



NARRATIVE REVIEW

**SBA 2020: Regional anesthesia guideline for using anticoagulants update**



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**Abstract** The development of protocols to prevent perioperative Venous Thromboembolism (VTE) and the introduction of increasingly potent antithrombotic drugs have resulted in concerns of increased risk of neuraxial bleeding. Since the Brazilian Society of Anesthesiology 2014 guideline, new oral anticoagulant drugs were approved by international regulating agencies, and by ANVISA. Societies and organizations that try to approach concerns through guidelines have presented conflicting perioperative management recommendations. As a response to these issues and to the need for a more rational approach, managements were updated in the present narrative review, and guideline statements made. They were projected to encourage safe and quality patient care, but cannot assure specific results. Like any clinical guide recommendation, they are subject to review as knowledge grows, on specific complications, for example. The objective was to assess safety aspects of regional analgesia and anesthesia in patients using antithrombotic drugs, such as: possible technique-associated complications; spinal hematoma-associated risk factors, prevention strategies, diagnosis and treatment; safe interval for discontinuing and reinitiating medication after regional blockade.

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**PALAVRAS-CHAVE**

Anestesia regional;  
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condução;  
Antitrombóticos;  
Tromboembolismo

**SBA 2020: Atualização na diretriz da anestesia regional em uso de anticoagulantes**

*Resumo:* Os padrões evolutivos para a prevenção do tromboembolismo venoso perioperatório e a introdução de medicações antitrombóticas cada vez mais potentes resultaram em preocupações com o aumento do risco de sangramento neuroaxial. Após o consenso da Sociedade Brasileira de Anestesiologia em 2014, novos medicamentos anticoagulantes orais foram aprovados pelas instituições reguladoras internacionais, assim como pela ANVISA. As sociedades que buscam abordar o manejo perioperatório desses fármacos apresentam recomendações conflitantes. Em resposta a essas questões e à necessidade de uma abordagem mais racional, as condutas foram atualizadas nesta revisão narrativa, e foram feitas novas recomendações, projetadas para encorajar a assistência ao paciente de forma segura e de qualidade, mas não podem garantir um resultado específico. Tal como acontece com qualquer recomendação de orientação clínica, estas estão sujeitas a revisão com o conhecimento de avanços específicos de complicações. O objetivo foi avaliar aspectos da segurança da anestesia e analgesia regional em pacientes em uso de medicações antitrombóticas, tais como: possíveis complicações decorrentes da técnica; fatores de risco associados ao hematoma espinhal, estratégias de prevenção, diagnóstico e tratamento; intervalo seguro para suspensão e reinício da medicação após o bloqueio regional.

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**Objective**

Assess safety aspects of regional analgesia and anesthesia in patients using antithrombotic drugs, such as: possible technique-associated complications; spinal hematoma-associated risk factors, prevention strategies, diagnosis and treatment; safe interval for discontinuing and reinitiating medication after regional blockade.

Brand names are presented here only as illustrations, and therefore the authors do not have any conflicts of interest.

**Update of the regional anesthesia safety guideline for using anticoagulants**

The development of protocols to prevent perioperative Venous Thromboembolism (VTE) and the introduction of increasingly potent antithrombotic drugs have resulted in concerns of increased risk of neuraxial bleeding. Since the most recent guideline of the Brazilian Society of Anesthesiology (SBA),<sup>1</sup> new oral anticoagulant drugs were approved by international regulating agencies, and by ANVISA. Moreover, societies and organizations that try to approach concerns through guidelines have presented conflicting perioperative management recommendations. As a response to patient safety issues and the need for a more rational management approach, SBA called for an update of the guideline. The information was updated to include data available since the previous publication.

The reviewed guideline statements envisage encouraging safe and quality patient care, but cannot assure a specific result. As any clinical guideline recommendations, they are subject to review as knowledge grows, on specific complications, for example.

The present document also deals extensively with the risk of bleeding of patients submitted to plexus or peripheral regional blockades. The recommendations are aimed at anesthesiologists and other physicians and health care work-

ers who perform regional neuraxial and peripheral blockade for anesthesia and/or analgesia. The recommendations can, however, be a resource to other health professionals involved in management of patients submitted to similar procedures (for example, myelography and lumbar puncture).

**Method**

A narrative review was performed to update the SBA guideline on regional anesthesia on using anticoagulants. Articles published between January 1, 2012 and August 31, 2019 were selected in addition to the articles already included in the previous guideline.<sup>1</sup> A review protocol was designed to identify, retrieve, and assess evidence searched on MEDLINE, Cochrane, Library and LILACS databases. The search was limited to studies with humans, and publications in English, French, German, Portuguese and Spanish.

The studies selected dealt with management of several types of regional anesthesia techniques on individuals using drugs that modify blood coagulation, focusing on risk factors, etiology, prevention, diagnosis and treatment. Reports published on pharmacokinetics and pharmacodynamics of antithrombotic drugs, series of patients who took these drugs during neuraxial and peripheral blockade and case reports of neuraxial and perineural bleeding (associated with spontaneous and/or regional anesthesia) were also included.

Search strategies were the same used in the 2014 SBA document:

- 1 "regional anesthesia" OR "anesthesia, conduction" OR "anesthesia" AND "conduction" OR "conduction anesthesia" OR "regional" AND "anesthesia" OR "regional anesthesia" AND "antithrombotic";
- 2 "regional anesthesia" OR "anesthesia, conduction" [MeSH Terms] AND "infection" [MeSH

Terms] AND "thromboembolism" [MeSH Terms] OR "thromboembolism" [All Fields];  
 3 "thromboembolism" [MeSH Terms] OR "thromboembolism" [All Fields] AND "regional anaesthesia" [All Fields] OR "anesthesia, conduction" [MeSH Terms] OR "anesthesia" [All Fields] AND "conduction" [All Fields] OR "conduction anesthesia" [All Fields] OR "regional" [All Fields] AND "anesthesia" [All Fields] OR "regional anesthesia" [All Fields].

Task force participants represent SBA and specialists in regional anesthesia, acute pain and interventionist pain.

### Strength and level of recommendations

The recommendations adopted used the classification system based on level of evidence and strength of recommendations according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) description.

The GRADE level of classification of evidence gathers an objective description of the types of studies/specialists' consensus that support a recommendation. Spinal hematoma is a rare complication and the impossibility of performing randomized clinical trials, and meta-analyses, does not allow for making higher level of evidence (A) available. Many observational and epidemiological series (typically, level of evidence B) have described the conditions for performing safe neuraxial anesthesia and analgesia on anticoagulated patients. However, high quality evidence can come from large observational/epidemiological series, resulting in major risk reduction. Thus, depending on risk reduction, the recommendations of these sources can be classified as levels of evidence A or B. Frequently, recommendations involving anesthetic handling of new anti-thrombotic drugs, for which safety and/or risk data are scarce, are based on pharmacology of the drugs, surgical bleeding risk or opinion of specialists (level of evidence C).

The level of recommendation shows the strength of the guideline and the level of consensus. Level 1 represents general agreement on the efficacy, Level 2 provides conflicting evidence or opinion on the usefulness, and Level 3 suggests that the procedure may not be useful (and possibly harmful). The present guideline does not include Level 3 recommendations. The words "we recommend" are used for strong recommendations (notes 1A, 1B and 1C), and "we suggest" for weaker recommendations (notes 2A, 2B and 2C). For cases in which evidence is scarce (such as new oral anticoagulants), the authors valued greatly patient safety and have proposed conservative periods, (that is, longer) for treatment discontinuation before performing neural blockade. They will probably be reviewed as additional information becomes available on blood levels and anticoagulant effects, as well as the introduction of reversal agents.

Finally, although there are several sections representing antiplatelet and anticoagulant drugs recently introduced, and revised recommendations on agents previously included, in some cases, management has remained unchanged. To make the review easier, the status of the current recommendations is included in each section.

### Incidence, risk factors and neurological prognosis outcome of spinal hematoma

Spinal/epidural hematoma (SEH), defined as symptomatic bleeding inside the vertebral canal, is a rare and potentially catastrophic complication of neuraxial anesthesia.<sup>2</sup> SEH occurs more spontaneously than as a result of neuraxial anesthesia. Most spontaneous hematomas are idiopathic, but cases related to anticoagulant therapy and vascular malformations represent the second and third most common causes, respectively.

When associated with neuraxial anesthesia, the concomitant use of anticoagulants represents the major risk factor for SEH.<sup>3</sup> Spinal canal hemorrhage occurs more frequently in the epidural space, probably due to the abundant epidural venous plexus, although anesthetic variables, such as needle size and catheter positioning, can also affect a clinically significant bleeding site.<sup>4,5</sup>

The actual incidence of neurological dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is unknown. Early literature reviews have estimated the occurrence as 1 case per 150,000 epidural punctures and 1 case per 220,000 subarachnoid punctures.<sup>6</sup> However, the calculations were based on series of patients who were not on thromboprophylaxis. Other patient series and epidemiological data collected have suggested a higher risk.<sup>7,8</sup>

Moreover, as there is no mandatory reporting and/or centralized registration system, many SEH are probably not reported and the frequency may be higher than calculated. Despite the low incidence of SEH, its severe clinical consequences, along with the costs of disputes subsequent to adverse events, make the development of solid strategies crucial to the management of anticoagulated patients during neuraxial anesthesia.<sup>9</sup>

With the introduction in the United States of enoxaparin, 30 mg administered twice a day for thromboprophylaxis, an alarming number of cases of epidural hematoma, some with permanent paraplegia, were reported. The incidence of SEH associated with twice a day doses of enoxaparin was calculated as 1:40,800 after subarachnoid anesthesia, 1:6,600 after single-shot epidural puncture and 1:3,100 after epidural puncture with epidural catheter insertion.<sup>10</sup> In Europe, a single dose of 40 mg of enoxaparin, showed a lower incidence of SEH. A retrospective study performed in Sweden,<sup>7</sup> found a risk of 1:156,000 after subarachnoid anesthesia, and of 1:18,000 after epidural anesthesia, and that bleeding was rare in the obstetric population (1:200,000) when compared to women submitted to knee arthroplasty (1:3,600). Subsequent studies have shown incidences as high as 1:2,700 to 1:19,505.<sup>11</sup> At the Third National Audit Project of the Royal College of Anaesthetists, however, Cook et al presented updated results reporting only eight cases of SEH among 707,405 neuraxial blockades, of which only five fulfilled inclusion criteria with a calculated incidence of 1:88,000 to 1:140,000.<sup>12</sup>

Given the rarity of the event, recommendations of regional anesthesia and concomitant use of thromboprophylaxis or antithrombotic therapy is based on case reports and recommendations of specialists.<sup>13-15</sup> Due to the severity of SEH, prospective randomized studies are ethically for-

**Table 1** SEH associated risk factors.**1. Patient-related**

- a) Age (elderly);
  - b) Sex – Female;
  - c) Congenital coagulopathies;
  - d) Acquired coagulopathies (renal/liver failure, malignancies, HELLP Syndrome, DIC);
  - e) Thrombocytopenia;
  - f) Spinal abnormalities (bifid spine/spinal canal stenosis, osteoporosis, ankylosing spondylitis);
- 2. Procedure-related**
- a) Insertion or removal of the catheter;
  - b) Traumatic procedure (multiple attempts);
  - c) Presence of blood in catheter during insertion or removal;
  - d) Insertion of epidural catheter > single-shot epidural puncture > single-shot spinal puncture.
- 3. Drug-related**
- a) Anticoagulant, antiplatelet or fibrinolytic drugs;
  - b) Administration of drug immediately before/after neuraxial technique;
  - c) Use of antiplatelet/dual anticoagulant therapy.

bidden. Vandermeulen et al. showed a close relationship of spinal hematoma cases associated with subarachnoid or epidural blockade in patients with evidence of hemostatic abnormality, such as coagulopathy or thrombocytopenia, or treated with platelet antiaggregant drugs (aspirin, indomethacin, ticlopidine), oral (fondaparinux) or thrombolytic (urokinase) anticoagulants.<sup>8</sup>

The risk factors for SEH have been described by several authors<sup>1,2,7,8,13,14</sup> and are presented in Table 1. Use of anticoagulants and neuraxial anesthesia is a higher risk factor for the development of SHE.<sup>3</sup> The incidence of SEH varies according to type of surgery, patient age and gender. For example, the incidence in pregnant patients submitted to neuraxial anesthesia is estimated at 1:200,000, while knee arthroplasty in geriatric age group women, is estimated at 1:3,600.<sup>7</sup> The rationale for the fact can probably be the higher incidence in the age group of spinal abnormalities associated with osteoporosis, use of double antiaggregant/anticoagulant therapy and anticoagulant accumulation due to non-detected reduction in renal excretion.

Among the types of neuraxial blockade, the risk of SEH is higher with the use of epidural catheters, followed by single-shot epidural puncture and less frequently after single-shot spinal puncture, the latter probably due to using thinner needles to perform the technique.<sup>16–18</sup> There are evidences that epidural hematoma is more common in lumbar, when compared to thoracic puncture.<sup>19</sup> Epidural catheter removal is as critical as insertion, as vascular injury can occur with a similar incidence, that is, half of SEH cases occur during epidural catheter removal.<sup>8</sup>

Currently, it is considered impossible to conclusively determine the risk factors for SEH in patients submitted to neuraxial blockade exclusively by reviewing case series, which represent patients with complications and do not take into account patients submitted to neuraxial analgesia

without events. However, studies that have assessed frequency of complications (including SEH), and those that have identified subgroups of patients with higher or lower risks, increase risk stratification.<sup>2</sup>

Clinical manifestations of SEH are characterized by slow or no reversal of the motor or sensory blockade, back pain, urinary retention or return of motor or sensory deficit after complete previous reversal of blockade, separate or combined, suggesting the development of SEH.<sup>8</sup>

If SEH is suspected, an aggressive diagnostic and therapeutic strategy is mandatory. This includes emergency Magnetic Nuclear Resonance (MRI) or, if not available, Computerized Tomography (CT). SEH is a neurosurgical emergency, and protocols should be established to avoid any delay in diagnosis. Once the diagnosis is confirmed, decompression laminectomy should be performed up to 6–12 hours after initial symptoms emerge, enabling higher likelihood of complete neurological recovery.<sup>8,20</sup>

In this way, patients should be carefully assessed by investigating possible signs that point toward SEH, both after neuraxial blockade and epidural catheter removal. The recommendation is monitoring at regular intervals until the sensory blockade reverts at least two dermatomes, or until complete return of motor function, observed for at least 24 hours after epidural catheter removal.<sup>8,16,20</sup>

Guidelines have been published by anesthesia societies aimed at increasing safety upon performing neuraxial blockade on anticoagulated patients.<sup>1,2,13,21–24</sup> Recommendations include: (I) time interval to be respected between the most recent dose of anticoagulant and insertion of neuraxial needle/catheter or catheter removal; (II) interval to be respected between neuraxial needle/catheter insertion or removal of catheter and the next dose of anticoagulant; and (III) minimum coagulation time values required to perform neuraxial technique (if available for the drug being used).

Due to the ongoing development of anticoagulant drugs by pharmaceutical companies and their growing use in clinical practice, guiding clinical trials are lacking, which makes it difficult to make any statement as to performing neuraxial anesthesia on patients taking new anticoagulants.

Rosencher et al. have proposed that, to manage patients on new anticoagulants, when the insertion of a needle/catheter in the neuroaxis and subsequent catheter removal are required, the procedures should be performed with a period above two half-lives of drug elimination after the most recent dose used. The information is based on the fact that 30% to 40% of the function of coagulation factors are required for hemostasis, so that after two half-lives the concentration of the drug in the bloodstream is near to 25% of the initial concentration.<sup>25</sup> This management was changed after observing that the interval of two half-lives after discontinuation assures that roughly 75% of medication is eliminated, but, the residual effect of the drug still could be catastrophic in some scenarios, especially elderly patients with spinal canal stenosis. After this observation, the interval of five half-lives became recommended.<sup>26</sup>

### The cellular mechanism of coagulation

The physiological process of coagulation is complex and involves several tissue and plasma components. It is essen-

tial to understand the fibrin clot formation system at the site of the endothelial lesion and the mechanisms involved in the process to appreciate the mechanism of action of antiplatelet agents.

The components of the hemostatic system include platelets, vessels, blood coagulation proteins, natural anticoagulants and the fibrinolysis system. The functional balance of hemostasis is assured by a variety of mechanisms that involve interactions among proteins, complex cell responses and blood flow regulation.

Understanding hemostasis allows better understanding of the action of anticoagulants used. Hemostasis consists of the inter-relationship among biochemical, physical and cellular processes when the vascular endothelium is injured, with exposure of collagen rich subjacent subendothelial matrix. Platelets adhere to collagen via Glycoproteins (GP) Ia/IIa and GP-VI presents on their membrane. Adhesion also happens in high flow scenarios, such as the arterial bed, via Von Willebrand Factor (FvW) that adheres to platelets via GP-Ib and fixes them to collagen. Platelet adhesion through these membrane glycoproteins leads to intracellular signaling via phospholipase C, with subsequent increase in intracellular calcium and onset of platelet activation.<sup>27</sup>

Once activated, platelets release dense granules (ADP, serotonin and calcium) and alpha granules (fibrinogen, factor V). Increase in intracellular calcium also activates Phospholipase A-2 enzyme (PLA-2), that degrades membrane phospholipids into Arachidonic Acid (AA); the latter is transformed into tThromboxane-A<sub>2</sub> (TxA<sub>2</sub>) by the Cyclooxygenase type-1 enzyme (COX-1). The TxA<sub>2</sub> formed, ADP and serotonin released from dense granules, circulating adrenalin and vasopressin and thrombin generated, activate higher amounts of platelets, via protein G-linked receptors. Activated platelets, in addition to changing their shape from spheroid to discoid, modify the shape of glycoproteins IIb/IIIa and increase the number of these GP on the platelet membrane. GP IIb/IIIa intermediate bond to other platelets through FvW and fibrinogen molecules in a process called platelet aggregation. The cell signaling process can be interrupted by increase in intracellular AMPc generated by Prostacyclin (PGI-2) or by the inhibition of Phosphodiesterase Enzyme (PDE) that degrades AMPc<sup>27</sup> (Fig. 1).

Antiplatelet drugs are, therefore, represented by Non-Steroid Anti-Inflammatory Drugs (NSAIDs), thienopyridines or indirect inhibitors of ADP (P2Y<sub>12</sub>) (ticlopidine, clopidogrel, prasugrel), direct inhibitors of ADP (P2Y<sub>12</sub>) (ticagrelor, cangrelor), phosphodiesterase (PDE) inhibitors (dipyridamole, cilostazol) and glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban).

## Neuraxial anesthesia and using antiplatelet agents

### Acetylsalicylic acid (ASA) and NSAIDs

NSAIDs inhibit the production of prostaglandin H<sub>2</sub> required for synthesis of Thromboxane A<sub>2</sub> (TxA<sub>2</sub>), a potent platelet activator, by inhibiting Cyclo-Oxygenase enzyme (COX). The enzyme has two forms, type 1 Cyclo-Oxygenase (COX-1) is responsible for regulating constitutive mechanisms, and type 2 Cyclo-Oxygenase (COX-2) is inducible and is part

of the inflammatory process.<sup>2</sup> There are several classes of NSAIDs, such as salicylates (acetylsalicylic acid), acetic acid derivatives (diclofenac, ketorolac), enolic acid derivatives (piroxicam, tenoxicam), propionic acid (ketoprofen, ibuprofen) and selective COX-2 inhibitors (parecoxib, celecoxib).

ASA inhibits COX-1 irreversibly, blocking the production of TXA<sub>2</sub> for the entire platelet mean life (7 to 10 days); thus, it inhibits the entire platelet activation and aggregation process.<sup>1,15</sup> Other NSAIDs also inhibit COX-1, but reversibly and proportionally to the half-life of the agent used<sup>1</sup> and for most NSAIDs, the process returns to normality between 12 and 24 hours after the discontinuation of those NSAIDs.<sup>28</sup> On the other hand, selective COX-2 inhibitors are anti-inflammatory drugs that do not cause platelet dysfunction, given COX-2 is not expressed in platelets.<sup>29</sup>

Vandemeulen et al. identified only one case of SEH associated with the isolated use of ASA as a risk factor.<sup>8</sup> However, in this case, in addition to the high dose of ASA (650 mg 12/12 hours initiated 4 hours after surgery), there were multiple attempts of epidural technique, with accidental puncture of the dura and placement of a subarachnoid catheter.<sup>30</sup> Contrary to the isolated report, a prospective multicentric study with 4,603 patients submitted to surgical treatment for hip fracture receiving either 160 mg.day<sup>-1</sup> of ASA or placebo did not observe any case of SEH after neuraxial anesthesia.<sup>31</sup>

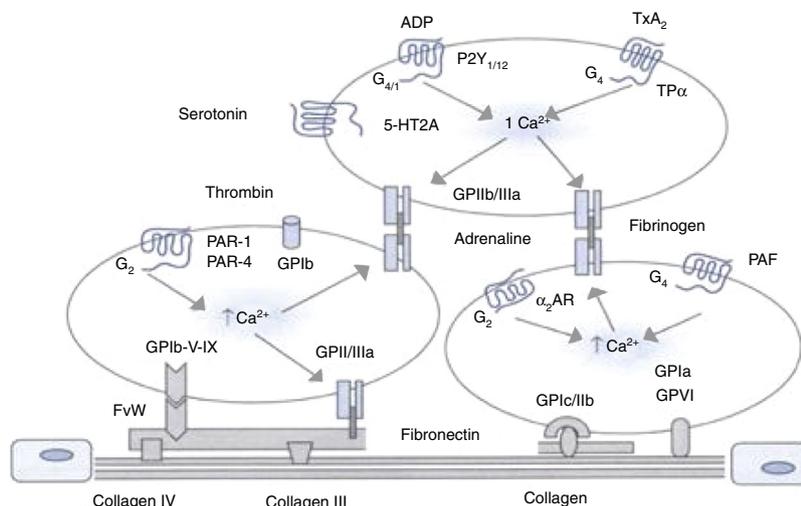
Two major prospective studies performed in the obstetric population showed safe neuraxial anesthesia using low doses of ASA. In a study that assessed the effect of ASA in preventing pre-eclampsia, 9,634 pregnant women were randomized to receive either 60 mg of ASA or placebo. Of the 1,422 patients in the ASA group and who received epidural anesthesia, there were no cases of SEH reported.<sup>32</sup> In another study, with 3,531 pregnant women; 451 patients received ASA and were submitted to epidural anesthesia, and there were also no cases of SEH.<sup>33</sup> The results corroborate evidence that using ASA in the obstetric and orthopedic population is safe.<sup>31-33</sup>

Regarding other NSAIDs, of the 1,035 patients submitted to the epidural injection of corticosteroids to treat chronic pain, 249 received an epidural injection while on treatment with those drugs and no HEP was observed,<sup>34</sup> suggesting safety of neuraxial anesthesia in patients on NSAIDs.

Thus, the isolated use of ASA and other NSAIDs does not increase significantly the risk of SEH. However, the combination of these drugs with other agents that interfere in normal coagulation, such as non-fractionated heparin, low molecular weight heparin, oral anticoagulants and other antiplatelets, have shown increased risk of SEH.<sup>8,35,36</sup>

#### Recommendations

1 Aspirin used alone does not seem to represent an additional risk for the development of SEH in patients submitted to epidural or subarachnoid anesthesia. For patients using the drug, there is no specific concern as to the interval between spinal/epidural punctures or catheter insertion and the latest dose administered of the drug. Likewise, there is no need to wait after aspirin discontinuation for catheter removal or for postoperative aspirin administration after catheter removal (1B).<sup>2,31-33</sup>



**Figure 1** Mechanisms involved in platelet activation and adhesion to the subendothelial layer. The Von Willebrand factor (FvW), collagen and proteins link to membrane glycoprotein receptors (GP), which assures stability with subendothelial matrix by interaction with collagen. Platelet activation and aggregation are triggered by thrombin, endogenous mediators released from storage granules, platelet activation factor (PAF) and thromboxane A<sub>2</sub> (TxA<sub>2</sub>). Aar, α<sub>2</sub> adrenergic receptor; ADP, Adenosine Diphosphate; 5-HT<sub>2A</sub>, Serotonin (5-Hidroxitriptamine)-2A; PAR-1, Protease type 1 Activated Receptor; PAR-4, Protease type 4 Activated Receptor; P2Y<sub>12</sub>, p2y Purinergic Receptor; TPα, αthromboxane receptor.

Source: Adapted from Anfossi et al, Nascimento JCR, Reis NMGT. Coagulação do sangue e coagulopatias. in: James Manica. *Anestesiologia*, 4.ed. Porto Alegre (RGS): Artmed Editora, 2018;547.

- Other NSAIDs used alone do not seem to pose an additional risk of SEH in patients submitted to subarachnoid or epidural anesthesia.<sup>11</sup> For patients on those drugs there is no specific concern as to the interval between spinal/epidural punctures or catheter insertion and the latest dose administered of the drug. Likewise, there is no need for a drug discontinuation interval to remove the catheter or for postoperative administration of the drug after catheter removal (1B).<sup>34</sup>
- For patients receiving ASA or other NSAIDs, we suggest caution to perform neuraxial blockade techniques, in case of simultaneous use of other medications that affect coagulation mechanisms – such as oral anticoagulants, UFH and LMWH – due to the increase risk of hemorrhagic complications (2C).<sup>1,2</sup>
- Due to the absence of effect on platelet function with selective COX-2 inhibitors and low risk of perioperative bleeding, these drugs do not need to be discontinued (1B).<sup>29,37</sup> Moreover, COX-2 inhibitors should be preferred for patients who need anti-inflammatory treatment in the presence of anticoagulation (2C) because of their minimum effect on platelet function.<sup>1,2</sup>
- Analgesics, such as dipyron and paracetamol, do not seem to contraindicate neuraxial anesthesia, given to date, there are no cases of SEH associated with using these drugs (2C).<sup>1,13</sup>

## Thienopyridines

Ticlopidine (Ticlid®), Clopidogrel (Plavix®) and Prasugrel (Effient®) are platelet inhibitors that belong to the class of thienopyridines. They are prodrugs cleaved in vivo in the liver by CYP450 into active metabolites that antago-

nize the platelet receptor of adenosine diphosphate (ADP – P2Y<sub>12</sub> receptor) and interfere in activation and platelet aggregation; the effect cannot be antagonized and it is irreversible.<sup>1,2</sup>

Ticlopidine is less and less used due to its slow and lasting anti-platelet effect (platelet function become normal after 10–14 after discontinuation). Moreover, it can produce hypercholesterolemia, thrombocytopenia, aplastic anemia and thrombotic thrombocytopenic purpura.<sup>15</sup>

Clopidogrel is also a prodrug that undergoes biotransformation in the liver in two stages and is more commonly used.<sup>38</sup> There are, however, some limitations, that include failure in response in 4%–30% of users, susceptibility to interactions with several drugs, given its action depends on conversion in the liver by CYP 3A4 (isoform that participates in 40%–80% of metabolization of all drugs in the body), and enzyme variations by genetic polymorphism. Its peak of action is slow, around 24 hours, however, after a loading dose of 300–600 mg, the peak of action falls to 4–6 hours. The maximum platelet inhibition effect reached by clopidogrel is 50%–60% that disappears 7 days after discontinuation.<sup>15</sup>

Prasugrel causes irreversible inhibition of the P2Y<sub>12</sub> receptor. However, unlike clopidogrel, it requires only one step to be biotransformed into its active compound.<sup>38</sup> It has a 90% effect of inhibiting platelet function, compared to 60% of clopidogrel, and fast onset of action (peak effect in 30 minutes). Platelet function returns to normal after 7 to 10 days.<sup>15</sup> It has a higher risk of bleeding and occasionally is fatal.

A study assessed 306 patients on clopidogrel submitted to vascular surgery procedures, in which epidural anesthesia was performed with the catheter staying 3 days, and there were no cases of SEH.<sup>39</sup> However, three cases in the liter-

ature described SEH after neuraxial techniques on patients using ticlopidine or clopidogrel.<sup>35,40,41</sup> There were no cases with prasugrel. Prospective studies assessing safety of performing neuroaxis blockade in the presence of treatment with thienopyridines are required.

The recommendation of the thienopyridine manufacturing industry is for the discontinuation of ticlopidine 10 days before surgery, 5 days for clopidogrel, and 7 days for prasugrel. Platelet function test studies have shown safety in performing neuraxial blockade 5 days after interrupting use of clopidogrel, given over 70% of platelet function will be reestablished.<sup>42</sup> For prasugrel, studies have shown that platelet function returns to normal only 7 days after the drug is discontinued.<sup>43</sup>

#### Recommendations

- 1 Neuraxial blockade or catheter removal should be performed 10 days after ticlopidine discontinuation (1C).<sup>2</sup>
- 2 Neuraxial blockade or catheter removal in patients using clopidogrel can be done 5 to 7 days after drug discontinuation. (1C).<sup>2,42</sup> Although there is a study showing safety in neuraxial procedures when using the drug,<sup>39</sup> we do not recommend the practice.
- 3 There are no studies available assessing the combination prasugrel and neuraxial anesthesia. It seems reasonable, however, based on pharmacological studies that the treatment with prasugrel be discontinued at least 7 days<sup>43</sup> before neuraxial blockade or removal of the epidural catheter (1C).<sup>1,2,15</sup>
- 4 According to recommendations of the American College of Chest Physicians, pharmacological treatment with thienopyridines should be reinitiated 24 hours postoperatively (2C).<sup>44</sup>

### Direct inhibitors of ADP receptors

Direct inhibitors of ADP receptors are non-thienopyridine drugs that antagonize receptor P2Y<sub>12</sub> non-competitively and reversibly, without requiring biotransformation in the liver. Ticagrelor is the most important one and is increasingly becoming the drug of choice of this class of medications due to its higher safety profile. Cangrelor was recently approved by regulating agencies, aimed at intravenous use and it has rapid onset and offset of action.

Ticagrelor is a non-direct competitor and reversible antagonist of P2Y<sub>12</sub> receptor, and does not require liver metabolism for its activation. It has a rapid onset of action, with a platelet inhibition peak 2 to 4 hours after administration. It has a 90% platelet activity inhibition effect.<sup>45</sup> After discontinuation, platelet function recovers in 5 days.<sup>46</sup> Unlike prodrugs, its effect does not depend on enzyme genetic polymorphisms, which makes it less prone to individual variability and with a better safety profile compared to thienopyridines. Both considerations, including its efficacy, have made this a preferred drug among ADP receptor antagonists in patients with acute coronary syndrome.

Cangrelor is the first direct intravenous inhibitor of the ADP receptor (P2Y<sub>12</sub>), in addition to not being competitive and it is reversible. It is administered in an initial bolus dose followed by continuous infusion, action beginning at 2 minutes and its plasma half-life is 3.6 minutes.

It has a platelet aggregation inhibition effect of 95% to 100%.<sup>47</sup> After discontinuation, platelet resumes activity quickly, within 90 minutes in 90% of patients.<sup>48</sup> These pharmacodynamic characteristics make the drug attractive in scenarios in which immediate platelet anti-aggregation is required, for patients unable to swallow pills and as a bridging therapy for surgical procedures when oral antiplatelet treatment discontinuation can generate increased risk of thrombosis.<sup>38</sup>

To present there are no prospective studies involving neuraxial anesthesia and using this class of drugs. Moreover, there are no cases in the literature of SEH related to these drugs. According to the manufacturer of ticagrelor, whenever possible, it should be discontinued at least 5 days before any surgical procedure, which corroborates the findings of Gurbel et al., that showed complete recovery of platelet function 5 days after discontinuation of the drug.<sup>46</sup> Despite cangrelor's short plasma half-life of 3–6 minutes,<sup>48</sup> its discontinuation is recommended 3 hours before surgical procedures, based on a randomized clinical trial that showed hemorrhagic complications similar to placebo with a median of 3 hours of discontinuation.<sup>49</sup>

#### Recommendations

- 1 There are no available studies that assess the combination ticagrelor and neuraxial anesthesia, but according to pharmacological studies,<sup>24</sup> it seems reasonable to discontinue ticagrelor treatment at least 5 days before neuraxial blockade or removal of epidural catheter (2C).<sup>1,2,15</sup>
- 2 According to recommendations of the American College of Chest Physicians, pharmacological treatment with ticagrelor should be reinitiated 24 hours postoperatively (2C).<sup>44</sup>
- 3 Keeping epidural catheter in situ while on treatment with ticagrelor is not recommended due to its quick onset of action (2C).<sup>2</sup>
- 4 Despite its short half-life, the recommendation is that cangrelor be discontinued at least 3 hours before neuraxial puncture (2C).<sup>2,15,49</sup>
- 5 Based on the 8 hour period required for stable blood clot formation and the immediate onset of action of cangrelor, one should wait at least 8 hours after neuraxial puncture to start administration of cangrelor (2C).<sup>2</sup>

### Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors include abciximab, eptifibatide and tirofiban. They are currently the most effective drugs available to inhibit platelet aggregation, and normally used during percutaneous coronary interventions.<sup>1</sup> They block platelet glycoprotein IIb/IIIa, binding site of fibrinogen between platelets and, therefore, the final common path of platelet aggregation. They are available exclusively for intravenous use.

Abciximab (Reopro<sup>®</sup>) inhibits GP IIb/IIIa non-competitively and irreversibly. It has a rapid onset of action, with complete inhibition of platelet aggregation in 2 hours. It has a short half-life (10–30 minutes) and recovery of platelet function is slow, occurring 24–48 hours after discontinuation. Eptifibatide (Integrilin<sup>®</sup>) and tirofiban

(Aggrastat®) have a rapid onset of action and faster platelet function recovery, that is 4 hours for epifibatide and 4–8 hours for tirofiban.<sup>15,50</sup> The most common side effects are thrombocytopenia and bleeding.<sup>50</sup>

To date, there are no studies assessing safety of regional anesthesia in patients on this class of medications; thus, intervals for discontinuation of the drugs should obey pharmacokinetic characteristics.

#### Recommendations

- 1 According to pharmacological properties, one should wait for complete platelet aggregation recovery to perform neuraxial anesthesia or remove the catheter. That is, 8 hour discontinuation for tirofiban/epitifibatide and 48 hour discontinuation for abciximab, and providing any thrombocytopenia is ruled out by a recent platelet count (2C).<sup>2,15</sup>
- 2 GP IIb/IIIa inhibitors are used in acute coronary syndrome, in combination with anticoagulants and ASA. In this scenario, in emergency procedures that generally involve heart surgery with continued anticoagulation, any neuraxial blockade is contraindicated (2C).<sup>1</sup>
- 3 GP IIb/IIIa inhibitors have a rapid onset of action, therefore, if the administration of these drugs is required in the postoperative, the interval necessary to form a stable blood clot should be respected; thus, an 8–12 hour interval is probably appropriate (2C).<sup>15</sup> These drugs, are contraindicated, however within 4–6 weeks after surgical procedures (1C).<sup>2</sup>

### Phosphodiesterase inhibitors (PDE)

Phosphodiesterase inhibitors are also used as anti-platelet drugs. Platelets express three isoforms of this enzyme: PDE-2, PDE-3 and PDE-5. Drugs representing this class include dipyridamole (Persantin®) and cilostazol (Vasogard®, Pletal®, Cebrelat®). PDE inhibitors lead to increase in intracellular AMP-c and GMP-c, which impair the development of second messengers inside platelets, essential in platelet activity. PDE-3 inhibitors (Cilostazol) lead to increase in AMP-c, while PDE-5 inhibitors lead to increase in GMP-c.<sup>15</sup> The drugs are also responsible for arterial dilation through the same mechanism.

Dipyridamole acts blocking both PDE-3 and PDE-5, and normally is used associated with ASA for primary and secondary prevention of vascular cerebral disease. It has an elimination half-life of 10 hours.<sup>3</sup> Cilostazol only inhibits PDE-3 and is indicated in peripheral arterial disease and intermittent claudication in patients who do not respond to treatment with exercise, and with a low likelihood of undergoing surgical intervention.<sup>1</sup> The plasma concentration peak of cilostazol after oral administration is 2 hours, its elimination half-life is approximately 10 hours and, after 50 hours (approximately 5 half-lives), less than 5% of the drug is found in the plasma, with recovery of platelet aggregation.<sup>15,51</sup>

There is only one case described of SEH in a patient using cilostazol; the patient was elderly, and in addition to using cilostazol, had a platelet count below 100,000 mm<sup>3</sup> and was submitted to multiple epidural punctures with catheter implant and subarachnoid puncture.<sup>52</sup> There are no cases of

SEH after regional anesthesia in patients using dipyridamole, however, the combination of the drug with ASA increases the risk of bleeding.<sup>53</sup>

#### Recommendations

- 1 It seems reasonable, according to data from pharmacological studies, that the treatment with cilostazol should be discontinued 2 days before neuraxial or removal of epidural catheter (2C).<sup>[215,51,53]</sup>
- 2 Due to its early plasma peak (2 hours), it is recommended to give the first postoperative dose of cilostazol 6 hours after neuraxial puncture or removal of epidural catheter (2C).<sup>2</sup>
- 3 Due to the increased risk of bleeding in patients using the ASA and dipyridamole combination, prior discontinuation of dipyridamole for 48 hours (approximately 5 half-lives) is recommended when combined with ASA. Dipyridamole alone does not seem to increase the risk of SEH (2C).<sup>15</sup>

### Perioperative management of patient on dual anti-platelet therapy (DAPT)

DAPT is prescribed after percutaneous coronary interventions and is essential during the re-endothelization period due to endothelial injury caused by angioplasty balloon or stent coating, to decrease the risk of future ischemic and atherothrombotic events. It consists in the association of antiplatelets, normally ASA, and an ADP receptor inhibitor (P2Y12).

DAPT in the perioperative period of non-cardiac surgeries raises major clinical concerns. On one hand, discontinuation of DAPT is associated with a higher risk of myocardial infarction, stent thrombosis and death, attributed to increased platelet adhesion caused by the surgical inflammatory stress.<sup>54</sup> On the other hand, continuing these drugs is associated with increased risk of bleeding and blood product transfusion.<sup>54</sup>

Thus, in the preoperative period, the risk of thromboembolic events and the risk of bleeding of the surgical procedure should be balanced. Resuming postoperative antiplatelet therapy depends on the cardiovascular risk profile of each patient, of bleeding risks associated with the specific surgical procedure and the pharmacokinetics of each drug. The objective should be to reestablish the antiplatelet regimen as soon as possible.<sup>54</sup>

The thrombotic risk for a patient submitted to a percutaneous route coronary procedure was classified recently by Rossini et al.<sup>55</sup> according to time and type of intervention (Table 2). In the same guideline, the authors classify procedures according to low, intermediate or high risk of bleeding (Table 3).

Decision on using DAPT drugs should be made along with patient's attending cardiologist. For patients with a high risk of thrombosis scheduled for elective surgeries, the procedure should be postponed for a period above: 2 weeks after percutaneous balloon angioplasty; 30 days after metal stent implant; 3–6 months after implant of new drug-eluting stent (zotarolimus or everolimus coated stents), in that a period of 3 months is considered acceptable, despite 6 months being considered ideal; and 12 months after implant of first gen-

**Table 2** Thrombotic risk in terms of time and type of intervention.<sup>55</sup>

Low risk (< 1%) <sup>a</sup>	Intermediate risk (1%–5%) <sup>a</sup>	High risk (> 5%) <sup>a</sup>
> 4 weeks after balloon angioplasty	> 2 weeks and ≤ 4 weeks after balloon angioplasty	≤ 2 weeks after balloon angioplasty
> 6 months after metal stent implant	> 1 month and ≤ 6 months after metal stent implant	≤ 1 month after metal stent implant
> 12 months after drug-eluting stent implant	> 6 months and ≤ 12 months after drug-eluting stent	≤ 6 months after drug-eluting stent
> 6 months after ACS or MR	> 12 months after complex intervention with drug-eluting stent (long, multiple stents, bifurcations, overlapped stent, LMCA etc.)	≤ 12 months after complex intervention with drug-eluting stent < 1 month after ACS or MR

ACS, Acute Coronary Syndrome; MR, Myocardial Revascularization; LMCA, Left Main Coronary Artery.

<sup>a</sup> Rate of 30 day ischemic events.<sup>56</sup>

**Table 3** Classification of surgical procedures in terms of bleeding potential.

Low	Intermediate	High
Hernioplasty, incisional hernia, cholecystectomy, breast surgery, hand surgeries, arthroscopy, cystoscopy, ureteroscopy, tooth extraction, digestive tube endoscopy, colonoscopy	Hemorrhoidectomy, splenectomy, gastrectomy, gastroplasty, knee and shoulder implant, prostate biopsy, rectosigmoidectomy, otorhinolaryngology, orchiectomy,	Neurosurgery, posterior eye chamber, complex heart, de thoracoabdominal aorta aneurysm, pancreaticoduodenectomy, hepatectomy, radical prostatectomy, nephrectomy, transurethral prostate resection, hip replacement revision

Adapted from Rossini et al.<sup>55</sup>

eration drug-eluting stent (sirolimus or paclitaxel coated stents).<sup>45,47</sup>

DAPT can be maintained in urgent cases in patients with high thrombotic event risk whose low-bleeding risk surgical procedure cannot be postponed for the period recommended above.<sup>55,58</sup> For cases of moderate to high risk of bleeding, in patients with high thrombotic risk, ASA should continue, ADP receptor inhibitors should be discontinued for the period required for each drug and bridge therapy with GP IIb/IIIa inhibitors should be considered.<sup>32,33,36</sup> In emergencies in patients with a high risk of thrombosis, surgery should occur in the presence of DAPT, and platelet concentrates should be administered in the presence of death threatening bleeding.<sup>45</sup>

Ideally, for patients with a moderate thrombosis risk, surgery should be postponed until the risk becomes low. For surgeries that cannot wait this period, it is recommended to continue ASA and interrupt ADP inhibitor drugs for the required period, and reinstitute them after 24–72 hours with a loading dose.<sup>55–58</sup>

In low thrombosis risk cases and on DAPT (for example, patient submitted to drug-eluting stent placement more than 12 months) and submitted to low to moderate bleeding risk surgeries, ASA can be continued, while ADP inhibitor can be discontinued. In the same low risk population, when submitted to high risk bleeding surgery, ASA and ADP receptor inhibitor should be discontinued.<sup>45,55,58</sup>

Discontinuing aspirin for patients with stents in the perioperative period is associated with significant increase in major adverse cardiac events.<sup>37</sup> In a descriptive study underscoring catastrophic results of patients submitted to

non-cardiac surgery after stent implant and discontinuation of aspirin, time between stent implant and surgery was also one of the main determinants of outcome.<sup>59</sup> Evidence of the POISE-2 study (Aspirin in Patients Undergoing Noncardiac Surgery) showing the lack of benefit in using aspirin before surgery and during the early postoperative period are less relevant to this discussion in the scenario of DAPT, taking into account that of the total patients in the study, less than 5% had a previous history of percutaneous coronary intervention.<sup>60</sup>

## Neuraxial anesthesia and anticoagulant agents

According to the new cellular clotting model, the termination phase of the coagulation process leads to fibrin production after the initiation, amplification and propagation phases. Therefore, there is an ongoing balance between antithrombotic and pro-thrombotic phenomena. Depending on the intensity of the intervention, whether vascular lesion, extensive trauma or using anticoagulant agents, there can be a predominance of one process over the other. Anticoagulant agents are indirect action drugs (vitamin K antagonists) or direct-action drugs.

Within this scope, there are new oral agents that interfere in the coagulation process with a safer and more predictable action if compared, for example, with classic warfarin. The present section aims to approach the consolidated and updated aspects of classic therapies practiced, and present a flow chart of recommendations for new drugs (Table 4).

**Table 4** Recommendation for clinical management of patients on anticoagulants in relation to neuraxial blockade.

Agent class	Drug	Interval between last dose and blockade	Interval between last dose and catheter removal	Interval between puncture and next dose	Interval between catheter removal and next dose
Thrombolytics	Streptokinase Urokinase	Avoid blockade			
Fibrinolytics	T-PA (alteplase, tecteplase)				
Low Molecular Weight Heparin (LMWH)	Enoxaparin (prophylactic)	> 12 hours	> 12 hours	>12 hours	> 4 hours
	Enoxaparin (therapeutic)	> 24 hours	> 24 hours	> 24 hours if low postoperative bleeding risk surgery and > 48 hours if high risk	> 4 hours
	Dalteparin 5000 U.day <sup>-1</sup> (prophylactic)	> 12 hours	> 12 hours	> 12 hours	> 4 hours
	Dalteparin 200 U. kg <sup>-1</sup> .day <sup>-1</sup> or 120 mg 2×/day (therapeutic)	> 24 hours	> 24 hours	> 24 hours if low postoperative bleeding risk surgery and > 48 hours if high risk	> 4 hours
	Tinzaparin (prophylactic)	> 12 hours	> 12 hours	> 12 hours	> 4 hours
	Tinzaparin 175 U. kg <sup>-1</sup> .day <sup>-1</sup> (therapeutic)	> 24 hours	> 24 hours	> 24 hours if low postoperative bleeding risk surgery and > 48 hours if high risk	> 4 hours
	Nadroparin (prophylactic)	> 12 hours	> 12 hours	> 12 hours	> 4 hours
	Nadroparin 86 U. kg <sup>-1</sup> 2×/day or 171 U. kg <sup>-1</sup> .day <sup>-1</sup> (therapeutic)	> 24 hours	> 24 hours	> 24 hours if low postoperative bleeding risk surgery and > 48 hours if high risk	> 4 hours
Unfractionated heparin (UFH)	IV UFH	4–6 hours (check if clotting is normal)	4–6 hours (check if clotting is normal)	1 hour	1 hour
	UFH 15,000 U.day <sup>-1</sup> (prophylactic – low dose)	SC 4–6 hours	SC 4–6 hours	1 hour	1 hour
	UFH 7,500–10,000 U 2×/day or daily dose < 20000 U (prophylactic – high dose)	SC 12 hours	SC 12 hours	1 hour	1 hour
	UFH > 10,000 U per dose or daily dose > 20,000 U (therapeutic)	SC 24 hours	SC 24 hours	1 hour	1 hour

Table 4 (Continued)

Agent class	Drug	Interval between last dose and blockade	Interval between last dose and catheter removal	Interval between puncture and next dose	Interval between catheter removal and next dose
Anti- factor Xa agents	Fondaparinux (Arixtra®) – IV	36–42 hours	Do not install catheter Inadvertent dose: 2 half-lives	12 hours	12 hours
	Rivaroxaban (Xarelto®)	72 hours	Do not install catheter Inadvertent dose: 2 half-lives	6 hours	6 hours
	Apixabana (Eliquis®)	72 hours	Do not install catheter Inadvertent dose: 2 half-lives	6 hours	6 hours
	Edoxaban (Lixiana®, Savaysa®)	72 hours	Do not install catheter Inadvertent dose: 2 half-lives	6 hours	6 hours
	Betrixaban (Bevyxxa®) – VO	72 hours	Do not install catheter Inadvertent dose: 2 half-lives	5 hours	5 hours
Direct thrombin inhibitors (Anti-factor IIa agents)	Desirudin (Revasc®) – IV Bivalirudin (Angiomax®) – IV Argatroban (Acova®) – IV Dabigatran (Pradaxa®) – VO	Avoid blockade Avoid blockade Avoid blockade ClCr < 30 mL.min <sup>-1</sup> – do not do 30–49 mL.min <sup>-1</sup> , 5 days 50–79 mL.min <sup>-1</sup> , 4 days ClCr > 80 mL.min <sup>-1</sup> , 3 days ClCr unknown, 5 days	Do not insert catheter Inadvertent dose: 2 half-lives	6 hours	6 hours
Vitamin K antagonists	Warfarin	5 days with INR ≤ 1.5	Discontinue if INR < 1.5 (if it was reintroduced it can be discontinued between 12 and 24 hours after – Unknown risk if 48 hours after)	Right after puncture	Right after catheter removal
Antiplatelet – non-steroid anti-inflammatory (NSAID)	Aspirin, ibuprofen, diclofenaco and indomethacin	No restrictions. Careful with concomitant use of other drugs that affect coagulation	No restrictions. Careful with concomitant use of other drugs that affect coagulation		

Table 4 (Continued)

Agent class	Drug	Interval between last dose and blockade	Interval between last dose and catheter removal	Interval between puncture and next dose	Interval between catheter removal and next dose
Antiplatelet Thienopyridines (P2Y12 inhibitors)	Ticlopidine (Ticlid®)	10 days	Catheter can remain for maximum 48 hours as long as no loading dose is given	24 hours	24 hours
	Clopidogrel (Plavix®)	5–7 days	Catheter can remain for maximum 48 hours as long as no loading dose is given	24 hours	24 hours
Antiplatelets (ADP inhibitors)	Prasugrel (Effient®)	7–10 days	Do not install catheter	24 hours	24 hours
	Ticagrelor (Brilinta®)	5–7 days	do not insert catheter	24 hours	24 hours
	Cangrelor (Kengreal®)	3 hours Short half-life – use as bridge therapy	Remove catheter before reintroduction of cangrelor	8 hours	8 hours
Antiplatelet – antagonists GP IIa/IIIa (IGP)	Abciximab (Reopro®)	24–48 hours	24–48 hours	Contraindicated for 4 weeks after surgical procedure. Inadvertent dose: 8–12 hours	Contraindicated for 4 weeks after surgical procedure. Inadvertent dose: 8–12 hours
	Eptifibatide (Integrilin®)	4–8 hours	4–8 hours		
	Tirofiban (Aggrastat®)	4–8 hours	4–8 hours		
Other antiplatelet drugs (phosphodiesterase Inhibitors)	Cilostazol (Pletal®)	2 days	Remove catheter before reintroduction of cilostazol	6 hours	6 hours
	Dipyridamol (Persantin®)	24 hours. Major bleeding risk if associated with aspirin.	Remove catheter before reintroduction of dipyridamol	6 hours	6 hours
Herbal therapy	Ginkgo biloba, ginseng and garlic	No additional risk if isolated use			

## Heparin

### Unfractionated heparin (UFH)

The main anticoagulant effect of unfractionated heparin is due to the pentasaccharide present in roughly one third of molecules of heparin. The pentasaccharide binds to antithrombin III (ATIII)<sup>2</sup> and after this binding, UFH catalyzes the inactivation of factors IIa (thrombin), Xa and IXa, and to a lesser extent, of factors XIa and XIIa.<sup>9</sup> In the absence of heparin, antithrombin III has low affinity to thrombin; however, when UFH binds to ATIII, the thrombin binding rate speeds up 100 to 1,000 times, similar to other coagulation factors inhibited by UFH. UFH also binds strongly to several plasma proteins and endothelial cells, macrophages and Platelet Factor 4 (PF4), which results in low bioavailability, inaccurate pharmacokinetics and Heparin-Induced Thrombocytopenia (HIT).<sup>61</sup>

The anticoagulant activity of UFH depends both on the number of heparin molecules with the pentasaccharide chain in their composition and the size of molecules that have the pentasaccharide. Heparin molecules with high molecular weight will catalyze the inhibition of factors IIa and Xa. Conversely, heparin molecules with low molecular weight will only inhibit factor Xa. Moreover, the optimal time for heparin anticoagulation action depends on its administration, in that for the subcutaneous route of the drug the anticoagulant effect is only observed after roughly 40–60 minutes, and eliminated within 4–6 hours.<sup>61,62</sup>

Intravenous administration of UFH results in immediate anticoagulation, while subcutaneous administration, has onset of action of 1 to 2 hours. The anticoagulant effect depends on molecular weight and on the dose administered non-linearly, increasing disproportionately with increase in dose.<sup>2</sup> The biological half-life of heparin increases with the dose administered,<sup>62</sup> 30 minutes with 25 UI.kg<sup>-1</sup> IV, 60 minutes with 100 UI.kg<sup>-1</sup> and 150 minutes with 400 UI.kg<sup>-1</sup>.

When administered in therapeutic doses, anticoagulation of UFH is monitored with aPTT (Activated Partial Thromboplastin Time). During extracorporeal circulation, coagulation inhibition by high doses of heparin is monitored by ACT (activated clotting time). The administration of small subcutaneous doses (5,000 UI) for Deep Venous Thrombosis (DVT) prophylaxis in general does not change aPTT. One of the advantages of heparin anticoagulation is reversal by protamine. Each milligram of protamine can neutralize 100 UI of heparin.<sup>61</sup>

Therapeutic anti-coagulation is definitely associated with increased risk of SEH. A study comparing the incidence of SEH in patients using UFH in therapeutic doses or not, and submitted to lumbar puncture showed an incidence of 2% in the group on therapeutic UFH. The associated risk factors were: (i) Interval of less than 1 hour between start of heparinization and lumbar puncture; (ii) concomitant use of ASA at the time of lumbar puncture; and (iii) traumatic procedure.<sup>63</sup> Two cases of epidural hematoma associated with therapeutic UFH and neuraxial blockade were described.<sup>64,65</sup>

Intraoperative heparinization involves using 5,000 to 10,000 UI of intravenous heparin during surgical procedures, particularly in vascular surgeries, to prevent thrombosis dur-

ing arterial vessel clamping.<sup>62</sup> Most case series published use the same guidelines for management of neuraxial anesthesia of patients, based on exclusion of high risk patients (pre-existing coagulopathy) and performing neuraxial procedures at least 1 hour before heparin administration.<sup>66</sup> Stafford-Smith showed increased incidence of bleeding in patients on ASA associated with intraoperative intravenous heparin. The risk of spinal/epidural hematoma increased to 1:8,500 after epidural puncture and to 1:12,000 after subarachnoid anesthesia, even when heparinization occurred more than 1 hour after neuraxial puncture.<sup>5</sup>

For patients undergoing heart surgery, epidural anesthesia presents clear benefits on pulmonary function and analgesia, shows less effect on arrhythmia control, and no effect on hospital and ICU length of stay and on mortality.<sup>66,67</sup> However, the benefits should be assessed in relation to the high risk of SEH. The likelihood of SEH in patients submitted to heart surgery with complete heparinization is 1:1,528 with epidural and 1:3,610 with subarachnoid techniques.<sup>68</sup> Neuraxial blockade of the neuroaxis is recommended on the day before surgery due to complete surgical heparinization.<sup>13,69,70</sup> Given neuraxial blockade in cardiac surgery shows significant risks without improving morbidity and mortality, the rationale for its use in this scenario is debatable, with the recommendations leaning towards abandonment of the techniques in this group.<sup>69</sup>

The low dose of Subcutaneous (SC) UFH is commonly used for VTE prophylaxis in general, and urological surgery. The administration of 5,000 UI of subcutaneous heparin twice a day (BID) or three times a day (TID) has been used extensively and efficaciously for deep venous thrombosis prophylaxis. Frequently there are no detectable changes in coagulation parameters, measured by the level of aPTT, antifactor Xa or heparin. The widespread use of SC heparin and scarcity of complications suggest low risk of SEH associated with treatment.

There are nine series published, totaling over 9,000 patients submitted to neuraxial blockade in the presence of prophylactic doses for TVP with heparin without SEH.<sup>66</sup> However, isolated cases were described after the study.<sup>8,11,71</sup> For patients receiving a two-dose daily regimen of 5,000 U of UFH SC, there is no contraindication for neuraxial techniques.<sup>2</sup> However, there are not enough data showing safety to perform neuraxial techniques on the TID regimen, despite it being more efficient to prevent DVT.<sup>72</sup>

The safety of high dose subcutaneous UFH (doses above 5,000 UI or daily dose over 15,000 UI) remains controversial due to the marked variability in patient response to dosage regimens. Specifically, given the anticoagulant effect of heparin is not linear and increases disproportionately with increase in doses, the administration of more than 5,000 UI will increase the intensity and duration of the anticoagulant effect.<sup>62</sup>

ESA guidelines, as well as British and German guidelines,<sup>13,24,73</sup> allow 5,000 UI 3×/day, but also suggest that the time of inserting the needle and removing the catheter – regardless of the dose 2×/day or 3×/day – coincide with lower levels of anticoagulant activity. The recommendations are based on the pharmacology of the SC dose of 5,000 UI of UFH that has anticoagulant effect 1 hour after the administration and persists for 4–6 hours.

Thus, before inserting the needle, it is reasonable to wait 4 to 6 hours after the last UFH dose administration. For an individual heparin dose of 7,500 to 10,000 UI twice a day or a daily dose below 20,000 UI, neuraxial blockade 12 hours after administration of SC heparin and assessment of coagulation status is proposed. Likewise, for therapeutic UFH (for example, individual dose > 10,000 UI SC per dose or > 20,000 UI total daily dose), the suggestion is to perform neuraxial blockade 24 hours after administration of SC heparin and assessment of coagulation status.<sup>2</sup>

#### Recommendations

- 1 Assess daily medication used by patient particularly drugs that modify coagulation activity, such as: antiplatelet agents, low molecular weight heparin (1B).<sup>2</sup>
- 2 Daily platelet count for patients on heparin treatment regimen for more than 4 days due to the risk of heparin induced thrombocytopenia (1C).<sup>2</sup>
- 3 Discontinue heparin infusion between 4–6 hours for performing neuraxial procedures, including removal of epidural catheters (1A).<sup>2</sup>
- 4 Avoid invasive neuraxial techniques in patients with other coagulation disorders (1A).<sup>2</sup>
- 5 Waiting one hour before heparin administration after neuraxial procedures and after epidural catheter removal is recommended (1A).<sup>1,2,15</sup>
- 6 Wait 4–6 hours after the most recent heparin administration to perform neuraxial procedures in patients on prophylactic dose SC UFH regimen (5,000 UI 2 or 3 times a day), preferably after coagulation status assessment (2C).<sup>2</sup>
- 7 On patients using high doses of SC UFH (7,500–10,000 UI twice a day or single dose below 20,000 UI a day), perform neuraxial procedures 12 hours after heparin administration or after coagulation status assessment (2C).<sup>2,15</sup>
- 8 For patients on regimens of UFH doses higher than 10,000 UI per dose or daily doses over 20,000 UI, wait 24 hours after heparin administration to perform neuraxial procedures (2C).<sup>2</sup>

### Low molecular weight heparin (LMWH)

LMWH are becoming the treatment of choice both for prevention and treatment of DVT due to its higher bioavailability (almost 100%) after subcutaneous administration, resulting in superior anticoagulant effect without increasing bleeding tendency, and easier use, without requiring blood coagulation monitoring.<sup>3</sup>

The pharmacology of LMWH differs from UFH. The major differences consist in higher inhibitor activity of factor Xa compared to thrombin (IIa), difficulty in monitoring anticoagulant effect (levels of factor Xa), prolonged elimination half-life and absence of complete reversibility with protamin.<sup>61</sup> With subcutaneous administration, maximum plasma levels are reached in approximately 3–4 hours, and elimination half-life, with normal renal function, is 4–6 hours.<sup>74,75</sup> However, it retains considerable antifactor Xa activity (50%) 10–12 hours after administration. If creatinine clearance falls below 30 mL·min<sup>-1</sup>, the elimination half-life doubles.<sup>74</sup> Compared to UFH, there is a 10 times lower risk of occurrence of Thrombocytopenia (HIT); however, they

are contraindicated in high risk HIT, approximately 90%, of cross-reaction.<sup>76</sup>

If thromboprophylaxis with LMWH was ordered in two daily doses (30 mg twice a day), in comparison to the single daily dose regimen, the risk of SEH can increase, because the minimum levels of anti-Xa activity are higher.<sup>77</sup>

LMWH in patients submitted to neuraxial blockade was adopted in Europe in 1987. A single dose of 20 to 40 mg 12 hours before the surgical procedure was used. To avoid the occurrence of SEH, recommendations oriented the insertion/removal of epidural catheter at a minimum interval of 10–12 hours after the most recent dose of LMWH. The subsequent dose was reinitiated after 8–12 hours.<sup>8,10</sup> In this way, reviews involving data of millions of patients showed that neuraxial blockade while using the European LMWH regimen was safe, with only one case of SEH described.<sup>78</sup>

On the other hand, in the United States, enoxaparin, introduced in 1993, did not have a recommendation related to time between its administration and performance of neuraxial blockade or catheter removal. Enoxaparin was routinely administered in the immediate postoperative, at a dose of 30 mg twice a day. After 5 years of use, the FDA (Food and Drug Administration) totaled reports of 43 patients submitted to neuraxial blockades who developed SEH.<sup>79</sup> In 1998, 13 cases of SEH associated with LMWH had been described in Europe, while the United States totaled 60 cases.<sup>80</sup> The reasons for the high rates were attributed to a: (i) prescription of higher daily dose of LMWH; (ii) more frequent doses, possibly leading to higher minimum blood levels during catheter insertion/removal; (iii) lack of practice guidelines for neuraxial blockade.<sup>17,80</sup>

After the 2003 resolution of the second guideline of the American Society of Regional Anesthesia (ASRA), 10 cases were reported in the English language literature related to the SEH and LMWH combination. Five additional cases were reported by the Royal College of Anaesthetists guideline in the United Kingdom, in 97,925 epidural blockades; however, without proven evidence of association with anticoagulant medication.<sup>12</sup>

Based on the analysis of the cases published and on the clinical experience of using LMWH in Europe and the United States, the specific risk factors associated with SEH were proposed, as age above 65 years, female sex, administration twice a day and additive, if not synergic effect, of multiple drugs that alter hemostasis<sup>7,80</sup> (Table 1).

#### Recommendations

- 1 Oral anticoagulant and antiplatelet drugs administered simultaneously to LMWH increase the risk of SEH, a blockade being contraindicated in these conditions, or discontinuation of adjuvant drugs if neuraxial procedures are scheduled (1A).<sup>2</sup>
- 2 Bleeding during needle or catheter insertion does not require cancelation of the surgery. The suggestion is to begin LMWH therapy, in these circumstances, 24 hours after the end of the surgery (2C).<sup>2</sup>
- 3 For patients on preoperative thromboprophylaxis with LMWH, neuraxial blockade is recommended 12 hours after the most recent dose of LMWH (1C).<sup>2,15</sup>
- 4 For patients on therapeutic doses of LMWH – such as enoxaparin 1 mg·kg<sup>-1</sup> every 12 hours, enoxaparin 1,5 mg·kg<sup>-1</sup> a day, dalteparin 120 UI·kg<sup>-1</sup> every 12 hours,

dalteparin 200 UI.kg<sup>-1</sup> a day or tinzaparin 175 UI.kg<sup>-1</sup> a day – an interval over 24 hours between last dose and neuraxial blockade is suggested to assure normal hemostasis (2C).<sup>2</sup>

- 5 Regarding LMWH postoperative use, the first dose of LMWH should be administered 12 hours after surgery. For catheter being kept in situ safely, the second dose of LMWH should not be administered before 24 hours of the first dose. However, epidural catheter should only be withdrawn 12 hours after the last dose. The subsequent dose of LMWH, after catheter removal, should be after 4 hours. Any drug that alters hemostasis should not be administered due to the risk of additive effects (1C).<sup>2</sup>
- 6 The two daily doses regimen brings higher risk of SEH, and continued monitoring is recommended. The first dose of LMWH should be administered 24 hours after the end of surgery, if there is no risk of bleeding. In the case of risk of bleeding, the first dose should be postponed to 48–72 hours after the end of the surgery (1C).<sup>2,15</sup>

### Vitamin K antagonists (Coumarins)

Coumarins include acenocumarol, phenprocoumon and warfarins. The drugs inhibit the synthesis and gamma-carboxylation of vitamin K dependent factors: II, VII, IX, X, proteins C and S, which makes them unable to bind to phospholipid platelet membranes during coagulation. Prothrombin Time (PT) or INR (International Normalized Ratio) are the most widely used tests to monitor these drugs, and reflect plasma activity of three of the four coagulation factors (II, VII and X). Clinical data suggest that a 40% level of activity is appropriate for each factor for normal or near to normal hemostasis.<sup>81</sup> An INR of 1.5 is associated with a 40% factor VII activity. Given factor VII has a shorter half-life (approximately 6 hours), the initial INR increase during coumarin administration, reflects loss of factor VII activity.

The therapeutic effect, however, of these drugs depends more on the reduction of factors II or X, that have relatively longer half-lives; 60–72 hours and 24–36 hours, respectively. After interrupting the use of warfarin, factor II is the last to normalize<sup>82</sup> and the INR can return to near normal values due to restored factor VII activity; however, factors II and X may not be restored to normal hemostatic levels.<sup>83</sup> Its anticoagulant effect can be effectively reverted with administration of vitamin K, fresh frozen plasma or prothrombin concentrate complex (factors II, VII, IX and X).<sup>3</sup>

Although ASRA has recommended epidural catheter removal with an INR below 1.5, this figure has been considered conservative. Reports have shown removal of epidural catheters with a higher INR and uneventful.<sup>84–86</sup> If it occurs in the initial 48 hours of medication use, there is likely to be more adequate activity of coagulation factors, particularly factors II and X. Beyond this period, all vitamin K dependent factors will be affected. There were no SEH case reports in 11,235 patients who received epidural analgesia after total knee arthroplasty, treated with warfarin (5–10 mg) initiated on the night before the procedure. Epidural catheters were removed up to 48 hours of postoperative. The mean (range) INR at time of removal was 1.5 (0.9–4.3). INR was less than 1.5 in approximately 40% of cases. These series suggest that not only INR values, but also duration of warfarin therapy

should be considered to manage epidural catheter, and that extending for more than 48 hours can represent a significant increase in the risk of hematoma.<sup>85</sup>

The control of patients on warfarin in the perioperative remains controversial. The recommendations are based on the pharmacology of the drug, clinically relevant levels, deficiency of vitamin K-dependent clotting factors, and on case series and case reports of SEH.<sup>2</sup> Evidence-based guidelines on perioperative management of antithrombotic therapy were established by the ACCP (American College of Chest Physicians). They state that during the preoperative evaluation, warfarin should be discontinued at least 5 days before the elective procedure, the INR assessed 1 to 2 days before surgery, and if INR > 1.5, 1 to 2 mg of oral vitamin K should be administered. If reversal for surgery/procedure is urgent, consider 2.5–5 mg orally or IV vitamin K; and for immediate reversal, administer fresh frozen plasma. Patients with high risk of thromboembolism should receive bridge therapy with therapeutic SC LMWH (preferable) or intravenous UFH.<sup>44</sup>

#### Recommendations

- 1 Neuraxial procedures are recommended to be performed 5 days after discontinuation of coumarins and normalization of INR (1B).<sup>1,2</sup>
- 2 Discontinue drugs that modify normal coagulation activity, such as anti-inflammatory, thienopyridines, UFH, HBPM (1A).<sup>1,2</sup>
- 3 It is suggested that INR be checked in patients who received a dose of warfarin more than 24 hours before surgery or received a second dose (2C).<sup>2</sup>
- 4 If a patient is on low doses of warfarin during epidural analgesia, monitor INR daily; (2C).<sup>2</sup>
- 5 It is suggested that patients receiving epidural analgesia undergo routine neurological assessment, using titrated doses of anesthetic solutions in order not to impair assessment (2C).<sup>2</sup>
- 6 It is suggested that after beginning thromboprophylaxis with warfarin, epidural catheters be removed when the INR is below 1.5. Removal of the epidural catheter 12–24 hours after warfarin dose does not seem to increase risk of bleeding (2C).<sup>1,2,85,86</sup>
- 7 It is suggested that patients with INR above 1.5 and below 3.0 be carefully monitored regarding catheters. In this scenario, the catheter should be kept based on the INR and on duration of warfarin therapy (2C).<sup>1,2</sup>
- 8 Patients with INR above 3.0, dose of medication should be maintained or decreased (1A). There is no recommendation on management of patients with epidural catheters at this level of anticoagulation (2C).<sup>1,2</sup>
- 9 Neurological assessment every 2 hours for 24 hours after catheter removal is suggested (2C).<sup>2</sup>

### Factor Xa inhibitors

#### Fondaparinux (Arixtra®)

Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa selectively through antithrombin III. Unlike LMWH, it has no effect on factor IIa (thrombin) and, therefore, platelet aggregation is not affected.<sup>13</sup> The compound is

approximately 100% bioavailable after subcutaneous administration and elimination half-life is 18 to 21 hours, with elimination mainly through kidneys. Elimination half-life is prolonged to 36 to 42 hours when creatinine clearance is below 50 mL·min<sup>-1</sup>, and contraindicated in patients with a clearance below 30 mL·min<sup>-1</sup>. The prophylactic dose is 2.5 mg subcutaneous once a day.<sup>3</sup>

It is usually administered 6 to 12 hours postoperatively, because when used in the preoperative period, it can increase risk of surgical bleeding without improving antithrombotic efficacy.<sup>87</sup> Due to postoperative use, there are no problems with single-shot neuraxial anesthesia; however, if catheter is placed, it should be withdrawn only in the absence of plasmatic levels of the agent. Recommendations for epidural catheter management in patients on fondaparinux comply with the conditions used in the study of Singelyn et al.<sup>26</sup> The study assessed 5,387 patients, 1,428 of which were submitted to regional anesthetic procedures in which a single dose of fondaparinux was omitted on the night previous to catheter removal. Thus, 36 hour intervals between last dose of the drug and catheter removal, and 12 hours between catheter removal time and next dose of fondaparinux were assured. No cases of SEH were described.<sup>26</sup>

According to the American College of Chest Physicians (ACCP), even with 2 cases of HIT described with the use of fondaparinux, LMWH or UFH are suggested as alternatives for patients with a history of HIT.<sup>88</sup>

#### Recommendations

- 1 At prophylactic postoperative dose (2.5 mg), neuraxial anesthesia can be used as long as atraumatic. If this is not possible, another pharmacological strategy should be chosen (1C).<sup>2</sup>
- 2 Epidural catheters are suggested to be removed at least 6 hours before first postoperative dose (2C).<sup>2</sup>
- 3 Epidural catheter should be removed only 36 hours after the last prophylactic dose of fondaparinux, and the subsequent dose should be administered only 12 hours after removal (2C).<sup>13,26</sup>

### Rivaroxaban (Xarelto®)

Rivaroxaban is a selective and direct inhibitor of factor Xa. It is administered orally and is used to prevent DVT after total knee arthroplasty surgery, as well as primary prevention of VTE after elective surgery, prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, and prevention and treatment of VTE (recurrent) and pulmonary embolism.<sup>2</sup> Treatment is initiated 6–8 hours after surgery and with a single 10 mg dose, and maximum plasma levels are reached in 2–4 hours.<sup>89</sup> Studies have shown better efficacy in comparison to enoxaparin for thromboprophylaxis,<sup>90</sup> and likewise, when compared to heparins and vitamin K antagonists to treat DVT.<sup>91</sup>

Rivaroxaban has a 5 to 9 hour elimination half-life, poorly influenced by kidney function (33% of elimination occurs through the kidney), given it also is eliminated by the liver. In the elderly, however, half-life can be extended to 11 to 13 hours.<sup>13,89</sup> In individuals with light, moderate and severe

renal failure, exposure to rivaroxaban increases 1.4, 1.5 and 1.6 times, respectively.<sup>92</sup>

Rivaroxaban prolongs aPTT and Heptest, but these tests are not recommended to assess the anticoagulant effect of the drug. Prothrombin Time (PT) is influenced by rivaroxaban on a dose-dependent basis, with close correlation to plasma concentrations, and should be measured in seconds, and not by INR.<sup>93</sup> However, routine monitoring is not considered necessary. Recently, a reversal agent of factor Xa direct inhibitors called Andexanet alfa was launched in the market with promising results.<sup>2</sup>

Clinical studies on neuraxial anesthesia in patients treated with rivaroxaban are scarce. The literature describes seven neuraxial hematomas associated with rivaroxaban.<sup>2</sup> Three cases were submitted to neuraxial blockade, but, in 2 cases, other antithrombotic agent was used immediately in the postoperative and hematomas occurred after hospital discharge.<sup>94,95</sup> In the remaining case, the epidural catheter was removed 18 hours after the first dose of rivaroxaban, that is, in a time interval inferior to the 26 hours recommended by the manufacturer.<sup>96</sup>

#### Recommendations

- 1 Discontinuation of rivaroxaban roughly 72 hours before the neuraxial procedure is suggested. If not possible wait during this period, consider measuring plasmatic rivaroxaban value or anti-Xa factor level (2C).<sup>2</sup>
- 2 Removal of catheter 6 hours before the first postoperative dose is suggested (2C).<sup>2</sup>
- 3 If in the presence of an epidural catheter there is administration of an unanticipated dose of rivaroxaban, the drug should be held for 22–26 hours, or measure anti-Xa factor, before catheter is removed (2C).<sup>2</sup>

### Apixaban (Eliquis®)

It is a selective direct inhibitor of factor Xa and administered orally. It has 60% bioavailability and does not require biotransformation to be activated.<sup>97</sup> In contrast to vitamin K antagonists, apixaban does not interact with food. Maximum plasma levels are obtained in 3 hours, with a half-life of approximately 12 hours (10 to 15 hours), and 2 daily doses are required.<sup>97,98</sup> It does not require routine coagulation monitoring. Only 25% is eliminated by kidneys and 75% by liver and biliary metabolism, and it is excreted by the bowel.

Both PT and aPTT are not appropriate for assessing the effects of apixaban qualitatively and quantitatively. These tests are not reliable due to low sensitivity and a major variability among assays, and depend on the reagents used.<sup>99</sup>

Randomized studies have shown efficacy and safety of apixaban after knee and hip replacement surgeries.<sup>100,101</sup> Assessment of 18,201 individuals with atrial fibrillation, comparing apixaban with warfarin, showed that apixaban was superior in thromboprophylaxis, with a low risk of bleeding and lower mortality index.<sup>102</sup> Based on these studies, apixaban was approved for anticoagulation in non-valvular atrial fibrillation and has been indicated for thromboprophylaxis in hip and knee surgeries. In the latter scenario, a dose of 2.5 mg twice a day is used and initiated 12–24 hours after surgery.<sup>2</sup>

#### Recommendations

- 1 Discontinuation of apixaban roughly 72 hours before neuraxial procedures is suggested. Consider checking levels of apixaban or anti-Xa factor if discontinued less than 72 hours (2C).<sup>2</sup>
- 2 Epidural catheter removal is suggested 6 hours before the first postoperative dose (2C).<sup>2</sup>
- 3 If in the presence of an epidural catheter, there is administration of an unanticipated dose of apixaban, the drug should be held for 26–30 hours or assess anti-Xa factor, before the catheter is removed (2C).<sup>2</sup>

### Edoxaban (Lixiana®)

One of the major leaders of the new generation of oral anticoagulants is edoxaban, which had an impact on this new class of drugs, mainly after ENGAGE AF-TIMI 48.<sup>103</sup> Its notoriety does not come from the superiority presented in comparison to warfarin, which was already expected, but because it allows an effective adjustment of posology. This is due to edoxaban's pharmacological profile, with plasma levels reached within 1 to 2 hours, 62% bioavailability and 55% plasma protein binding.<sup>2</sup>

Renal excretion is responsible for roughly 50% of drug elimination, and the remainder is metabolized and excreted by the liver and bowel. In this way, it is prudent to make a therapeutic adjustment of edoxaban in cases of renal failure, given the elimination half-life can vary, in these cases, from 8.75 to 14 hours.<sup>2,15</sup> PT and aPTT are not effective for assessing the activity of edoxaban, and therefore chromogenic assays are required.

#### Recommendations

- 1 It is suggested to discontinue edoxaban 72 hours before neuraxial procedures. Acceptable residual levels of edoxaban have not been determined yet (2C).<sup>2</sup>
- 2 Neuraxial catheter is suggested to be removed 6 hours before the first dose in the postoperative period (2C).<sup>2</sup>
- 3 If the drug is administered before catheter removal, it is recommended to hold edoxaban for 20 to 28 hours or perform anti-factor Xa test before the catheter is removed (2C).<sup>2</sup>

### Betrixaban (Bevyxxa®)

It is the most recent of the drugs known as NOACs (new oral anticoagulants), and their role is being underscored after phase III of the APEX study,<sup>104</sup> showing advantage in the prevention of venous thromboembolism when compared to enoxaparin, which was not attained in a remarkable manner with apixaban and rivaroxaban. It is also a selective and reversible inhibitor of factor Xa, which has a plasma peak in 3–4 hours, bioavailability of 34% and plasma protein binding of 60%.<sup>105</sup>

Betrixaban has pharmacokinetic profile less dependent of renal function, which corresponds only to 5% to 11% of drug excretion, and most of the drug is eliminated in the primary state, that is, without active metabolites by the hepatobiliary system. It has a 37 hour elimination half-life, while the pharmacodynamic effects are evident in 19 to 27 hours.<sup>105,106</sup> Betrixaban is indicated for hospitalized patients submitted to TEV prophylaxis protocols, with the

limitation that patients' hepatic and renal functions for posterior dose adjustments are required.

#### Recommendations

- 1 Discontinuation of betrixaban 72 hours before neuraxial procedures is suggested. If neuraxial procedures are required before this period, the levels of betrixaban or anti-Xa factor should be checked (2C).<sup>2</sup>
- 2 We suggest to suspending neuraxial blockades in patients with ClCr below 30 mL.min<sup>-1</sup> (2C).<sup>2</sup>
- 3 We suggest to remove neuraxial catheter 5 hours before the next dose of betrixaban (2C).<sup>2</sup>
- 4 After unanticipated dose of betrixaban, we suggest serial measurements of the drug during the following 72 hours, before catheter removal (2C).<sup>2</sup>

## Thrombin inhibitors

### Dabigatran (Pradaxa®)

Dabigatran is a pro-drug that after conversion into the active principle becomes a reversible thrombin inhibitor, administered orally and approved for DVT prophylaxis in patients submitted to hip or knee arthroplasty.<sup>75</sup> Dabigatran has been marketed in Brazil since 2011, after the RE-LY trial results.<sup>107</sup> Dabigatran has a 12 to 17 hour half-life and is eliminated mainly (80%) by the kidneys. After administration, its maximum plasma levels are reached in 2 to 4 hours.<sup>108,109</sup>

Treatment is initiated 1 to 4 hours after surgery, with doses ranging from 75 mg (creatinine clearance between 30 and 50 mL.min<sup>-1</sup>) to 110 mg (normal renal function). On subsequent days, the dose is increased to 150 mg and then to 220 mg. Dabigatran extends aPTT without a linear effect. Thrombin Time (TT) is particularly sensitive, and it is used as reference for controlling anticoagulation, due to dose-response linearity in therapeutic concentrations.<sup>108,109</sup>

The efficacy of dabigatran (220 mg) in DVT prevention is comparable to enoxaparin (40 mg.day<sup>-1</sup>) and without increasing bleeding.<sup>110</sup> Preliminary studies with dabigatran and neuraxial blockade were performed, withdrawing the epidural catheter 4 to 6 hours before the first dose. There are no studies with patients on dabigatran and using epidural catheter. The available studies are limited and none with continuous use of epidural catheter, given in all cases they were removed up to 2 hours after end of surgery, and 4 to 6 hours before the first dose of dabigatran.<sup>110,111</sup> Dabigatran was not used if the epidural catheter remained in situ to relieve postoperative pain.<sup>110,112</sup>

The effect of dabigatran can be reverted by idarucizumab, monoclonal antibody fragment that binds to dabigatran and reverts its anticoagulant effects. A clinical trial with patients either bleeding or requiring urgent surgery showed that idarucizumab reverted the anticoagulant effect of dabigatran completely in a few minutes.<sup>113,114</sup>

#### Recommendations

- 1 Discontinuation of dabigatran is suggested 120 hours before neuraxial blockade. However, if renal function assessment is reliable and there are no risk factors for bleeding (age over 65 years, hypertension and

antiplatelet drugs, concomitantly), the period should be reassessed (2C).<sup>2</sup>

- 2 Discontinuation of dabigatran is suggested roughly 72 hours before for patients with a CrCl over or equal to 80 mL.min<sup>-1</sup> (2C).<sup>2</sup>
- 3 Discontinuation of dabigatran is suggested roughly 96 hours before for patients with CrCl of 50–79 mL.min<sup>-1</sup> (2C).<sup>2</sup>
- 4 Discontinuation of dabigatran is suggested roughly 120 hours before for patients with CrCl of 30–49 mL.min<sup>-1</sup> (2C).<sup>2</sup>
- 5 We suggest not to perform neuraxial blockades in patients on dabigatran with a CrCl below 30 mL.min<sup>-1</sup> (2C).<sup>2</sup>
- 6 We suggest that neuraxial catheters be withdrawn 6 hours before the first dose of postoperative dabigatran (2C).<sup>2</sup>
- 7 If there is an unanticipated administration of dabigatran in the presence of a neuraxial catheter, consider discontinuing the dose of the drug for roughly 34–36 hours (2C).<sup>2</sup>

### Argatroban (Acova®)

A carboxylic acid-derived drug that binds to thrombin with a non-covalent binding, argatroban is a direct reversible thrombin inhibitor, administered intravenously, and that binds in different ways to thrombin (free or clot-linked).<sup>115,116</sup> Argatroban is indicated for patients with thrombosis associated with Heparin Induced Thrombocytopenia (HIT) due to the absence of interaction with Platelet Factor 4 (PF4).<sup>3</sup>

Argatroban is administered by a continuous IV infusion and is eliminated exclusively by the liver, and can be used in cases of renal failure. A dose of 0.5 to 2 µg.kg.min<sup>-1</sup> is adjusted to keep aPTT between 1.5 and 3 times the normal value. In patients with appropriate liver function, aPTT normalizes 2 to 4 hours after infusion discontinuation due to the short half-life (35 to 45 minutes).<sup>117</sup>

#### Recommendations

If a patient is on a therapeutic dose of argatroban due to acute HIT, treatment should not be discontinued due to the risk of thromboembolism, and therefore, blockade is contraindicated (2C).<sup>2</sup>

### Desirudin (Iprivask®), bivalirudin (Angiomax®) and lepirudin (Refludan®)

Recombinant hirudins, desirudin, bivalirudin and lepirudin, are first generation intravenous direct thrombin inhibitors. They do not interact with Platelet Factor 4 (PF4) and, therefore, do not trigger Heparin-Induced Thrombocytopenia (HIT). Desirudin is indicated in the DVT prophylaxis and lepirudin for treating DVT patients with a history of HIT.<sup>13</sup>

Both lepirudin and desirudin have a 1.3 to 2 hour half-life, which increases significantly with renal failure. Due to the potential risk of bleeding, the anticoagulant effect of hirudins should be routinely monitored by aPTT or ECT (Ecarin Clotting Time).<sup>118</sup>

#### Recommendation

For patients receiving intravenous thrombin inhibitors, performance of neuraxial blockade is not recommended (2C).<sup>2</sup>

### Neuraxial blockade and laboratory tests

Current guidelines determine that the neuraxial blockade should not be performed in patients with thrombocytopenia, however, none of them determine the minimum platelet count to perform neuraxial blockade.<sup>9</sup> Platelet function seems to be more important than platelet count alone,<sup>119</sup> and studies in obstetric anesthesia suggest that platelet count > 50,000 mm<sup>3</sup> with preserved function is acceptable, while a count > 100,000 mm<sup>3</sup> is acceptable without considering the assessment of platelet function.<sup>120,121</sup>

A study<sup>122</sup> assessing 573 women in labor submitted to neuraxial anesthesia (epidural or spinal) and with a platelet count < 100,000 mm<sup>3</sup> reported no case of SEH even in 15 patients with platelet count below 50,000 mm<sup>3</sup>. In this same study, a systematic review was performed using other literature reports to calculate the risk of SEH in women in labor with thrombocytopenia, and the risk of hematoma in patients with a count > 70,000 mm<sup>3</sup> was found to be extremely low (< 0.2%). However, the exact risk of SEH with a platelet count < 70,000 mm<sup>3</sup> remains unknown, with an upper limit of 3% for platelet count between 50,000 and 69,000 mm<sup>3</sup>, and 11% for platelet count < 49,000 mm<sup>3</sup>. Professionals should bear this uncertainty in mind when making the difficult assessment of risk and benefit of neuraxial anesthesia in women in labor with a platelet count below 70,000 mm<sup>3</sup>.

If there are no risk factors, a platelet count > 80,000 mm<sup>3</sup> is considered safe for performing spinal/epidural blockades, and a count > 40,000 mm<sup>3</sup>, for simple lumbar puncture.<sup>123</sup> A systematic review showed that there is not enough evidence to recommend prophylactic transfusion of platelets in thrombocytopenic patients aimed at reducing the risk of SEH in patients submitted to neuraxial anesthesia.<sup>124</sup>

Regarding to secondary hemostasis, the level of activity of 40% of each factor is appropriate for normal or near to normal hemostasis.<sup>81</sup> INR of 1.5 is associated with a 40% activity of factor VII. Bleeding can occur if the level of any coagulation factor is reduced 20%–40% of its usual value.<sup>83</sup>

#### Recommendations

- 1 Spinal or epidural blockades in the absence of risk factors for bleeding, can be performed with a platelet count > 80,000 mm<sup>3</sup> (2C).<sup>123</sup>
- 2 INR should be below 1.5 to safely perform neuraxial blockades (2C).<sup>2</sup>

### Considerations during pregnancy

Although there is an increased risk of thrombosis during normal pregnancy, thromboembolic events have a low incidence in perigestational periods. Venous thromboembolism, however, is one of the most common causes of maternal morbidity-mortality, especially in developed countries.<sup>125</sup> Common risk factors that increase the incidence of thrombosis in pregnant women include age above 35 years, prolonged immobilization, obesity, thrombophilia, previous thromboembolism and cesarean section.<sup>126,127</sup>

For most healthy women with uneventful pregnancy and vaginal delivery, the benefits of thromboprophylaxis do not surpass maternal and fetal risks. However, for maternal con-

ditions such as acquired or hereditary thrombophilia, and for women on prolonged bed rest, the benefits of thromboprophylaxis can surpass risks. Thus, anticoagulation to prevent thromboembolism in patients is becoming more frequent.<sup>128</sup>

The incidence of SEH after neuraxial blockade (with or without altered hemostasis) in the obstetric patient is very difficult to determine. Bateman et al. assessed 142,287 patients submitted to epidural anesthesia/analgesia and found seven cases of epidural hematomas that required decompression laminectomy, resulting in an incidence of SEH of 1:22,189. However, none of the cases were obstetric patients, suggesting obstetric patients submitted to epidural catheter insertion present a significantly lower SEH risk when compared to non-obstetric surgical patients.<sup>129</sup>

The relatively hypercoagulable state of pregnancy can be protective and offers a possible reason for a lower rate of neuraxial hematomas in this population. Normal anatomic changes that occur in the vertebral spine with aging can provide another explanation for the difference in incidence. The prevalence of vascular disease, osteoporosis and degenerative changes in the spine increases with age, resulting, eventually, in a decrease in the volume of the epidural space. On the other hand, the younger obstetric patient has a more compliant epidural space, with the capacity to accommodate a higher volume of blood before onset of symptoms.<sup>129</sup>

Neuraxial blockade is essential for obstetric patient care in comparison to alternative pain treatment modes. For labor, neuraxial analgesia provides pain relief superior to other analgesic modalities and decreases circulating levels of catecholamines, which can be particularly beneficial for patients with pregnancy hypertension disorders or pre-existing comorbidities. Likewise, in cesarean delivery, neuraxial anesthesia has many maternal and fetal benefits in comparison to general anesthesia, including decreased risk of lung complications, in addition to enabling better mother-baby relationship immediately after labor.<sup>130-132</sup>

Physiological changes during pregnancy result in increased volume of distribution, clearance, bioavailability and metabolism of many drugs and can lead to decreased peak effect and decreased plasma levels throughout time after the administration of anticoagulants. Thus, there is the recommendation of prophylaxis with non-fractionated heparin with a higher than usual dosage.<sup>128,133,134</sup>

When UFH is used, the recommended doses are 7,500 to 10,000 UI every 12 hours or up to 20,000 UI subcutaneous daily. When on prophylactic therapy, in these doses, the neuraxial blockade should be performed 12 hours after administration of the latest dose. When used in therapeutic doses, surpassing 10,000 UI per dose or 20,000 UI daily, the blockade should be performed 24 hours after the administration of the latest dose.<sup>2</sup>

LMWH is the preferred prophylaxis or therapy in our environment. Recommended doses are similar to non-obstetric patients. The prophylactic dose of enoxaparin used is 40 mg daily for patients between 50 and 90 kg, 60 mg, between 91 and 130 kg, and 80 mg for those above 130 kg. The therapeutic dose is 1 mg.kg<sup>-1</sup> every 12 hours. The recommendations concerning the time of drug administration and the time to perform the blockade are the same for obstetric and non-obstetric patients.<sup>2,135</sup>

Recommendations

- 1 Pharmacological data are limited regarding anti-thrombotic agents in pregnancy. In the absence of large series of cases with neuraxial blockade in the pregnant population on prophylaxis or treatment for VTE, we suggest that the same general guidelines be applied to women in labor (2C).<sup>2</sup>
- 2 In circumstances that involve high risk women in labor that receive prophylaxis for VTE and require urgent interventions due to maternal or fetal conditions, and with a higher risk of general anesthesia than neuraxial anesthesia, we suggest changes in guidelines, with follow-up with neurological assessment every 2 hours after recovery of anesthesia (2C).<sup>2</sup>
- 3 Pregnant women on prophylactic UFH in the dose of 7,500–10,000 UI every 12 hours or below 20,000 UI.day<sup>-1</sup>, we suggest 12 hour intervals between the latest dose and neuraxial puncture. In women in labor using therapeutic doses, that is, above 10,000 UI per dose or total daily dose over 20,000 UI, we suggest an interval of 24 hours between the latest dose and neuraxial blockade (2C).<sup>2</sup>
- 4 For pregnant women on preoperative thromboprophylaxis with LMWH, neuraxial blockade is recommended 12 hours after the latest dose of LMWH (1C).<sup>2,15</sup>
- 5 For pregnant women on therapeutic doses of LMWH, such as enoxaparin 1 mg.kg<sup>-1</sup> every 12 hours, enoxaparin 1.5 mg.kg<sup>-1</sup> a day, dalteparin 120 UI.kg<sup>-1</sup> every 12 hours, dalteparin 200 UI.kg<sup>-1</sup> a day, or tinzaparin 175 UI.kg<sup>-1</sup> a day, an interval of at least 24 hours between the latest dose and neuraxial blockade is recommended to ensure normal hemostasis (2C).<sup>2</sup>

## Plexus and peripheral blockade in the anticoagulated patient

Although SEH is the major hemorrhagic complication of regional anesthesia, due to the catastrophic nature of bleeding in restricted and non-compressible spaces, the associated risk after plexus and peripheral nerve blockades remains undefined.<sup>1</sup> Case reports of clinically significant bleeding/hematoma after plexus or peripheral techniques, both in patients with normal hemostasis and in those on antithrombotic therapy and who present some degree of neurological deficit, described satisfactory nerve function recovery between 6 and 12 months. Thus, while bleeding within a neurovascular sheath can result in significant hematocrit decrease, the expandable nature of the peripheral site can lower the likelihood of irreversible neural ischemia.<sup>2</sup>

There are reports in the literature of cases with hemorrhagic complications in patients submitted to peripheral nerve blockades. They describe patients with normal hemostasis,<sup>136-138</sup> or on antithrombotic therapy, or presenting coagulopathies.<sup>139-142</sup> Although most cases progress without prolonged neurological damage, there was longer hospital length of stay, with harm and dissatisfaction of patients, and requirement of packed red blood cell transfusion. In one case there was massive bleeding-associated death.<sup>143</sup>

The American Society of Regional Anesthesia 2018 guideline revised all cases of hemorrhagic complications related to deep plexus or peripheral nerve blockades.<sup>2</sup> A series of 32 cases were found, with 14 cases in patients with normal

hemostasis and 18 cases in patients on antithrombotic medication or history of coagulopathy. Most severe hemorrhagic complications occurred during performance of deep plexus blockades. An interesting observation is that ultrasound was not used as a method to find peripheral nerve or deep plexus in any of the cases.

With the increasing use of ultrasound to guide peripheral and plexus blockades, the number of complications, such as vascular puncture, fell due to dynamic visualization of structures adjacent to the nerve to be blocked.<sup>144</sup> This enhances safety for patients taking antithrombotic drugs or with inborn hemostasis disorders that offer challenge to performing regional anesthesia.<sup>145</sup> Despite small, a recent case series of 9 patients showed that using ultrasonography to guide superficial peripheral nerve blockades is safe for patients that were anticoagulated or taking anti-platelet drugs, and did not result in any case of hemorrhage when used by experienced professionals.<sup>146</sup>

#### Recommendations

- 1 For patients submitted to deep (paravertebral, lumbar plexus, lumbar sympathetic blockades, etc.) blockades or around the neuroaxis, we recommend adopting the same recommendations that refer to neuraxial blockade techniques (1C).<sup>1,2</sup>
- 2 For patients submitted to superficial blockades or peripheral techniques, the anesthesiologist should consider performing the blockade along with use of antithrombotic medication, according to local compressibility, vascularization and consequences of bleeding, if it is the case (2C).<sup>1,2</sup>
- 3 Until larger studies are performed, the present task force suggests using ultrasonography to perform superficial and deep peripheral blockades aimed at reducing the risk of inadvertent vascular puncture (2C).<sup>146</sup>

## Conflicts of interest

The authors declare no conflicts of interest.

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