis. Premature discontinuation of dual therapy led to a risk of death estimated between 20 and 45% and a risk of myocardial infarction of 64% [33].

The hemorrhagic risk depends on the type of surgery. There is no classification of the bleeding risk in the gastrointestinal surgery literature. However, this risk is increased in major oncological surgery. Within the framework of gastrointestinal surgery, it is equally important to consider the hemorrhagic risk as it relates to specific analgesic procedures such as epidural or spinal anesthesia. Blind puncture may lead to bleeding: in the limited epidural space, there is a risk of compressive hematoma.

Consequently the HAS recommends an individual case-by-case consideration of the benefit/risk ratio for "major" surgery, irrespective of the specialty, emphasizing the maintenance of aspirin therapy in high-risk cardiovascular patients. A randomized study of 291 patients, 20% of whom underwent gastrointestinal surgery, has shown that continuing aspirin therapy (vs. discontinuation for 10 days) did not worsen the incidence of early post-operative bleeding [34]. If discontinuation of APA is judged mandatory because of the unacceptable risk of bleeding, the recommendation is to discontinue aspirin for 3 days, clopidogrel and ticagrelor for 5 days and prasugrel for 7 days (so-called "3-5-7" rule) before surgery. Continuation of aspirin alone does not increase the risk of epidural hematoma and does not contraindicate performing neuraxial anesthesia. Spinal anesthesia should be preferred because it is less traumatic. In this case, it is wise to start thromboprophylaxis post-operatively. The European Society of Anesthesiology recommends discontinuing ticagrelor for 5 days, clopidogrel for 7 days and prasugrel for 7–10 days before performing neuraxial anesthesia [35]. This delay, substantially longer than the HAS recommendations, is related to the precautionary principle because it is impossible to obtain hemostasis in the epidural space. In all cases, the strategic choice is the fruit of concerted reflection between surgeons, anesthesiologists and prescriber of APA.

Management of patients treated with APA in the emergency setting

Emergency surgery exposes the patient taking APA to an increased risk of bleeding. The level of platelet inhibition can be determined by specific laboratory tests. These tests are not performed routinely and are usually reserved for very high-risk patients to adjust their long-term treatment or in case of unexplained stent thrombosis [31]. Platelet transfusion is not indicated prophylactically. Nonetheless, such transfusion becomes licit in case of bleeding. In cardiac surgery, intra-operative administration of tranexamic acid has been shown to decrease platelet dysfunction induced by dual therapy if the latter was not discontinued before surgery [36].

Management of patients taking anticoagulant therapy

Vitamin K antagonist (VKA) therapy

Peri-operative management of patients on VKA therapy has been largely defined in the French guidelines published by HAS in 2008 [37]. For elective surgery, the last dose of VKA should be taken 5 days before surgery. The goal is to obtain an international normalized ratio (INR) value < 1.5 the day of surgery. Pre-operative substitution is not necessary if the patient is at low risk of thrombosis (atrial fibrillation [AF] without any history of neurologic event or systemic embolism, VTE older than 3 months, without any recent accident or recurrence). Conversely, alternative anticoagulation therapy, called bridging, is necessary for patients (a) who have had a mechanical heart valve implant, (b) who have AF and antecedent of transient ischemic events or vascular cerebral accidents or systemic embolism, (c) who have had recent or recurrent VTE events such as proximal DVT or PE within 3 months. In these instances, bridging should be started 48 h after the last dose of fluindione (Previscan™) or warfarin (Coumadine®) and 24 h after the last dose of acenocoumarol (Sintrom™). Therapeutic doses with 2 injections per day (usually LMWH or subcutaneous NFH) are recommended for patients with mechanical heart valve(s) or AF. One therapeutic dose per day is suitable for VTE disease. Briding using intravenous NFH is much more rarely proposed; this implies pre-operative hospitalization.

Therapeutic doses of LMWH should be discontinued 24 hours before surgery, 12 hours for subcutaneous NFH, or 4 hours for intravenous NFH. INR should be measured the evening before surgery to assess the absence of residual effect of VKA therapy. If the INR is > 1.5, correction is possible by oral administration of 5 mg of vitamin K.

Resumption of VKA treatment post-operatively depends on the hemorrhagic risk of the surgical procedure. In patients at high-risk for thrombosis as defined above, therapeutic doses of heparin should resume not later than 48 h after the procedure. Thromboprophylaxis should be started early in the post-operative period. Compression stockings or IPC are efficacious in association or as stand-alone first-line therapy in cases of major risk of bleeding. Resumption of VKA depends on the patient’s ability to take medications orally. Overlapping heparin and VKA therapy for several days is necessary in order to achieve a stable therapeutic INR (2–3 most often) for two tests separated by 24 h.

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Table 3  Pharmacokinetics and therapeutic doses of NOACs available in France.

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<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
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<tbody>
<tr>
<td>Target</td>
<td>Anti-IIa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
<tr>
<td>T max (h)</td>
<td>2</td>
<td>2–4</td>
<td>3–4</td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces 20%</td>
<td>Feces 65%</td>
<td>Feces 75%</td>
</tr>
<tr>
<td></td>
<td>Renal 80%</td>
<td>Renal 33%</td>
<td>Renal 25%</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>14–17</td>
<td>7–13</td>
<td>8–15</td>
</tr>
<tr>
<td>Therapeutic dose</td>
<td>110 mg × 2</td>
<td>15 mg × 2</td>
<td>5 mg × 2</td>
</tr>
<tr>
<td></td>
<td>250 mg × 2</td>
<td>20 mg</td>
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NOAC: new oral anticoagulant; T max: peak effect.

For a patient on VKA therapy in the emergency setting, rapid correction of the INR to <1.5 is possible by intravenous injection of PCCs (25 IU/kg of factor IX or more simply 1 mL/kg) in combination with oral administration of 5 mg of vitamin K. A control INR should be performed 30 min later to confirm the correction or to indicate prescription of additional PCCs as necessary.

New direct oral anticoagulants

The new oral anticoagulants (NOACs) were initially marketed for thromboembolic prophylaxis in orthopedic surgery (total hip and knee replacements). The indications for their use have expanded in patients with cardiovascular disease. Their goal is to replace VKA therapy in most indications. They include anti-factor IIa agents [dabigatran (Pradaxa®)] or anti-factor Xa agents [rivaroxaban (Xarelto®), apixaban (Elisquis®)]. All three drugs have been studied in patients with AF [38] but also in other cardiovascular diseases (coronary syndrome, acute venous thrombosis, pulmonary embolism...). The patients to be treated could potentially represent about 1% of the French population (similar to VKA). Most of these patients will be exposed to severe untoward situations (overdose, bleeding, emergency or elective procedure, especially in gastrointestinal surgery).

Pharmacology of NOACs available in France

The pharmacological properties of NOACs available in France are provided in Table 3. Unlike VKA therapy for which an INR < 1.5 represents the threshold of hemostatic safety, the minimal plasma concentration constituting an identical bleeding risk for an untreated patient is not known. Moreover, NOACs alter the usual coagulation tests without providing any pertinent information about the anticoagulation status of the patient. Thus, an INR at 1.5 (hemostatic threshold for VKA) can correspond to an in vitro concentration of 200 mg/mL of rivaroxaban (corresponding to the peak effect after 20 mg given orally) [39]. For more precise information, specific tests, sometimes not available in all laboratories, are necessary. These tests provide an answer in terms of concentrations, which can be useful in the emergency setting. They are currently available in most university hospital laboratories.

Lastly, unlike VKA therapy whose effect can be reversed rapidly by injection of PCCs and oral vitamin K, no specific antidote exists for NOACs.

Peri-operative management of NOACs for elective gastrointestinal surgery

In the light of the elements developed above since there is no experience yet in the peri-operative management of the NOACs, two French groups (GIHP—Groupe d’Intérêt en Hémostase Périopératoire and GEHT—Groupe d’Études en Hémostase et Thrombose) [40] have made proposals based on the published recommendations of the HAS for VKA management. These recommendations do not specifically deal with each type of drug, instead, assimilating them into one homogeneous class with the idea of simplification and harmonization. Two situations can be envisioned within the framework of elective interventions.

For procedures with a low risk of bleeding, recommendations are similar to procedures for which it is not necessary to interrupt VKA therapy, as long as the pre-operative INR remains in the target zone (cataract surgery, skin surgery, dental surgery or digestive tract endoscopy). Gastrointestinal surgery is not included in these situations. However, some non-invasive diagnostic procedures can be included. Under these conditions, irrespective of the type of anticoagulant drug, the usual schedule of medication, or the procedure, the principle is the following: no NOACs the evening before and the day of surgery.

For procedures with a moderate to elevated risk of bleeding, including most gastrointestinal surgery procedures, NOACs should be discontinued pre-operatively sufficiently early to avoid bleeding during surgery. Considering the wide inter-individual variability observed and the wish to ensure 100% hemostatic safety, the standard scheme for VKA management can be reproduced, with no intake of NOACs within 5 days before surgery. Of note, this delay is longer than suggestions published by the pharmaceutical companies. During the 5-day interval before surgery, two scenarios are possible:

- for patients at high risk of thrombosis (AF with previous cardioembolic accident, VTE within <3 months or recurrent VTE, PE within <3 months), bridging by twice daily injection of therapeutic doses of heparin are recommended (cf. HAS recommendations for VKAs). Treatment should start 24 h after the last intake of NOACs in the patient with no risk factors of bleeding, and 48 h or longer after NOACs cessation in patients at increased risk (weight loss, kidney or hepatic failure, concomitant pharmacotherapy that may interfere with the metabolism of the NOACs) in order to avoid the enhanced risk of hemorrhagic accidents during the overlapping phase;

- for patients at low risk of thrombosis (other situations), there is no need for pre-operative heparin bridging after the last intake of NOACs.

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The moment when therapeutic doses of NOACs can be resumed post-operatively depends on how early the patient can absorb the orally-ingested drug and the risk of post-operative bleeding. Since NOACs have a rapid onset of action (2-4 h), it is important to ensure that the risk of post-surgical bleeding is past and to avoid all overlapping between NOACs and heparin administration. An interval of 12 h must separate the last injection of heparin and the oral intake of NOACs. If the intake is deferred, VTE prophylaxis must be initiated according to the recommendations of the SFAR [1,2]. The overall scheme of elective management is shown in Fig. 1.

Emergency gastrointestinal surgery

The need for emergency surgery is questionable for patients on NOACs since the hemostatic threshold of these drugs is unknown, and, unlike VKAs, there is no known specific antidote capable of reversing their effect. A case report was published in 2013 of fatal hemorrhage after laparotomy in an 88-year-old woman taking dabigatran for thromboprophylaxis following a total hip replacement [41].

This complicated situation has been the subject of several recent updates [42–46]. Numerous parameters have been proposed to adapt a management plan for these patients:

Figure 1. Peri-operative management of new oral anticoagulants (NOACs) in the elective setting. *High risk: atrial fibrillation with cardioembolic event, thromboembolic (TE) event <3 months or recurrent TE episodes. **Patient at high risk of bleeding: low weight, kidney or liver failure, pharmacological inhibitors of metabolism of NOACs; LMWH: low molecular weight heparin; UFH: unfractionned heparin.

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• dabigatran or rivaroxaban concentrations ≤ 30 ng/mL are not associated with an increased bleeding risk. These values are theoretically obtained 24–72 hours after discontinuing dabigatran [47] or 48 hours after discontinuing rivaroxaban [48], corresponding to approximately four half-lives; • in emergency situations, the residual concentration of NOACs can be assessed in certain laboratories. Concentrations between 25 and 500 ng/mL can be measured [49]. If such testing is not available, standard hemostasis testing (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT]) represents a partial solution that may be helpful in certain situations. When the tests are normal, the residual concentrations of the drug are probably low. Douxfils et al. have shown that the aPTT ratio between the patient and a healthy volunteer was less than 1.2 for a serum concentration of 10 ng/mL of dabigatran. Likewise, the INR was ≤ 1.2 when rivaroxaban concentrations were between 30 and 50 ng/mL [50,51]; • reversal of the anticoagulant effect of NOACs using procoagulant drugs [PCCs, FEIBA or recombinant activated factor VII (FVIIa)] has also been studied in both animal models and healthy volunteers [52–54]. These results are not impressive, especially as concerns FVIIa; therefore the preventive use of these drugs was not recommended by the GHa; they should be injected to treat active bleeding. Research is ongoing to find and commercialize specific antidotes [55].

These findings have led the GHa to publish therapeutic strategies for managing dabigatran and rivaroxaban in the emergency setting [46]. These need to be extended for apixaban for which recommendation is not available today.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Management of patients treated with therapeutic doses of dabigatran or rivaroxaban in the emergency setting according to their plasma concentration (specific dosages) [17].</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td>≤ 30 ng/mL</td>
<td>Operate</td>
</tr>
<tr>
<td>30–200 ng/mL</td>
<td>Wait up to 12 h then Repeat test</td>
</tr>
<tr>
<td>200–400 ng/mL</td>
<td>Wait up to 12–24 h Repeat test Maximum delay surgery Discuss hemodialysis if creatinine clearance &lt; 50 mL/min</td>
</tr>
<tr>
<td>&gt; 400 ng/mL</td>
<td>Overdosage Hemorrhagic risk +++ Discuss hemodialysis before any surgery</td>
</tr>
</tbody>
</table>

If impossible to delay surgery, operate and if abnormal bleeding is encountered, use prothrombin complex concentrate (PCC): 25–50 IU/kg or activated prothrombin complex concentrate (FEIBA): 30–50 IU/kg.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Step-by-step management procedure for patients in the emergency setting treated with therapeutic doses of dabigatran or rivaroxaban if measurements of plasma levels are unavailable. The activated partial thromboplastin time (aPTT) and prothrombin time (PT) can be disturbed by other causes [46].</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td>aPTT ratio ≤ 1.2</td>
<td>Operate</td>
</tr>
<tr>
<td>And PT ratio ≤ 1.2</td>
<td>Wait up to 12 h and Obtain specific dosage or aPTT and PT</td>
</tr>
<tr>
<td>1.2 &lt; aPTT ratio ≤ 1.5</td>
<td>Wait up to 12–24 h And obtain specific dosage If not, use aPTT and PT Maximum delay surgery</td>
</tr>
<tr>
<td>And PT ratio &gt; 1.2</td>
<td>Creatinine clearance &lt; 50 mL/min: specific dosage, discuss hemodialysis</td>
</tr>
</tbody>
</table>

If impossible to delay surgery, operate and if abnormal bleeding is encountered, use prothrombin complex concentrate (PCC): 25–50 IU/kg or activated prothrombin complex concentrate (FEIBA): 30–50 IU/kg. aPTT: activated partial thromboplastin time; PT: prothrombin time.

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Overall, when emergency gastrointestinal surgery is necessary with a risk of bleeding, one must determine the nature of the drug, its modality of administration (once or twice daily), the time of the last intake, renal function (creatinine clearance), and then specifically request specific testing by the laboratory.

Several management scenarios are possible for dabigatran and rivaroxaban (Tables 3–5).

If surgery cannot be delayed, procoagulant drugs should be used only in case of abnormal bleeding (PCCs 25–50 IU/kg or FEIBA 30–50 IU/kg) contrarily to VKA management where PCCs are injected before incision to correct hemostasis.

In patients treated with NOACs who present with severe bleeding (hemoperitonum, polytrauma…) FEIBA by injection 30–50 IU/kg or second line PCCs (50 IU/kg) have been suggested (Table 6).

When no specific hemostatic tests are available, the standard tests of hemostasis as the aPTT and PT ratios can help for decision-making.

In conclusion, management of hemostatic drugs during the peri-operative period depends on concerted collaboration between the different actors taking care of the patients (surgeons, anesthesiologists, cardiologists…). Decision-making is based on recommendations and on expert opinion allowing both the management of each specific case based on a risk/benefit ratio.

Disclosure of interest
S.D.: no conflict of interest.
A.S.: expert boards of Bayer, Bristol Meyers Squibb and Sanofi-Aventis, invitation to Bayer, Boehringer-Ingelheim, Bristol Meyers Squibb, Sanofi-Aventis, Laboratoire français du fractionnement et des biootechnologies (LFB), Covidien, CSL Behring symposiums.

Table 6 Management plan in case of bleeding with dabigatran or rivaroxaban with or without specific dosage [46].

<table>
<thead>
<tr>
<th>Hemorrhage in a critical organ</th>
<th>FEIBA 30–50 IU/kg</th>
<th>Or PCC 50 IU/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other severe hemorrhage</td>
<td>Plasma level ≤ 30 ng/mL (aPTT and PT ratios &lt;1.2)</td>
<td>⇒ No reversal</td>
</tr>
<tr>
<td></td>
<td>Plasma level &gt; 30 ng/mL (aPTT and PT ratios &gt;1.2)</td>
<td>And no hemostatic procedure possible</td>
</tr>
</tbody>
</table>

PCC: prothrombin complex concentrate; FEIBA: activated prothrombin complex concentrate; aPTT: activated partial thromboplastin time; PT: prothrombin time.

ESSENTIAL POINTS
Concerning the update of thromboprophylaxis recommendation in gastrointestinal surgery:

- post-operative prophylaxis is recommended for 1 month after oncological surgery;
- twice daily injections of low-molecular weight heparin (LMWH) (without exceeding 10,000 IU anti-Xa per dian) are suggested after bariatric surgery.

Concerning peri-operative management of antiplatelet therapy (APT):

- for ‘’major surgery’’, irrespective of the specialty, the French National Authority for Health (Haute Autorité de santé) advises considering the individualized benefit/risk ratio for each patient, targeted on maintaining aspirin in patients at high cardiovascular risk;
- if discontinuation of APT is absolutely necessary, this should be as brief as possible (aspirin: 3 days, ticagrelor and clopidogrel: 5 days, prasugrel: 7 days) with early resumption post-operatively.

Concerning the peri-operative management of the new oral anticoagulant drugs (NOACs):

- pre-operative management before elective surgery is similar to that for classical VKA therapy;
- post-operatively, there should be no overlap between heparin and NOACs (major increase in hemorrhagic risk) because, unlike VKA, the anticoagulant effect of NOACs is maximal 2–4h after absorption;
- in the emergency setting, specific hemostasis tests should allow detection of residual concentration of the drug. Surgery is possible when dabigatran and rivaroxaban levels are ≤30 ng/mL. Beyond this limit, it is preferable to delay surgery. If this is not possible, administration of prothrombin complex concentrates (PCCs), or factor eight inhibitor bypassing activity FEIBA® (Baxter) can be proposed if abnormal bleeding is observed.

References


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Peri-operative management of anticoagulation and antiplatelet therapy


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