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GUIDELINES

# Regional anaesthesia in patients on antithrombotic drugs

## *Joint ESAIC/ESRA guidelines*

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**BACKGROUND** Bleeding is a potential complication after neuraxial and peripheral nerve blocks. The risk is increased in patients on antiplatelet and anticoagulant drugs. This joint guideline from the European Society of Anaesthesiology and Intensive Care and the European Society of Regional Anaesthesia aims to provide an evidence-based set of recommendations and suggestions on how to reduce the risk of antithrombotic drug-induced haematoma formation related to the practice of regional anaesthesia and analgesia.

**DESIGN** A systematic literature search was performed, examining seven drug comparators and 10 types of clinical intervention with the outcome being peripheral and neuraxial haematoma. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used for assessing the methodological quality of the included studies and for formulating recommendations. A Delphi process was used to prepare a clinical practice guideline.

**RESULTS** Clinical studies were limited in number and quality and the certainty of evidence was assessed to be GRADE C throughout. Forty clinical practice statements were formulated. Using the Delphi-process, strong consensus (>90% agreement) was achieved in 57.5% of recommendations and consensus (75 to 90% agreement) in 42.5%.

**DISCUSSION** Specific time intervals should be observed concerning the adminstration of antithrombotic drugs both prior to, and after, neuraxial procedures or those peripheral nerve blocks with higher bleeding risk (deep, noncompressible). These time intervals vary according to the type and dose of anticoagulant drugs, renal function and whether a traumatic puncture has occured. Drug measurements may be used to guide certain time intervals, whilst specific reversal for vitamin K antagonists and dabigatran may also influence these. Ultrasound guidance, drug combinations and bleeding risk scores do not modify the time intervals. In peripheral nerve blocks with low bleeding risk (superficial, compressible), these time intervals do not apply.

**CONCLUSION** In patients taking antiplatelet or anticoagulant medications, practitioners must consider the bleeding risk both before and after nerve blockade and during insertion or removal of a catheter. Healthcare teams managing such patients must be aware of the risk and be competent in detecting and managing any possible haematomas.

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## Introduction

Bleeding is a potential complication of both neuraxial and peripheral nerve blocks (PNBs).[1] The risk is increased in patients on antiplatelet agents (APAs) and anticoagulant drugs.[2] Existing guidelines recommend observing specific time intervals before and after both blockade and catheter removal to reduce the risk of antithrombotic drug-induced haematoma formation.[3,4] However, as yet, no guidelines explore whether these time intervals should be adjusted in various clinical scenarios such as prophylactic and therapeutic dosing of antithrombotic drugs, drug combinations, with and without factors such as the use of reversal agents, assessment of bleeding risk scores, drug measurements and ultrasound guidance. Therefore, a systematic literature search was performed with the objective of finding answers to specific predefined clinical questions.

## Materials and methods

### Objectives

In a collaborative effort, the European Society of Anaesthesiology and Intensive Care (ESAIC) and the European Society of Regional Anaesthesia (ESRA) nominated a joint panel of experts to evaluate the available literature on the prevention of bleeding complications of neuraxial and PNBs in patients on antithrombotic drugs. The aim was to prepare an evidence based pragmatic guideline about reducing the risk of antithrombotic drug-induced haematoma formation related to the practice of regional anaesthesia and analgesia.

### Types of participants

The qualitative and quantitative analysis of the literature was confined to adult surgical patients, 16 years of age or older, requiring neuraxial or PNBs and obstetric patients requiring neuraxial blocks. This guideline focuses on anaesthetic and analgesic blocks and not on specific diagnostic interventions such as cerebrospinal fluid drainage. Studies relating solely to paediatric patients were excluded due to the differences between adults and children in anatomy, physiology, indications for antithrombotic drugs and overall clinical approach.

### Types of clinical queries

We identified three clinical questions regarding timing of administration of anticoagulation or antiplatelet medications:

(1) What should the time interval be before and after neuraxial blockade or catheter removal to prevent antithrombotic drug-induced haematoma formation in surgical or peri-operative patients?
(2) What should the time interval be before and after peripheral nerve blockade or catheter removal to prevent antithrombotic drug-induced haematoma formation in surgical or peri-operative patients?
(3) What should the time interval be before and after neuraxial blockade or catheter removal to prevent antithrombotic drug-induced haematoma formation in obstetric patients?

### Types of comparators

Each clinical question was expanded further into seven elements for the search strategy according to the treatment or intervention (I):

(1) Vitamin K antagonists (VKA) (warfarin, acenocoumerol, phenprocoumon)
(2) Direct oral anticoagulants (DOAC) (rivaroxaban, apixaban, edoxaban, dabigatran)
(3) Low molecular weight heparins (LMWH; enoxaparin)
(4) Unfractionated heparin (UFH)
(5) Aspirin
(6) $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor)
(7) No antithrombotic drug intake was defined as the comparison (C).

On the basis of the above elements, 21 PICOs (Population/Intervention/Comparison/Outcome) were developed (Appendix 1, http://links.lww.com/EJA/A621) for the literature search in collaboration with the methodologist and the trial search specialist (Appendix 2, http://links.lww.com/EJA/A622).

Studies on enoxaparin were included in the search. For other LMWH such as dalteparin, nadroparin, tinzaparin, bemiparin extrapolations were considered. Studies on unfractionated heparins included both calcium and sodium heparins in the search.

The panel decided not to include heparinoids (danaparoid, pentosane), phosphodiesterase inhibitors (cilostazol, dipyramidole), ticlopidine in the systematic search given these are currently rarely used in clinical practice. Parenteral direct thrombin inhibitors (argatroban, bivalirudin, desirudin), prostaglandins (prostacyclin, epoprostenol), glycoprotein IIb/IIIa inhibitors (abciximab) were not included because these are predominantly used in critically unwell patients in whom regional anaesthesia is rarely indicated. However, drug combinations used in cardiac emergencies were included. The panel decided not to include drug classes other than antithrombotic drugs, such as analgesic drugs, including NSAIDs, antidepressant drugs including selective serotonin reuptake inhibitors (SSRIs), dietary supplements including gingko and ginger.

The panel decided to use the wording 'low' and 'high' doses of antithrombotic drugs instead of 'prophylactic' and 'therapeutic' doses (Table 1).

The bleeding risk related to the chronic use of an antithrombotic drug is determined by both the dose of drug administered and individual patient

**Table 1** Categorisation of DOAC doses

| | Rivaroxaban | Apixaban | Edoxaban | Dabigatran |
|---|---|---|---|---|
| Venous thromboembolism prophylaxis after major orthopaedic surgery (hip or knee replacement surgery) → *low doses* | | | | |
| Dosage | 10 mg daily | 2.5 mg BID | NA | 220 mg x1 daily |
| Dosage adjustments | No | No | | 150 mg x1 daily if: CrCl 30 to 50 ml min$^{-1}$; or age≥75; or concomitant use of verapamil, amiodarone, or quinidine |
| Stroke prevention in nonvalvular atrial fibrillation → *high doses* | | | | |
| Dosage | 20 mg daily | 5 mg BID | 60 mg daily | 150 mg BID |
| Dosage adjustments | 15 mg daily if CrCl 15 to 50 ml min$^{-1}$ | 2.5 mg BID if two of three criteria met: age ≥80; body weight ≤60 kg; Creatinine ≥133 micromol l$^{-1}$<br>If CrCl 15 to 29 ml min$^{-1}$: 2.5 mg BID | 30 mg daily if: CrCl 15 to 50 ml min$^{-1}$; or body weight ≤60 kg; or concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole | 110 mg BID if age ≥80 or concomitant use of verapamil<br>110 or 150 BID if CrCl 30 to 50 ml min$^{-1}$ or age 75 to 80 |
| Acute venous thromboembolism treatment → *high doses* | | | | |
| Dosage | 15 mg BID x 21 days, then 20 mg once daily | 10 mg BID x 7 days, then 5 mg BID | 60 mg daily | 150 mg BID |
| Dosage adjustments | 15 mg BID x 21 days, then 15 mg once daily if CrCl 15 to 50 ml min$^{-1}$ | No dose adjustment | 30 mg daily if: CrCl 15 to 50 ml min$^{-1}$; or body weight ≤ 60 kg; or concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole | 110 mg BID if age≥80 or concomitant use of verapamil<br>110 or 150 BID if CrCl 30 to 50 ml min$^{-1}$ or age 75 to 80 |
| Extended prevention of recurrent DVT and PE → *low doses* | | | | |
| Dosage | 10 mg once daily or 20 mg once daily | 2.5 mg BID | | |
| Dosage adjustments | If CrCl 15 to 50 ml min$^{-1}$: for 10 mg, no adjustment; but consider 15 mg once daily instead of 20 mg once daily | No | | |
| Acute coronary syndrome → *low doses* | | | | |
| Dosage | 2.5 mg BID | NA | NA | NA |
| Prevention of atherothrombotic events in symptomatic peripheral artery disease → *low doses* | | | | |
| Dosage | 2.5 mg BID | NA | NA | NA |

Data for DOAC indications from the respective Summary of Product Characteristics (SmPC). BID, twice a day; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; NA, not applicable.

characteristics, which may influence the level of anticoagulation. These include factors such as bodyweight, age, renal and hepatic function and the concomitant use of other drugs [e.g. P-glycoprotein (P-gp)-inhibitors, P-gp inducers and protease inhibitors]. As a result, a low dose in a patient with a CrCl more than 90 ml min$^{-1}$ may be a high dose in patient with a CrCl less than 50 ml min$^{-1}$. Even with normal kidney function however, the same 'high' dose may be considered 'prophylactic' in some circumstances and 'therapeutic' in others and vice versa. High doses of a LMWH or a DOAC in the treatment of deep venous thrombosis (DVT) being 'therapeutic', whereas secondary prevention after recurrent venous thrombo-embolism (VTE) or pulmonary embolism being 'prophylactic'. Thus, when considering regional anaesthesia in an individual patient, not only the dose of the drug should be considered, but also the indication and the presence of risk factors that may influence drug pharmacokinetics. National licensing restrictions for antithrombotic drugs also need to be considered when applying these guidelines.

## Types of interventions

For each PICO population and intervention, the panel searched the literature and considered 10 clinical questions with delegated panel members' initials in brackets:

(1) Is there a difference in time intervals between low (prophylactic) and high (therapeutic) dosing of the antithrombotic drug? (E.V.)
(2) Is there a difference in time intervals between combinations of antithrombotic drugs? (T.V.)
(3) Is there a difference in time intervals between patients with and without bleeding risk score assessment? (A.G.)

(4) Is there a difference in time intervals between patients with and without drug measurements? (C.J.S.)
(5) Is there a difference in time intervals between patients with and without reversal? (Cv.H.)
(6) Is there a difference in time intervals between patients with and without ultrasound guidance? (A.M.)
(7) Is there a difference in time intervals between needle/catheter insertion versus removal? (M.W.)
(8) Is there a difference in time intervals between superficial and deep PNBs? (C.L.)
(9) Descriptive information on neuraxial haematoma (J.L.) and peripheral haematoma (R.F.) was gathered.

A further clinical question was added later during the guideline preparation phase because the task force considered it clinically relevant:
(10) Is there a difference in time intervals between patients with and without blood in the neuraxial needle/catheter? (E.V.)

In these guidelines, 'procedures' means any of needle insertion, blockade, insertion of a catheter and withdrawal of a catheter. Although the absolute probability of occurrence is low, the clinical consequence of procedure related bleeding ranges from severe, devastating or organ-threatening to only a minor impact. Accordingly, blocks were categorised into high risk of bleeding blocks (neuraxial blocks, deep PNBs) and low risk of bleeding blocks (superficial PNBs) (Table 2).

**Table 2** Categorisation of nerve blocks

| | Deep nerve blocks / neuraxial blocks | Superficial nerve blocks |
|---|---|---|
| General considerations | Consequence of block-induced bleeding is clinically significant, and may be catastrophic.<br>Management of bleeding complications is difficult because site may be deep and/or noncompressible. Invasive intervention (surgical control) may be required.<br>Clinical consequence: Withdrawal of antithrombotic drugs for block-dependent bleeding risk reduction is recommended (Table 3). | Consequence of block-induced bleeding with superficial haematoma is of less clinical significance.<br>Management of bleeding complications is easy, at compressible location, less likely to require invasive intervention to correct.<br>Clinical consequence: Withdrawal of antithrombotic drugs for block-dependent bleeding risk reduction is not compulsory (Table 4). |
| Examples for blocks | | |
| Head, neck | Stellate ganglion<br>Deep cervical plexus<br>Cervical paravertebral | Occipital<br>Peribulbar<br>Sub-Tenon's<br>Superficial cervical plexus |
| Upper limb | Infraclavicular | Interscalene<br>Supraclavicular<br>Axillary<br>Suprascapular<br>Ulnar, radial, medial (forearm or wrist level) |
| Thorax | Epidural<br>Thoracic paravertebral | Parasternal intercostal plane (deep, superficial)<br>Serratus anterior (deep, superficial)<br>Erector spinae plane<br>Intercostal<br>Interpectoral plane and pecto-serratus plane |
| Abdomen, pelvic | | Ilioinguinal<br>Iliohypogastric<br>Transversus abdominis plane (TAP)<br>Rectus sheath<br>Genital branch of genitofemoral nerve<br>Pudendal nerve |
| Lower limb, back | Lumbar plexus<br>Psoas compartment<br>Lumbar sympathectomy<br>Lumbar paravertebral<br>Quadratus lumborum<br>Fascia transversalis<br>Sacral plexus<br>Pericapsular nerve group (PENG)<br>Sciatic (proximal approaches)<br>Spinal<br>Epidural<br>Lumbar paravertebral | Femoral<br>Femoral triangle<br>Adductor canal<br>Sciatic (subgluteal, popliteal level)<br>Fascia iliaca<br>Lateral cutaneous nerve of the thigh<br>Femoral branch of genitofemoral nerve<br>Sural, saphenous, tibial, peroneal (deep, superficial) |

Distance between the region of interest (nerves) and the body surface is not a criterion to differentiate between deep and superficial blocks. Distance varies depending on anatomy and BMI. The list is neither definitive nor absolute. Institutional or individual block categorisation may vary according to the specific technique applied and to operators' experience and skills. Individual risk-benefit analysis must be made before any block. This is particularly important if the only reason the drug is being withheld is to facilitate regional anaesthesia. Anaesthesiological alternatives (e.g. general anaesthesia) should be considered in patients with high thromboembolic or ischaemic risk where it may be preferable to continue antithrombotic drugs peri-operatively without withdrawal, and in cases wherein the bleeding risk due to the block itself is high and potentially catastrophic.

## Types of outcomes

Spinal or epidural haematoma or peripheral tissue haematoma formation was defined as the clinical outcome of interest (O). Descriptive information was gathered for

(1) spinal or epidural haematoma and
(2) peripheral haematoma.



## Search methods for identification of studies

The panel was divided into subgroups and each was allocated one clinical question. Each expert suggested keywords for the literature search. The list of PICO questions and the accompanying keywords were sent to the entire panel for discussion, amendment and approval. The final list of keywords framed the literature search.

### *Electronic searches*

The literature search strategy was developed by a Cochrane Anaesthesia and Intensive Care trial search specialist (Janne Vendt, Copenhagen, Denmark) in close collaboration with the panel of experts, the ESAIC group methodologist and Cochrane editor (A.A.). The literature search was conducted in MEDLINE (OvidSP), EMBASE (OvidSP), and Cochrane Central Register of Controlled Trials (CENTRAL). All searches were restricted to the English, French, Italian and Spanish languages and until April 2019. A similar search strategy was used for all the databases. The electronic database searches were run twice in May 2019. The panel members were also encouraged to add any missing papers of interest that they were aware of and to conduct a 'snowballing' search themselves.

After removal of all duplicates, the authors screened the abstracts and titles. All relevant papers were retrieved for full-text assessment and data extraction. In the event that the search strategy yielded no literature or evidence to answer our clinical questions and PICOs, the task force members were allowed to include studies and publications outside the search date range by including either newer or older publications of relevance. For such purposes, the studies of best quality were included.

### *Selection of studies*

Data analysis included all randomised and quasi-randomised comparative trials (including cross-over studies) and observational studies performed in adult humans that compared any of the above types of nerve blocks for any bleeding outcome. Because bleeding complications following nerve blocks are rare and the number of relevant RCTs are few, data from retrospective studies, reviews, case series and case reports were also included. All studies meeting inclusion criteria were included. Experts examined the titles and abstracts of the articles identified during the search and screened them for suitability.

### *Additional resources*

For trials not yet completed, a search was conducted in clinical trials registries (clinicaltrials.gov; controlled-trials.com; anzctr.org.au; and who.int/ictrp). Unpublished trials were not included and trial authors were not contacted to determine whether any additional data were pending. However, we planned to include published data (preliminary results) if they were accessible on the clinical trials registries. We failed to include any preliminary data. The reference lists of eligible trials were also screened for additional, previously unidentified, studies. The following were not sought: published abstracts from conference proceedings of any society or new studies of potential interest.

## Data analysis

### *Assessment of quality of the evidence*

In accordance with ESAIC policy,[5] GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluation) was used for assessing the methodological quality of the included studies and for formulating recommendations.[6]

### *Development of recommendations*

Subgroups of experts developed recommendations and an evidence summary relevant to their PICO questions using GRADE (Appendix 3, http://links.lww.com/EJA/A623).[7] The strength of guidance (strong recommendations GRADE 1, weak suggestions GRADE 2) was discussed amongst the entire expert panel taking into account data synthesis, the risk of bias and the quality of the evidence. The clinical studies included following the literature search were of limited in number and quality, and the certainty of evidence was assessed to be GRADE C throughout. Each draft and its revisions were reviewed by the entire panel. The final version of the document was endorsed by all members of the expert panel.

### *Development of consensus*

All recommendations and suggestions were merged into a shared summary document of clinical practice guidelines by the coordinating author (S.K.). A first Delphi process within the entire expert panel was performed on the final version of this summary document. The following definition of the strength of the consensus was used:

(1) Strong consensus: more than 90% agreement (11 out of 12)
(2) Consensus: 75 to 90% agreement (9 or 10 out of 12)
(3) Majority: 50 to 74% agreement (6, 7 or 8 out of 12)
(4) No consensus: less than 50% agreement (5 or less out of 12)

A second Delphi round was conducted only on those statements where there was an agreement of 50 to 74% and not enough to reach a consensus threshold of 75%. This procedure permits checking if statements can achieve a consensus after a second reconsideration and revoting.[8–10] Votes were conducted online during the COVID pandemic under the auspices of ESAIC.

## Results

The systematic search retrieved 65 577 publications. Following critical appraisal of the literature, removal of duplicates and irrelevant studies and after inclusion of additional references recommended by the authors, 602 references were selected as the systematic search result. To formulate our recommendations and statements regarding the original 10 clinical questions, a total of 216 references were used.

Strategies to prevent haematoma formation in patients on antithrombotic drugs are summarised in Tables 3 and 4. We implied the principle of simplicity, for example when suggesting only one time interval for certain classes of drugs, for example direct Xa inhibitor (DXA) with half-life ($t_{1/2}$) differences of up to 5 h among apixaban, rivaroxaban and edoxaban. To calculate time intervals from last intake or administration of anticoagulant drugs, we used the $t_{1/2}$ as reported in the drug's Summary of Products Characteristics (SmPC) for healthy younger and elderly populations. Twice $t_{1/2}$ was used for calculating time intervals from last intake or administration of low

**Table 3** Management in high bleeding risk blocks (neuraxial and deep nerve blocks)

| | High risk of bleeding block (neuraxial and deep nerve blocks)[a] | | |
|---|---|---|---|
| **Drug and dose** | **Time from last drug intake to intervention[c]** | **Target laboratory value at intervention** | **Time from intervention to next drug dose** |
| VKA | Until target lab value: (about 3 days acenocoumarol; 5 days warfarin, fluindione; 7 days phenprocoumon) | INR normal | |
| DXA low[b] | 24 h rivaroxaban, edoxaban (30 h if CrCl <30 ml min$^{-1}$), 36 h apixaban | No testing | |
| DXA high | 72 h or until target laboratory value (until target laboratory value if CrCl <30 ml min$^{-1}$) | DXA level <30 ng ml$^{-1}$ (alternative: anti-Xa ≤ 0.1 IU ml$^{-1}$) | Low doses: according to guidelines on postOP VTE prophylaxis[d] (about 8 h – $t_{max}$ = 6 h postop). Consider prolonged time interval after bloody tap[e] |
| Dabigatran low[b] | 48 h | No testing | |
| Dabigatran high | 72 h or until target laboratory value (until target laboratory value if CrCl <50 ml min$^{-1}$) | DTI level < 30 ng ml$^{-1}$ (alternative: thrombin time in normal range of local laboratory) | High doses: according to guidelines on therapeutic anticoagulation[f] (about 24 h postop) |
| LMWH low ≤50 IU anti-Xa kg$^{-1}$ day$^{-1}$ enoxaparin ≤40 mg day$^{-1}$ | 12 h (24 h if CrCl <30 ml min$^{-1}$) | No testing | |
| LMWH high | 24 h (48 h if CrCl <30 ml min$^{-1}$) or until target lab value (especially if CrCl <30 ml min$^{-1}$) | anti-Xa ≤ 0.1 IU ml$^{-1}$ | VKA, DOAC, LMWH high, UFH high; should not be administered with a catheter in situ |
| UFH low ≤200 IU kg$^{-1}$ day$^{-1}$ SC ≤100 IU kg$^{-1}$ day$^{-1}$ i.v. | 4 h | No testing | UFH low: 1 h for i.v. in cardiovascular surgery |
| UFH high | Until target lab value (about 6 h if i.v., 12 h if SC) | aPTT or anti-Xa or ACT in normal range of local laboratory | |
| Fondaparinux low ≤2.5 mg day$^{-1}$ | 36 h (72 h if CrCl <50 ml min$^{-1}$) | No testing | |
| Fondaparinux high | until target lab value (about 4 days) | Calibrated anti-Xa ≤ 0.1 IU ml$^{-1}$ | |
| Aspirin low ≤ 200 mg day$^{-1}$ | 0 | No testing | Routinely prescribed next time point |
| Aspirin high | 3 days (in normal platelet counts) to 7 days | (consider specific platelet function tests in normal range of local laboratory) | 6 h |
| $P2Y_{12}$ inhibitor | 5 days ticagrelor<br>5 to 7 days clopidogrel<br>7 days prasugrel<br>or until target laboratory value | | 0-h clopidogrel 75 mg<br>24 h<br>prasugrel, ticagrelor<br>2 days clopidogrel 300 mg |
| Aspirin low + anticoagulant | Aspirin: 0<br>+ time interval of specific anticoagulant | specific laboratory test for combined anticoagulant | Aspirin low: routinely prescribed next time point<br>Combined anticoagulant, antiplatelet drug: according to guidelines on therapeutic anticoagulation, platelet inhibition[f] (about 24 h postOP) |
| Aspirin low and antiplatelet drug | Aspirin: 0 and time interval of specific antiplatelet drug | (consider specific laboratory test for combined antiplatelet drug) | |

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; DTI, direct thrombin inhibitor; DXA, direct Xa antagonist; i.v., intravenous; INR, International Normalised Ratio; LMWH, low molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin; VKA, Vitamin K antagonist. [a] Definition and examples of high bleeding risk blocks are summarised in Table 2. [b] Definitions of low and high DOAC doses are summarised in Table 1. [c] Times are given in hours (h) up to 72 h and days if longer. [d] For example, ESAIC guidelines on VTE prophylaxis.[11,12] [e] Blood in the needle/catheter. [f] For example, EHRA guidelines.[13]

**Table 4** Management in low risk of bleeding blocks (superficial nerve blocks)

| Drug and dose | Block with low risk of bleeding (Superficial nerve blocks)[a] Time from last drug intake to intervention | Time from intervention to next drug dose | Target laboratory value at intervention |
|---|---|---|---|
| DXA<br>DTI<br>LMWH low<br>$\leq$ 50 IU anti-Xa $kg^{-1}$ $day^{-1}$<br>Enoxaparin $\leq$40 mg $day^{-1}$<br>UFH low<br>$\leq$200 IU $kg^{-1}$ $day^{-1}$ SC<br>$\leq$100 IU $kg^{-1}$ $day^{-1}$ i.v.<br>Fondaparinux low<br>Aspirin low<br>$\leq$200 mg $day^{-1}$ | Zero | At routinely next prescribed time point | No testing (consider specific laboratory test if anticoagulant drug accumulation is suspected, e.g. in renal insufficiency) |
| VKA<br>LMWH high<br>UFH high<br>Aspirin high<br>$P2Y_{12}$ inhibitor<br>Drug combinations | Zero (If within or below the patient's individual therapeutic range) | | |

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; DTI, direct thrombin inhibitor; DXA, direct Xa antagonist; INR, International Normalised Ratio; IV, intravenous; LMWH, low molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin; VKA, Vitamin K-antagonist.
[a] Definition and examples of low risk of bleeding blocks are summarised in Table 2.

**Table 5** Summary of guidance: Clinical practice statements

| |
|---|
| **Is there a difference in time intervals between low and high dosing of a VKA?** |
| **R1** |
| Irrespective of the target INR, neuraxial procedures should be performed when VKA treatment has been withheld and the INR has returned to the normal range of the local laboratory (e.g. 1.1). 1C |
| An INR <1.5 may be acceptable in individual patients, if after a careful risk – benefit analysis a general anaesthetic is best avoided and a neuraxial anaesthetic technique should be used. 2C |
| A last VKA intake of 3 days (acenocoumarol), 5 days (warfarin, fluindione) and 7 days (phenprocoumon) before the procedure is proposed.2C |
| Following neuraxial procedures, the next dose of VKA should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C |
| In the presence of an indwelling neuraxial catheter the next dose of VKA should be administered only after its withdrawal. 1C |
| In the interim a low dose of LMWH may be used whilst a neuraxial catheter remains in place. 2C |
| **R2** |
| In obstetric patients (parturients) treated with a VKA and needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R1). 1C |
| In selected parturients at high risk for a thrombotic event and requiring an unplanned or urgent intervention for maternal or fetal indication, the risk of general anaesthesia may be greater than the risk of neuraxial anaesthesia. In these cases, after multidisciplinary discussion and individual risk-benefit analysis, a deviation from the current ESAIC/ESRA guidelines may be considered. C |
| **R3** |
| Superficial nerve procedures may be performed in the presence of VKA, irrespective of the target INR. 2C |
| Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C |
| Deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R1). 1C |
| If the INR is not below the minimum recommended level, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of (large) blood vessels and/or neuraxial structures. 2C |
| **Is there a difference in time intervals between low and high dosing of DOACs?** |
| **R4** |
| In low doses of DOACs[a] the last intake should be a minimum of 24 h for rivaroxaban and edoxaban, 36 h for apixaban, and 48 h for dabigatran before neuraxial procedures. 1C |
| If CrCl is < 30 ml $min^{-1}$, the last low-dose rivaroxaban, edoxaban intake should be at least 30 h before neuraxial procedures. 1C |
| In high doses of DOACs[a] the last intake should be a minimum of 72 h before neuraxial procedures. 1C |
| If CrCl is < 50 ml $min^{-1}$ with high-dose dabigatran treatment or if CrCl is < 30 ml $min^{-1}$ with high dose DXA treatment, neuraxial procedures may be performed if the appropriate laboratory assay is within the normal range of the local laboratory. 2C |
| Following neuraxial procedures, the next low dose of DOAC should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C |
| In the presence of an indwelling neuraxial catheter the next dose of DOAC should be administered only after its withdrawal;1C in the interim a low dose of LMWH or low dose UFH may be used whilst a neuraxial catheter remains in place. 2C |
| **R5** |
| In obstetric patients (parturients) treated with DOACs needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R4). 1C |
| **R6** |
| Superficial nerve procedures may be performed in the presence of DOACs at either high or low doses. 2C |
| Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C |
| Irrespective of the DOAC dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R4). 1C |
| If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of (large) blood vessels and/or neuraxial structures. 2C |

**Is there a difference in time intervals between low and high dosing of LMWH?**

**R7**

In low doses of LMWH, the last administration should be a minimum of 12 h before neuraxial procedures. 1C

If CrCl is $< 30\ ml\ min^{-1}$, the low dose of LMWH should be halved or the therapy-free interval doubled (to 24 h). 1C

In high doses of LMWH ($> 50\ IU$ anti-Xa $kg^{-1}\ d^{-1}$), the last administration should be a minimum of 24 h before neuraxial procedures. 1C

If CrCl is $< 30\ ml\ min^{-1}$, the high dose of LMWH should be halved or the therapy-free interval doubled (to 48 h). 1C

Following neuraxial procedures, the next low dose of LMWH should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

In the presence of an indwelling neuraxial catheter the next high dose of LMWH should be administered only after its withdrawal; in the interim a low dose of LMWH may be used whilst a neuraxial catheter remains in place. 2C

**R8**

In obstetric patients (parturients) treated with SC LMWH needing a neuraxial block for surgery, delivery or caesarean section, comparable recommendations (10 to 12 h) as used for the nonpregnant population should be applied (R7). 1C

In selected parturients at high risk for a thrombotic event and requiring an unplanned or urgent intervention for maternal or fetal indication, the risk of general anaesthesia may be greater than the risk of neuraxial anaesthesia. In these cases, after multidisciplinary discussion and individual risk-benefit analysis, a deviation from the current ESAIC/ESRA guidelines may be considered. C

**R9**

Superficial nerve procedures may be performed in the presence of LMWH at high or low doses. 2C

Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C

Irrespective of the LMWH dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R7). 1C

If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of (large) blood vessels and/or neuraxial structures. 2C

**Is there a difference in time intervals between low and high dosing of UFH?**

**R10**

In low doses of SC UFH ($\leq 200\ IU\ kg^{-1}\ day^{-1}$), the last administration should be a minimum of 4 h before neuraxial procedures.1C

In high doses of UFH ($> 200\ IU\ kg^{-1}\ day^{-1}$), neuraxial procedures may be performed if the anti-Xa activity, aPTT or ACT has returned to the normal range of the local laboratory. 2C

A last i.v. administration of high doses of UFH a minimum of 6 h and a last SC administration of high doses of UFH a minimum of 12 h before the procedure is proposed. 2C

Following neuraxial procedures, the next low dose of SC UFH should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

A shorter interval (1 h) may be acceptable in individual patients undergoing vascular surgery, after a careful risk-benefit analysis. 2C

In the presence of an indwelling neuraxial catheter the next high dose of UFH should be administered only after its withdrawal; in the interim a low dose of UFH or LMWH may be used whilst a neuraxial catheter remains in place. 2C

**R11**

In obstetric patients (parturients) treated with UFH needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R10).1C

In selected parturients at high risk for a thrombotic event and requiring an unplanned or urgent intervention for maternal or fetal indication, the risk of general anaesthesia may be greater than the risk of neuraxial anaesthesia. In these cases, after multidisciplinary discussion and individual risk-benefit analysis, a deviation from the current ESAIC/ESRA guidelines may be considered. C

**R12**

Superficial nerve procedures may be performed in the presence of UFH at high or low doses. 2C

Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C

Irrespective of the UFH dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R10). 1C

If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of (large) blood vessels and/or neuraxial structures. 2C

**Is there a difference in time intervals between low and high dosing of fondaparinux?**

**R13**

In low SC doses of fondaparinux ($\leq 2.5\ mg\ d^{-1}$), the last administration should be a minimum of 36 h before neuraxial procedures.1C

If CrCl is $< 50\ ml\ min^{-1}$, the last low dose fondaparinux should be at least 72 h before or the dose of fondaparinux should be reduced to $1.5\ mg\ d^{-1}$. 1C

In high SC doses of fondaparinux ($> 2.5\ mg\ d^{-1}$) neuraxial procedures is not recommended. 1C

If unavoidable, neuraxial procedures (e.g. catheter withdrawal) may be performed if the calibrated anti-Xa activity has returned to the normal range of the local laboratory. 2C

A last high SC dose of fondaparinux about 4 days before the procedure is proposed. 2C

Following neuraxial procedures, the next low SC dose of fondaparinux should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

**R14**

In obstetric patients (parturients) treated with fondaparinux needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R13). 1C

**R15**

Superficial nerve procedures may be performed in the presence of fondaparinux at high or low doses. 2C

Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C

Irrespective of the fondaparinux dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R13). 1C

If the minimum recommended therapy free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of (large) blood vessels and/or neuraxial structures. 2C

**Is there a difference in time intervals between low and high dosing of antiplatelet agents?**

**R16**

Low dose aspirin ($<200\ mg$) is not a contraindication for neuraxial procedures, if a careful risk-benefit analysis is favorable. 1C

Single-puncture spinal anaesthesia is preferable to epidural anaesthesia. 1C

In high doses of aspirin ($\geq 200\ mg$), the last intake should be a minimum of 3 days (in normal platelet counts) to 7 days before neuraxial procedures. 1C

The next high dose of aspirin may be administered a minimum of 6 h after neuraxial procedures. 2C

**R17**

Irrespective of the dose of $P2Y_{12}$ inhibitors, the last intake should be a minimum of 5 days (ticagrelor), 5 to 7 days (clopidogrel) or 7 days (prasugrel) before neuraxial procedures. 1C

The next dose of $P2Y_{12}$ inhibitors may be administered without delay (75 mg clopidogrel), a minimum of 24 h (prasugrel, ticagrelor) or a minimum of 2 days (300 mg clopidogrel) after neuraxial procedures. 2C

Regarding an indwelling neuraxial catheter, the next dose of $P2Y_{12}$ inhibitors should be administered only after its withdrawal. 2C

**R18**

Irrespective of the dose of antiplatelet agents, superficial nerve blocks may be performed, after careful risk-benefit analysis. 2C

Irrespective of the dose of the antiplatelet agents, deep nerve blocks should be performed according to the recommendations for neuraxial procedures (R17). 2C

**Is there a difference in time intervals between combinations of antithrombotic drugs?**

**R19**

When antithrombotic drugs are combined the therapy-free time interval should be that of the drug with the longest interval. 1C

**Clinical situation: urgent antiplatelet and anticoagulant therapy with a neuraxial / deep nerve catheter in situ**

**R20**

If urgent administration of combinations of antithrombotics is necessary when a neuraxial catheter is already in situ, interdisciplinary management is suggested, together with laboratory drug measurements and neurological monitoring after neuraxial procedures. 2C

With loading doses of aspirin and clopidogrel, a neuraxial catheter could be removed immediately, before clopidogrel reaches full effect. 2C

In cases of combined antiplatelet and anticoagulant drug treatment, a neuraxial catheter could be removed after reducing the anticoagulant dose or replacing the antiplatelet drug by a short acting antiplatelet drug (e.g. tirofiban, eptifibatide, cangrelor). 2C

**Clinical situation: critical illness and parenteral urgent antiplatelet and/or anticoagulant therapy with a neuraxial or deep nerve catheter in situ**

**R21**

In case of urgent indications for parenteral direct thrombin inhibitors (argatroban, bivalidurin, desirudin), prostaglandins (prostacyclin, epoprostenol) or glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), when a neuraxial or deep nerve catheter is already in situ, interdisciplinary management is recommended, together with laboratory drug measurements and neurological monitoring after neuraxial procedures. 2C

The catheter could be removed after pausing short acting drugs for 4 to 5 half-lives (e.g. argatroban 4 h, prostacyclin 1 h). 2C

**Is there a difference in time intervals between patients with and without bleeding risk score assessment?**

**R22**

Bleeding risk scores have no influence on the time interval from last drug intake to intervention or to next drug dose following a procedure. 2C

**Is there a difference in time intervals between patients with and without drug measurements?**

**R23**

In patients on VKA, a normal INR is targeted for neuraxial or deep nerve procedures, irrespective of the time interval after intake is withheld (R1). 1C

**R24**

In patients on high dose UFH, either an aPTT, an anti-Xa activity or ACT within or below the normal range of the local laboratory is targeted for neuraxial or deep nerve procedures, irrespective of the time interval after intake is withheld (R10). 1C

**R25**

In patients on high dose LMWH or fondaparinux, an anti-Xa activity of $\leq$0.1 IU ml$^{-1}$ is targeted for neuraxial or deep nerve procedures and may shorten or increase the time interval after administration is withheld (R7). 2C

Drug measurement (anti-Xa activity) of residual LMWH anticoagulant effect (either high dose or low-dose) may be considered in the presence of renal insufficiency (CrCl $<$30 ml min$^{-1}$), in older or frail patients, or very low body weight to guide the timing of neuraxial or deep nerve procedures. 2C

**R26**

In patients on high doses of DXA, calibrated DXA levels $<$ 30 ng ml$^{-1}$ or an anti-Xa activity of $\leq$0.1 IU ml$^{-1}$ is targeted for neuraxial or deep nerve procedures and may shorten or increase the time interval after intake is withheld (R4). 2C

Drug measurement of residual DXA anticoagulant effect may be considered in the presence of renal insufficiency (CrCl $<$30 ml min$^{-1}$) to guide the timing of neuraxial or deep nerve procedures. 2C

**R27**

In patients on high doses of dabigatran, a thrombin time within or below the normal range of the local laboratory or dabigatran level $<$30 ng ml$^{-1}$ is targeted for neuraxial or deep nerve procedures and may shorten the time interval after intake is withheld (R4). 2C

Drug measurement of the residual dabigatran anticoagulant effect may be considered in the presence of renal insufficiency (CrCl $<$50 ml min$^{-1}$) for guiding the time-point of neuraxial / deep nerve procedures. 2C

**R28**

In patients on low doses of anticoagulants no routine testing of laboratory values is suggested for neuraxial, deep, or superficial nerve procedures. 2C

Drug measurements may be considered in the presence of impaired anticoagulant elimination (e.g. renal insufficiency). 2C

**R29**

In patients on high doses of anticoagulants no routine testing of laboratory values is suggested for superficial nerve procedures. 2C

Specific laboratory values within or below the patient's individual therapeutic range of VKA, UFH, or LMWH are targeted for superficial nerve blocks 2C

Therapeutic ranges for DOACs have not been defined yet. C

**R30**

No recommendation can be proposed on monitoring aspirin and $P2Y_{12}$ inhibitors, before neuraxial, deep or superficial nerve procedures. Specific platelet function tests in the normal range of the local laboratory could be considered as targets for neuraxial or deep nerve procedures. 2C

**Is there a difference in time intervals between patients with and without reversal of VKA and DOAC?**

**R31**

From a pharmacological point of view, neuraxial or deep nerve procedures may be performed in emergency situations following an individual risk-benefit evaluation once the anticoagulant activity of VKA is fully reversed by prothrombin complex concentrate (PCC; INR-dependent dose adjusted) combined with vitamin K (10 mg). 2 C

**R32**

Neuraxial or deep nerve procedures may be performed in emergency situations once the anticoagulant activity of dabigatran is fully reversed by the specific antidote idarucizumab. 2C

Nonspecific haemostatic agents (PCC or activated PCC) do not affect time intervals for dabigatran. 2C

Andexanet alpha does not affect time intervals. 2C

Nonspecific haemostatic agents (PCC or activated PCC) do not affect time intervals for DXA. 2C

**Is there a difference in time intervals between patients with and without reversal of LMWH, UFH, fondaparinux?**

**R33**

From a pharmacological point of view, neuraxial / deep nerve procedures may be performed in emergency situations once the anticoagulant activity of UFH is fully reversed by protamine (sulfate or chloride) and protamine overdose is avoided. 2C

No suggestion can be proposed in emergency situations for LMWH reversal and for fondaparinux reversal.

| |
|---|
| **Is there a difference in time intervals between patients with and without reversal of aspirin or $P2Y_{12}$ inhibitors?** |
| **R34** |
| In peri-operative patients who are on low dose aspirin neuraxial or deep nerve procedures are not contraindicated; reversal cannot affect time intervals. 1C |
| Emergency situations (e.g. acute coronary syndrome) usually require loading doses of antiplatelet agents, and so that neuraxial or deep nerve procedures should not be performed. 1C |
| No recommendation can be proposed for $P2Y_{12}$ inhibitor reversal. |
| **Is there a difference in time intervals between patients with and without ultrasound guidance?** |
| **R35** |
| Ultrasound reduces vascular puncture and therefore its use is recommended in patients on anticoagulants and antiplatelet drugs. 1C |
| Ultrasound guidance has no influence on the time interval from last administration of antithrombotic drugs (VKA, DOAC, LMWH, UFH, fondaparinux, $P2Y_{12}$ inhibitors) prior to superficial or deep peripheral nerve blocks, or to the next drug dose after the block. 1C |
| In peri-operative patients who are on low dose aspirin (<200 mg) superficial or deep peripheral nerve blocks are not contraindicated and therefore ultrasound guidance does not affect time intervals. 1C |
| **Is there a difference in time intervals between needle / catheter insertion versus catheter removal?** |
| **R36** |
| Similar time intervals should be respected for insertion of a needle with or without a catheter and for removal of a catheter at neuraxial, deep, or superficial nerve block sites. 1C |
| **Is there a difference in time intervals between superficial and deep peripheral nerve blocks?** |
| **R37** |
| Superficial nerve blocks may be performed in the presence of anticoagulant or antiplatelet drugs. 1C |
| Deep nerve blocks should be performed according to the recommendations for neuraxial procedures (R3, R6, R9, R12, R16, R18). 1C |
| **R38** |
| Consequences of block-induced local bleeding should be considered and monitored. 1C |
| The lowest bleeding risk technique should be chosen and performed by an operator with experience in ultrasound guidance. 1C |
| **Is there a difference in time intervals between patients with and without blood in the neuraxial needle or catheter?** |
| **R39** |
| Manifestation of vessel puncture with a bloody tap may increase the time interval to the next drug dose, based on an interdisciplinary clinical judgement of the patient's thrombotic risk, the presence of peri-operative coagulopathies, the adequacy of postoperative haemostasis, and pharmacological profile of the antithrombotic. 2C |
| **Descriptive information on spinal or epidural haematoma after neuraxial block or catheter procedures** |
| **R40** |
| For patients receiving any anticoagulant or antiplatelet drug in the peri-operative period and undergoing a neuraxial or deep block technique, we recommend postinterventional vigilance by the multidisciplinary healthcare team for signs and symptoms related to any new or progressive neurological deficiency (new or increasing back pain, numbness or weakness of the legs, bowel or bladder dysfunction, duration or extension of the motor and/or sensory block that cannot be explained by the pharmacodynamic properties of the local anaesthetic used). 1C |
| Patients should be informed pre and postoperatively to report such symptoms as early as possible, especially in ambulatory surgery. 2C |
| Regular patient assessments by trained personnel should be performed for a minimum of 24 h after the intervention and longer in high risk patients. 2C |
| A neurological deficit that may indicate either a spinal or epidural haematoma should prompt a specialist neurological examination if available and/or immediate imaging (preferably MRI as the gold standard) for the diagnosis of a spinal or epidural haematoma. 1C |
| If indicated, surgical decompression should be performed within 6 h for neurologic recovery. 2C |

Procedures are defined as single-shot blockade, catheter insertion or catheter withdrawal. ACT, activated clotting time; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; DTI, direct thrombin inhibitor; DXA, direct Xa antagonist; i.v., intravenous; INR, International Normalised Ratio; LMWH, low molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin; VKA, Vitamin K antagonist. [a]Definition and examples of high bleeding risk blocks are summarised in Table 2. Definitions of low and high DOAC doses are summarised in Table 1.

drug doses, and four to five times $t_{1/2}$ for high drug doses. For patients with renal impairment, twice the $t_{1/2}$ of patients with renal insufficiency, according to the drug's SmPC, was used. For regional anaesthesia with high bleeding risk, a complete return of haemostatic competence is targeted. The time required for this target is determined by the $t^{1}/_{2}$ of the antithrombotic drug. However, in clinical practice, $t_{1/2}$ is not measured and $t_{1/2}$ varies between and within individuals. Clinicians are requested to adapt this proposal for antithrombotic drug management by considering individual bleeding risks at the puncture site, including bleeding diathesis of other origin, and anatomical factors. In these guidelines, in order to circumvent the imprecision of $t_{1/2}$-based time interval calculations, we propose that the biological residual effect of antithrombotic drugs might be assessed by sensitive drug measurements. Regarding the next dose of antithrombotic after blockade or procedures, we recommend applying the most recent guidelines on VTE prophylaxis, such as from the ESAIC[11,12] and those on therapeutic anticoagulation or APA, as those from the European Heart Rhythm Association (EHRA),[13] respectively. Accordingly, VTE prophylaxis would be administered about 6 h postoperatively (8 h – $t_{max}$ of the anticoagulant drug) and therapeutic anticoagulation or APA started about 24 h postoperatively.

Systematic reviews including randomised clinical trials evaluating different low-dose anticoagulant regimens for postoperative VTE prophylaxis have shown consistently that the shorter the time interval between the end of surgery and the first postoperative dose of an anticoagulant, the higher the risk for bleeding.[14,15] Postoperative bleeding was greater when a dose was given 4 to 8 h postoperatively, lower when given at 12 to 24 h and lowest when administered 24 h postoperatively. The same consideration may apply to regional anaesthesia related anticoagulant or APA dosing. Higher (therapeutic) dosing regimens were also associated with a significant increase in major postoperative bleeding.[16–19] As a result, the American College of Chest Physicians (ACCP) recommends that low-dose antithrombotic prophylaxis or therapy should only be resumed after considering the anticipated bleeding risk, the presence of pre-

operative coagulopathies and the adequacy of postoperative haemostasis.[20] High-dose antithrombotic therapy should be delayed for 48 to 72 h after a procedure with high bleeding risk, and should be administered only when adequate surgical haemostasis has been accomplished.[20] A similar approach is recommended in the more recent VTE guidelines from ESAIC[11,12] and the EHRA guidelines on oral anticoagulant use in atrial fibrillation.[13] As any anaesthesiological neuraxial procedure leading to bleeding would have important consequences, these recommendations may also be helpful in determining timing of the next anticoagulant or APA dose administration.

Clinical management in very rare clinical scenarios such as neuraxial procedures in patients taking fondaparinux, for example, was also discussed. In such rare scenarios, no recommendations were made, but suggestions were offered for consideration if the situation was unavoidable.

**Table 6** Delphi agreements

| | | |
|---|---|---|
| R 1 | Consensus | 9 / 12 |
| R 2 | Strong Consensus | 12 / 12 |
| R 3 | Consensus | 9 / 12 |
| R 4 | Consensus | 9 / 12[a] |
| R 5 | Strong Consensus | 12 / 12 |
| R 6 | Consensus | 10 / 12 |
| R 7 | Consensus | 9 / 12 |
| R 8 | Strong Consensus | 12 / 12 |
| R 9 | Strong Consensus | 11 / 12 |
| R 10 | Consensus | 10 / 12[b] |
| R 11 | Strong Consensus | 12 / 12 |
| R 12 | Strong Consensus | 11 / 12 |
| R 13 | Consensus | 10 / 12[b] |
| R 14 | Strong Consensus | 11 / 12 |
| R 15 | Strong Consensus | 11 / 12 |
| R 16 | Consensus | 10 / 12 |
| R 17 | Consensus | 10 / 12 |
| R 18 | Consensus | 10 / 12 |
| R 19 | Strong Consensus | 12 / 12 |
| R 20 | Consensus | 9 / 12[b] |
| R 21 | Strong Consensus | 12 / 12[a] |
| R 22 | Strong Consensus | 11 / 12 |
| R 23 | Consensus | 10 / 12 |
| R 24 | Strong Consensus | 12 / 12 |
| R 25 | Consensus | 10 / 12 |
| R 26 | Consensus | 10 / 12 |
| R 27 | Consensus | 9 / 12 |
| R 28 | Strong Consensus | 11 / 12 |
| R 29 | Consensus | 10 / 12 |
| R 30 | Strong Consensus | 11 / 12 |
| R 31 | Consensus | 9 / 12 |
| R 32 | Strong Consensus | 12 / 12[b] |
| R 33 | Strong Consensus | 11 / 12 |
| R 34 | Strong Consensus | 12 / 12 |
| R 35 | Strong Consensus | 12 / 12 |
| R 36 | Strong Consensus | 11 / 12 |
| R 37 | Strong Consensus | 12 / 12 |
| R 38 | Strong Consensus | 12 / 12 |
| R 39 | Strong Consensus | 11 / 12 |
| R 40 | Strong Consensus | 11 / 12[b] |

Second Delphi rounds were conducted only on those statements where there was agreement of 50 to 74%, that is not enough to reach the 'Consensus' threshold of 75%. [a] first voting: 7 / 12 (majority). [b] first voting: 8 / 12 (majority).

Clinical practice statements are summarised in Table 5. Results of the Delphi rounds are summarised in Table 6.

## Discussion

The strength of guidance and the certainty of evidence is included after each recommendation and suggestion below using GRADE.

### Clinical question 1

#### 1.1 Is there a difference in time intervals between low and high dosing of a VKA?

***Recommendation 1***

Irrespective of the target International Normalised Ratio (INR), neuraxial procedures should be performed when VKA treatment has been withheld and the INR has returned to the normal range of the local laboratory (e.g. 1.1). 1C

An INR less than 1.5 may be acceptable in individual patients, if after a careful risk–benefit analysis a general anaesthetic is best avoided and a neuraxial anaesthetic technique should be used. 2C

A last VKA intake of 3 days (acenocoumarol), 5 days (warfarin, fluindione) and 7 days (phenprocoumon) before the procedure is proposed. 2C

Following neuraxial procedures, the next dose of VKA should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

In the presence of an indwelling neuraxial catheter, the next dose of VKA should be administered only after its withdrawal. 1C

In the interim, a low dose of LMWH may be used whilst a neuraxial catheter remains in place. 2C

**Evidence Summary:** Low doses of VKAs are used when target values of the INR between 2 and 3 are required.[1,21] Higher doses will be used when higher INR values of 2.5 to 3.0[3] or even 3.0 to 4.0 are targeted.[4] There are no data comparing low and high doses of VKAs and the occurrence of a spinal haematoma. Data from patients congenitally deficient in clotting factors II, IX and X suggest that a 40% factor activity level is sufficient for (near) normal haemostasis.[22] In VKA-naive patients, an INR of 1.5 is associated with 40% factor VII activity and thus normal coagulation.[23,24] In contrast, in VKA treated patients, an INR of at least 1.3 may be associated with factor activity levels less than 40% and disturbed coagulation.[5] Recent data from retrospective studies found that an INR range of at least 1.0 to 1.25 after major orthopaedic surgery or 1.0 to 1.49 after major general surgery increased the occurrence of major surgical bleeding.[6,25,26] Similar results were reported after cholecystectomy,[27] wherein the bleeding frequency predominantly increased in the presence of an INR of at least 1.5.

***Recommendation 2***

In obstetric patients (parturients) treated with a VKA and needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R1). 1C

In selected parturients at a high risk for a thrombotic event and requiring an unplanned or urgent intervention for maternal or foetal indication, the risk of general anaesthesia may be greater than the risk of neuraxial anaesthesia. In these cases, after multidisciplinary discussion and individual risk–benefit analysis, a deviation from the current ESAIC/ESRA guidelines may be considered. C

**Evidence Summary:** In parturients, VKAs are used in a number of cardiac conditions such as native valvular heart disease, prosthetic valves, cardiomyopathies and heart failure.[28] Although lacking adequate randomised studies, there is evidence that VKAs throughout pregnancy, under strict INR control, are the safest regimen to prevent prosthetic valve thrombosis.[29–34] Depending on the thrombogenicity of the valve prosthesis and/or the cardiac condition and the presence of supplementary thrombogenic risk factors (a history of recurrent DVT and pulmonary embolism, atrial fibrillation, thrombophilia and antiphospholipid syndrome), increasing doses of VKAs may be used. Following the current ESC (European Society of Cardiology) and EACTS (European Association for Cardiothoracic Surgery) guidelines, and according to the context and term, a switch from VKAs to subcutaneous LMWH or intravenous (i.v.) UFH will be made at some time during the pregnancy.[4,28] The doses used will also depend on the risks of embryopathy, fetopathy, foetal loss and maternal or fetal bleeding. There is some evidence that LMWH may be superior to UFH to prevent thrombosis of prosthetic heart valves.[33–35] Finally, the ESC guidelines also recommend when to stop and re-initiate the anticoagulation before and after delivery, respectively.[28]

Pharmacological data on the use of VKAs in pregnancy are scarce and any prospective data on the occurrence of a spinal haematoma in the presence of low *versus* high doses of VKAs in parturients are lacking.

However, there may be circumstances in which certain anticoagulated parturients, at high risk for a thrombotic event, may need an unplanned or urgent intervention for maternal or foetal indications. If interrupting or antagonising the antithrombotic therapy is associated with an unacceptable risk of thromboembolism or ischaemia, it may be preferable to keep the antithrombotic free interval as short as possible. If the neuraxial bleeding risk is considered too high, alternative anaesthetic or analgesic techniques (e.g. general anaesthesia, remifentanil patient-controlled analgesia) should be considered. Still, the risks of a general anaesthetic may outweigh those of a neuraxial anaesthetic. In these cases, and after an individual risk–benefit analysis and a multidisciplinary discussion, a deviation or modification from the current ESA/ESRA guidelines may be considered.[36] The associated risks should always be discussed with the patient and the final decision noted in the patient's record.

***Recommendation 3***

Superficial nerve procedures may be performed in the presence of VKA, irrespective of the target INR. 2C

Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C

Deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R1). 1C

If the INR is not below the minimum recommended level, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of large blood vessels and/or neuraxial structures. 2C

**Evidence Summary:** Superficial nerve blocks are predominantly associated with ecchymosis and bruising. Nerve blocks in deep locations may result in haematoma formation, significant neurovascular damage and even exsanguination. The variation in severity of the complications following a deep block can be explained by different risk factors: incompressibility of the bleeding site; no cutaneous sentinel haematoma, which allows for early detection of a severe bleeding; a delayed onset of neurologic symptoms following the bleeding; and the proximity of either a large vessel or the spinal cord.[37] There are no randomised controlled or prospective data comparing the effect of low and high doses of VKAs on the incidence of haematoma formation following PNBs. The available literature on this topic mainly consists of retrospective analyses, individual case reports and reviews of case series.[38,39] Neurological deficits were seldomly reported, and all recovered completely within 6 to 12 months.

### 1.2 Is there a difference in time intervals between low and high dosing of DOACs?

***Recommendation 4***

In low doses of DOACs,[b] the last intake should be a minimum of 24 h for rivaroxaban and edoxaban, 36 h for apixaban and 48 h for dabigatran before neuraxial procedures. 1C

If CrCl is less than 30 ml $min^{-1}$, the last low dose rivaroxaban, edoxaban intake should be at least 30 h before neuraxial procedures. 1C

In high doses of DOACs[b] the last intake should be a minimum of 72 h before neuraxial procedures. 1C
If CrCl is less than 50 ml min$^{-1}$ with high-dose dabigatran treatment or if CrCl is less than 30 ml min$^{-1}$ with high-dose direct anti-Xa inhibitor (DXA) treatment, neuraxial procedures may be performed if the appropriate laboratory assay is within the normal range of the local laboratory. 2C
Following neuraxial procedures, the next low dose of DOAC should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C
In the presence of an indwelling neuraxial catheter, the next dose of DOAC should be administered only after its withdrawal. 1C
In the interim, a low dose of LMWH or low-dose UFH may be used whilst a neuraxial catheter remains in place. 2C

**Evidence Summary:** There are no RCTs investigating the influence of low doses of DOACs on the occurrence of neuraxial anaesthesia-related spinal haematoma in surgical or peri-operative patients. The recommended therapy-free interval of DOACs is therefore based on their biological half-lives.[40,41] In low doses, any DOAC treatment should be interrupted for at least two half-lives before performing a neuraxial procedure.[40] The time interval between the first and next dose of an antithrombotic drug following any neuraxial procedure is determined as 8 h (i.e. time needed for haemostasis) minus $T_{max}$ (2 h for DOACs).[40] If higher doses of DOACs are used, a minimum 4 to 5 half-lives therapy-free interval should be observed before any neuraxial procedure.[41] A residual plasma level of 30 ng ml$^{-1}$ is considered as a well tolerated haemostatic threshold,[42–44] although this threshold has never been clinically validated in preventing any bleeding.[45,46] Two recent prospective studies measured residual DOAC plasma levels after a five half-lives interruption. The CORIDA trial reported plasma levels less than 30 ng ml$^{-1}$ in 95% of the patients after a 49 to 72 h preprocedural discontinuation of high-dose apixaban, rivaroxaban or dabigatran.[46] The PAUSE trial found in a subgroup of 8% of patients with neuraxial procedures that a more than 72 h (110.2 h if CrCl 30 to 50 ml min$^{-1}$ with dabigatran) preprocedural interruption resulted in residual levels more than 30 ng ml$^{-1}$ in only a small fraction of the rivaroxaban (14.7%), apixaban (6.9%) and dabigatran (1.1%) treated patients.[47,48] An age of at least 75 years, female sex, weight less than 70 kg and a CrCl less than 50 ml min$^{-1}$, all were predictive of residual DOAC levels more than 30 ng ml$^{-1}$.[48] Similar data for edoxaban are lacking. The SmPCs of the apixaban, rivaroxaban and dabigatran clearly state that, independent of the doses used, the risk of spinal or epidural haematoma may be increased by the prolonged postoperative use of indwelling epidural or intrathecal catheters.[49–51] As an alternative to the interrupted DOAC treatment, a subcutaneous low dose of a LMWH (i.e. ≤50 IU anti-Xa kg$^{-1}$ day$^{-1}$) can be used as 'postoperative bridging', whilst a postoperative neuraxial catheter remains in place.

***Recommendation 5***

In obstetric patients (parturients) treated with DOACs needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R4). 1C

**Evidence Summary:** There are no RCTs investigating the influence of low or higher doses of DOACs on the occurrence of neuraxial anaesthesia related spinal haematoma in obstetric patients. In their public assessment reports (EPAR) filed with the European Medicines Agency (EMA), the manufacturers state that the use of apixaban, rivaroxaban and edoxaban is contraindicated in parturients,[49,52,53] whereas the use of dabigatran should be avoided.[54]

***Recommendation 6***

Superficial nerve procedures may be performed in the presence of DOACs at either high or low doses. 2C
Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C
Irrespective of the DOAC dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R4). 1C
If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of large blood vessels and/or neuraxial structures. 2C

**Evidence Summary:** There were no bleeding complications in a pooled analysis of three RCTs comparing enoxaparin versus dabigatran for thromboprophylaxis after total knee or hip arthroplasty under general or neuraxial anaesthesia with a PNB.[55] Postoperative low-dose rivaroxaban was associated with local puncture site haematomas of femoral catheters and minor bleeds at the insertion sites of femoral, sciatic and lumbar plexus catheters.[39] Similar results were found when continuous femoral catheters were removed 20 h after the first postoperative low dose of rivaroxaban.[56] Chelly *et al.*[57] removed femoral, sciatic,or lumbar plexus catheters after total knee or hip arthroplasty in 766 patients without any consideration for the timing of the postoperative low dose rivaroxaban and found local

puncture site bleeding in only 10 patients. One publication reported a massive thigh haematoma after an adductor canal block associated with a high dose of apixaban stopped 48 h before the block.[58]

### 1.3 Is there a difference in time intervals between low and high dosing of LMWH?

***Recommendation 7***

In low doses of LMWH, the last administration should be a minimum of 12 h before neuraxial procedures. 1C

If CrCl is less than 30 ml $min^{-1}$, the low dose of LMWH should be halved or the therapy-free interval doubled to 24 h. 1C

In high doses of LMWH (>50 IU anti-Xa $kg^{-1}$ $day^{-1}$), the last administration should be a minimum of 24 h before neuraxial procedures. 1C

If CrCl is less than 30 ml $min^{-1}$, the high dose of LMWH should be halved or the therapy-free interval doubled to 48 h. 1C

Following neuraxial procedures, the next low dose of LMWH should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

In the presence of an indwelling neuraxial catheter, the next high dose of LMWH should be administered only after its withdrawal; in the interim, a low dose of LMWH may be used whilst a neuraxial catheter remains in place. 2C

**Evidence Summary:** Low molecular weight heparins are used subcutaneously in low doses (enoxaparin ≤4000 IU anti-Xa $d^{-1}$, dalteparin ≤5000 IU anti-Xa $d^{-1}$, nadroparin ≤5700 IU anti-Xa $d^{-1}$, tinzaparin ≤4500 IU anti-Xa $d^{-1}$) and in higher doses (enoxaparin >4000 IU anti-Xa $d^{-1}$, dalteparin >5000 IU anti-Xa $d^{-1}$, nadroparin >5700 IU anti-Xa $d^{-1}$, tinzaparin >4500 IU anti-Xa $d^{-1}$). The threshold plasma anti-Xa level above which the neuraxial bleeding risk becomes significant remains unknown.[59,60] There are also insufficient data on the safety of neuraxial indwelling catheters in patients treated with higher SC doses of LMWH.

After a single SC injection of a low dose of a LMWH, peak plasma anti-Xa levels occur after 4 h and fall to 50% of their peak values 12 h later.[61] Higher SC doses increase the residual anti-Xa levels, even with longer, or almost doubled therapy free interval.[62,63] Advanced age, female sex and mild (CrCl 50 to 80 ml $min^{-1}$) to moderate (CrCl 30 to 49 ml $min^{-1}$) renal insufficiency were identified as risk factors causing elevated residual plasma anti-Xa levels.[38,63,64] In severe renal insufficiency (CrCl 15 to 29 ml $min^{-1}$), the LMWH dose used should be halved or the therapy-free interval doubled,[65] but recently, similar recommendations were also proposed in moderate renal insufficiency.[66]

***Recommendation 8***

In obstetric patients (parturients) treated with SC LMWH needing a neuraxial block for surgery, delivery or caesarean section, comparable recommendations (10 to 12 h) as used for the nonpregnant population should be applied (R7).1C

In selected parturients at a high risk for a thrombotic event and requiring an unplanned or urgent intervention for maternal or foetal indication, the risk of general anaesthesia may be greater than the risk of neuraxial anaesthesia. In these cases, after multidisciplinary discussion and individual risk–benefit analysis, deviation from the current ESAIC/ESRA guidelines may be considered.C

**Evidence Summary:** Pregnancy induces physiological changes that affect the pharmacokinetics of SC LMWHs and result in an increased volume of distribution and elimination rate leading to a lower peak antiXa activity and duration, thereby diminishing the antithrombotic effects when compared to nonpregnant women.[67–73] In addition, pregnancy results in a hypercoagulable state caused by an increase in platelet aggregation, an increased plasma level of various coagulation factors, an increased activated protein C resistance and a decrease in protein S levels.[74] This may explain the lower incidence of spinal haematoma after neuraxial blocks in this group of patients,[40,64,75,76] even in cases where the minimum recommended time interval between the last dose of antithrombotic and the neuraxial procedure was not observed.[76] Still, there are insufficient prospective pharmacological data on the anticoagulant effects of low and high doses of SC LMWH in pregnant women and on the incidence of spinal haematoma to recommend a more lenient approach regarding neuraxial anaesthesia.[36]

However, there may be circumstances in which selected anticoagulated parturients, at a high risk for a VTE/pulmonary embolism, may need an unplanned or urgent intervention for maternal or foetal indications. If interrupting or antagonising the antithrombotic therapy is associated with an unacceptable risk of thromboembolism or ischaemia, it may be preferable to keep the antithrombotic-free interval as short as possible. If the neuraxial bleeding risk is considered too high, alternative anaesthetic or analgesic techniques, for example general anaesthesia, remifentanil patient-controlled analgesia, should be considered. However, the risks of a general anaesthetic may outweigh those of a neuraxial anaesthetic. In these cases, and after an individual risk-benefit analysis and a multidisciplinary discussion, a deviation from the current ESA/ESRA guidelines may be considered.[36] The associated risks should always be discussed with the patient and the final decision noted in the patient's record.

***Recommendation 9***

Superficial nerve procedures may be performed in the presence of LMWH at high or low doses. 2C

Following a superficial nerve procedure, the next dose may be administered at the routinely prescribed next time point. 2C

Irrespective of the LMWH dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R7). 1C

If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of blood vessels or neuraxial structures. 2C

**Evidence Summary:** Neurovascular and haemorrhagic complications in patients treated with SC LMWHs in low or higher doses have been reported after PNBs.[40] Low doses were associated with local ecchymosis, bleeding and swelling at the puncture site, and in one patient, a thigh haematoma occurred, extending into the femoral nerve and causing severe motor and sensory deficits. Higher doses of enoxaparin have been associated with large retroperitoneal haematomas causing pain and motor deficits.[39]

**1.4 Is there a difference in time intervals between low and high dosing of UFH?**

***Recommendation 10***

In low doses of subcutaneous UFH ($\leq$200 IU kg$^{-1}$ d$^{-1}$), the last administration should be a minimum of 4 h before neuraxial procedures. 1C

In high doses of UFH (>200 IU kg$^{-1}$ d$^{-1}$), neuraxial procedures may be performed if the anti-Xa activity, activated partial thrombplastin time (aPTT) or ACT has returned to the normal range of the local laboratory. 2C

Regarding stopping i.v. administration of high doses of UFH a minimum of 6 h before the procedure is recommended and regarding SC administration of high doses of UFH a minimum of 12 h. 2C

Following neuraxial procedures, the next low dose of SC UFH should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

A shorter interval (1 h) may be acceptable in individual patients undergoing vascular surgery, after a careful risk–benefit analysis. 2C

In the presence of an indwelling neuraxial catheter, the next high dose of UFH should be administered only after its withdrawal; in the interim, a low dose of UFH or LMWH may be used, whilst a neuraxial catheter remains in place. 2C

**Evidence Summary:** Low-dose subcutaneous UFH is generally used as a two or three times a day injection of 5000 IU, thus 3 x 5000 IU d$^{-1}$or less. A single subcutaneous injection of 5000 IU of UFH caused a widely variable but substantial anticoagulant effect 1 to 2 h after the injection, only normalising after 4 to 6 h.[77,78] Nevertheless, several publications have demonstrated the safety of three times a day SC administration of 5000 IU UFH.[79–82] Using higher SC doses of UFH increases the half-life and anticoagulant effect in a nonlinear fashion.[83,84] Doses of SC UFH ranging from more than 15 000 to 20 000 IU or less per day may result in a significantly elevated aPTT 12 h after the administration,[85] and even longer if doses more than 20 000 IU per day are used. Data on the safety of neuraxial catheters in patients treated with higher subcutaneous doses of UFH are lacking. Intravenous doses of 5000 to 7500 IU of UFH following neuraxial anaesthesia have been used uneventfully in vascular surgery.[86]

The monitoring of UFH using anti-Xa levels compared with the aPTT results in an increased proportion of tests in the target range, while decreasing the overall number of tests and the frequency of dosage alterations.[87]

***Recommendation 11***

In obstetric patients (parturients) treated with UFH needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R10). 1C

In selected parturients at a high risk for a thrombotic event and requiring an unplanned or urgent intervention for maternal or foetal indication, the risk of general anaesthesia may be greater than the risk of neuraxial anaesthesia. In these cases, after multidisciplinary discussion and individual risk–benefit analysis, a deviation from the current ESAIC /ESRA guidelines may be considered. C

**Evidence Summary:** Pregnancy affects the pharmacodynamics and pharmacokinetics of UFH, reducing both the aPTT and the duration of action of UFH.[88–90] A single SC injection of 7500 IU UFH does not significantly change the aPTT nor the anti-Xa-activity from baseline values.[91] Large case series comparing the use of low ($\leq$15 000 IU d$^{-1}$) *versus* higher doses of UFH (>15 000 IU d$^{-1}$) in combination with neuraxial anaesthesia in obstetric patients are not available, but occurrence of spinal haematoma associated with a neuraxial anaesthetic procedures is extremely rare in this group, and notably lower than in surgical or peri-operative patients.[36,38,64,75]

However, there may be circumstances in which selected anticoagulated parturients, at a high risk for a VTE/ pulmonary embolism, may need an unplanned or urgent

intervention for maternal or foetal indications. If interrupting or antagonising the antithrombotic therapy is associated with an unacceptable risk of thromboembolism or ischaemia, it may be preferable to keep the antithrombotic-free interval as short as possible. If the neuraxial bleeding risk is considered too high, alternative anaesthetic or analgesic techniques, for example general anaesthesia or remifentanil patient-controlled analgesia, should be considered. Still, the risks of a general anaesthetic may outweigh those of a neuraxial anaesthetic. In these cases, and after an individual risk-benefit analysis and a multidisciplinary discussion, a deviation from the current ESA/ESRA guidelines may be considered.[36] The associated risks should always be discussed with the patient and the final decision noted in the patient's record.

### *Recommendation 12*

Superficial nerve procedures may be performed in the presence of UFH at high or low doses. 2C

Following superficial nerve procedures, the next dose may be administered at the routinely prescribed time point. 2C

Irrespective of the UFH dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R10). 1C

If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of blood vessels or neuraxial structures. 2C

**Evidence Summary:** The literature on the incidence of tissue haematoma following low ($\leq$15 000 IU d$^{-1}$) *versus* higher doses of UFH (>15 000 IU d$^{-1}$) is scarce. The case series by Horlocker and Joubert only reported on a small number of cases.[38,39] Low-dose UFH was associated with a large chest haematoma following intercostal nerve blocks, but a higher dose i.v. infusion of UFH was also used in the same patient.[38] Higher SC doses of UFH ($\geq$15 000 IU d$^{-1}$) were associated with a haemothorax following a supraclavicular brachial plexus block and a retroperitoneal haematoma after lumbar plexus and sciatic nerve block. A recent case report describes a quadratus lumborum block associated left flank haematoma in a patient receiving i.v. UFH 3.5 h after the block.[92]

**1.5 Is there a difference in time intervals between low and high dosing of fondaparinux?**

### *Recommendation 13*

In low SC doses of fondaparinux ($\leq$2.5 mg d$^{-1}$), the last administration should be a minimum of 36 h before neuraxial procedures. 1C

If CrCl is less than 50 ml min$^{-1}$, the last low dose fondaparinux should be at least 72 h before or the dose of fondaparinux should be reduced to 1.5 mg d$^{-1}$. 1C

In high SC doses of fondaparinux (>2.5 mg d$^{-1}$), neuraxial procedures are not recommended. 1C

If unavoidable, neuraxial procedures (e.g. catheter withdrawal) may be performed if the calibrated anti-Xa activity has returned to the normal range of the local laboratory. 2C

For high SC doses of fondaparinux, an interval of 4 days before the procedure is recommended. 2C

Following neuraxial procedures, the next low SC dose of fondaparinux should be administered according to guidelines on postoperative VTE prophylaxis or therapeutic anticoagulation. 1C

**Evidence Summary:** Fondaparinux is a parenteral factor Xa inhibitor with a $T_{max}$ of 2 h, and a renal function dependent elimination half-life of 16 to 21 h. It is used postoperatively in low dose ($\leq$2.5 mg d$^{-1}$) for the prevention of DVT and pulmonary embolism, in the treatment of unstable angina, NSTEMI or STEMI and as a substitute for UFH and LMWH in case of heparin included thrombocytopenia. Higher doses (5 to 10 mg) are used in the treatment of acute DVT and pulmonary embolism. There are no RCTs investigating the occurrence of neuraxial anaesthesia-related spinal haematoma in surgical patients treated with low or high doses of fondaparinux. The prospective EXPERT trial reported no spinal haematomas when a stoppage time interval of 36 h before catheter removal and a 12 h interval after catheter removal before the restarting fondaparinux were utilised.[93]

In the very few available case reports of a fondaparinux-related spinal haematoma, these were associated with either the use of high doses (>2.5 mg d$^{-1}$)[94–96] or not respecting the then recommended 36 to 42 h time interval[97] following a lower dose of fondaparinux before withdrawing the indwelling neuraxial catheter.[98] A meta-analysis by Turpie *et al.*[15] demonstrated that the administration of low-dose fondaparinux starting 6 h after surgery did not result in an increase in any clinically relevant bleeding, and even less if a 8 to 9 h delay was used.

The manufacturer recommends reducing the low dose of fondaparinux to 1.5 mg per day in patients with moderate renal insufficiency (CrCl 20 to 50 ml min$^{-1}$, half-life 29 h). Fondaparinux use is contraindicated in patients with severe renal insufficiency (CrCl <20 ml min$^{-1}$, half-life 72 h).[99] The SmPC also states that epidural and spinal haematomas resulting in long-term or permanent paralysis cannot be ruled out in patients receiving both fondaparinux and neuraxial anaesthesia or spinal puncture, especially if indwelling epidural catheters are used postoperatively. In patients receiving higher doses of fondaparinux for treatment of VTE or pulmonary embolism, neuraxial anaesthesia should not be used.

***Recommendation 14***

In obstetric patients (parturients) treated with fondaparinux needing a neuraxial block for surgery, delivery or caesarean section, the same recommendations as used for the nonpregnant population should be applied (R13). 1C

**Evidence Summary:** There are no clinical data on fondaparinux during pregnancy, and there are insufficient animal studies with respect to effects on pregnancy, embryo and foetal development, parturition and postnatal development. As a result, the SmPC states that fondaparinux should not be prescribed to pregnant women unless clearly necessary.[99] As a result, there are no RCTs investigating the influence of low or higher doses of fondaparinux on the occurrence of neuraxial anaesthesia-related spinal haematoma in obstetric patients.

***Recommendation 15***

Superficial nerve procedures may be performed in the presence of fondaparinux at high or low doses. 2C

Following superficial nerve procedures, the next dose may be administered at the routinely prescribed next time point. 2C

Irrespective of the fondaparinux dose, deep nerve procedures should be performed according to the recommendations for neuraxial procedures (R13). 1C

If the minimum recommended therapy-free time interval has not elapsed, regional anaesthetic management should depend on the compressibility of the puncture site, the vicinity of blood vessels or neuraxial structures. 2C

**Evidence Summary:** No RCTs exist that specifically study PNBs and fondaparinux. In a prospective study including 458 patients, Chelly *et al.*[100] removed lumbar plexus, femoral or sciatic catheters after joint arthroplasty without any consideration for the timing of postoperative low-dose fondaparinux administration and did not report any perineural haematomas. One case report described a thigh haematoma after sciatic plexus catheter insertion in a patient treated with low dose SC fondaparinux,[101] while the late occurrence of an abdominal oblique muscle haematoma was reported after a transverse abdominis plane block.[102]

**Is there a difference in time intervals between low and high dosing of antiplatelet agents?**

***Recommendation 16***

Low-dose aspirin (<200 mg) is not a contraindication for neuraxial procedures, if a careful risk-benefit analysis is undertaken. 1C

Single-puncture spinal anaesthesia is preferable to epidural anaesthesia. 1C

With high doses of aspirin (≥200 mg), the last dose should be a minimum of 3 days, assuming normal platelet counts, up to 7 days before neuraxial procedures. 1C

The next high dose of aspirin may be administered a minimum of 6 h after neuraxial procedures. 2C

**Evidence Summary:** The risk of spinal epidural haematoma related to aspirin is very low. It has only been reported anecdotally after many years of practice in a very large number of patients undergoing spinal anaesthesia.[97,103,104] No neuraxial haematoma attributed to aspirin has been reported in the large studies that evaluated this risk in orthopaedics and obstetrics. In the few case reports of spinal haematoma involving aspirin therapy, additional complicating factors were present, particularly injections of low-molecular-weight heparin close to a neuraxial procedure or catheter ablation.[75]

The risk of neuraxial haematoma is probably greater for epidural anaesthesia, especially with a catheter, than for spinal anaesthesia.[103]

There are no RCTs comparing aspirin doses at more than 200 or at less than 200 mg in patients requiring central neuraxial anaesthesia. In a prospective cohort of 1035 patients undergoing 1214 epidural steroid injections, including 158 aspirin-treated patients (and 30 patients on 325 mg or more per day), there were no spinal haematomas and no difference in the frequency of bleeding during needle placement in patients who reported aspirin doses of 325 mg $d^{-1}$ compared with larger daily doses.[105]

In an extensive retrospective review, out of 61 published cases of spinal haematoma after neuraxial anaesthesia, only in one was the isolated use of aspirin at high doses (650 mg every 12 h, starting 4 h after surgery) identified as a probable risk factor.[103] However, in this case, in addition to the use of high doses of aspirin, a repetitive and traumatic epidural technique with unintentional dural puncture and spinal catheter placement was described.

The rationale of a higher bleeding risk associated with higher doses of aspirin remains unclear because, whilst the bleeding risk associated with aspirin is dose-dependent, aspirin may also produce opposing effects on the haemostatic mechanism depending on the dose administered.[106] For example, platelet cyclo-oxygenase is inhibited by low-dose aspirin (60 to 325 mg $d^{-1}$), preventing the synthesis of thromboxane A2, which facilitates platelet aggregation. However, larger doses (1.5 to 2 g $d^{-1}$) also inhibit the production of prostacyclin (a potent vasodilator and platelet aggregation inhibitor) by vascular endothelial cells.

Therefore, small-dose aspirin produces a greater antiplatelet effect than larger doses.

In medical patients, comparison of low and high doses of aspirin resulted in contrasting results. In the CURRENT-OASIS 7 trial, wherein patients with an acute coronary syndrome who were referred for an invasive strategy, there was no significant difference between higher-dose aspirin (300 to 325 mg daily) or lower-dose aspirin (75 to 100 mg daily) with respect to major bleeding (2.3 versus 2.3%; hazard ratio, 0.99; 95% CI, 0.84 to 1.17; $P = 0.90$).[107] In contrast, in the PCI-CURE study, 2658 patients with acute coronary syndromes undergoing PCI were stratified into three aspirin dose groups at least 200 mg (high), 101 to 199 mg (moderate) and 100 mg or less (low). Major bleeding was increased with high-dose aspirin: 3.9, 1.5 and 1.9% in the high, moderate and low-dose groups respectively; hazard ratio of high versus low dose 2.05 (95% CI 1.20 to 3.50, $P = 0.009$).[108]

In the peri-operative setting, there is also limited evidence for a dose-related increased risk of bleeding complications. In a meta-analysis of studies of patients undergoing coronary artery bypass grafting, pre-operative aspirin increased postoperative bleeding compared with no aspirin or placebo.[109] However, subgroup analyses suggested that aspirin at doses 100 mg $d^{-1}$ or less might not increase the postoperative bleeding, and the dose of 325 mg $d^{-1}$ might not be a cut-off value that has clinical and statistical significance. The same results were observed in a previous meta-analysis of studies of patients undergoing CABG comparing pre-operative aspirin with no aspirin or placebo, highlighting that most of the RCTs were old.[110,111]

Several cases of neuraxial haematoma were reported following catheter removal, thus catheter insertion and removal carry similar risks to insertion.[112] Removal is associated with complex management of $P2Y_{12}$ inhibitors: several teams suggested removing the catheter after normalisation of platelet function and proposed to monitor platelet function or to transfuse platelets.[113–120]

### *Recommendation 17*

Irrespective of the dose of $P2Y_{12}$ inhibitors, the last intake should be a minimum of 5 days (ticagrelor), 5 to 7 days (clopidogrel) or 7 days (prasugrel) before neuraxial procedures. 1C

The next dose of $P2Y_{12}$ inhibitors may be administered without delay (75 mg clopidogrel), a minimum of 24 h (prasugrel, ticagrelor) or a minimum of 2 days (300 mg clopidogrel) after neuraxial procedures. 2C

In the presence of an indwelling neuraxial catheter, the next dose of $P2Y_{12}$ inhibitors should be administered only after its withdrawal. 2C

**Evidence Summary:** There is limited evidence that continuation of $P2Y_{12}$ inhibitors (clopidogrel, ticlopidine, ticagrelor and prasugrel) is associated with complications of significant bleeding and epidural haematomas. A small number of cases of perimedullary haematoma have been reported with clopidogrel.[121–123] In contrast, in small cohorts (<350) of patients, neuraxial anaesthesia has been performed despite uninterrupted clopidogrel with no cases of spinal or epidural haematoma.[124]

Experts usually consider that the $P2Y_{12}$ inhibitors carry a greater risk of bleeding than aspirin. In their most recent updates of the European public assessment report (EPAR) of clopidogrel, prasugrel and ticagrelor, the manufacturers have recommended that these drugs be stopped 7, 7 and 5 days before surgery, respectively.[53,125,126] In selected patients at a high risk for a thrombotic or ischaemic event, even shorter time intervals for clopidogrel withdrawal may be considered; well tolerated neuraxial procedures in the presence of clopidogrel have been reported.[123] A normal platelet count and/or aggregation test may assist in decision making and shorten the time interval for clopidogrel towards 5 days.

### *Recommendation 18*

Irrespective of the dose of antiplatelet agents, superficial nerve blocks may be performed, if a careful risk–benefit analysis is undertaken. 2C

Irrespective of the dose of the antiplatelet agents, deep nerve blocks should be performed according to the recommendations for neuraxial procedures (R17). 2C

**Evidence Summary:** Wound haematoma is a rare complication of PNBs. Haematoma carries three risks: the need for potential surgical evacuation, transfusion and nerve damage by compression. The estimated incidence of bleeding complications associated with PNBs in patients treated with an antiplatelet agent and/or an anticoagulant was low [0.67% (0.51to 0.83%)] in the systematic review by Joubert *et al.*[39] Although experts generally consider that the $P2Y_{12}$ inhibitors carry a greater risk of wound haematoma than aspirin there is limited evidence that continuation of $P2Y_{12}$ inhibitors (clopidogrel, ticlopidine, ticagrelor and prasugrel) is associated with more complications of significant bleeding than aspirin.

The risk of haematoma is greater during deep blocks, in the absence of compression and when antiplatelet and anticoagulant therapies are combined. Ultrasound guidance reduces the risk of vascular puncture.[127]

PNBs can be divided into two groups according to the degree of bleeding risk:

Low bleeding risk peripheral blocks where, if bleeding occurs, it is easily controllable and the area of bleeding

can be compressed. These include superficial blocks such as the femoral nerve block, the axillary plexus block and the popliteal sciatic nerve block. These blocks could be performed in patients on APA treatment if the risk–benefit analysis would justify this.

High bleeding risk blocks where in the event of bleeding the area cannot be compressed or the consequences of the bleeding are potentially serious. These include deep blocks such as the infraclavicular brachial plexus, the parasacral sciatic and the posterior lumbar plexus. These blocks are contraindicated in patients on $P2Y_{12}$ inhibitors and should only be performed in patients on high-dose aspirin if the risk–benefit analysis still favours the block.

Although peribulbar anaesthesia has been performed in ophthalmology without complications in large series of aspirin-treated patients, few data are available in patients treated with clopidogrel and even less with ticagrelor or prasugrel.[128] Nevertheless, if bleeding occurs, compression is not possible. Topical or sub-Tenon's anaesthesia may be preferred if these are practical.

**Clinical question 2**

**2.1 Is there a difference in time intervals between combinations of antithrombotic drugs?**

> ***Recommendation 19***
> When antithrombotic drugs are combined, the therapy-free time interval should be that of the drug with the longest interval. 1C

**Evidence Summary:** Combinations of antithrombotic drugs may lead to a higher bleeding risk. However, it is unknown whether these combinations necessitate altering recommendations for time intervals.

Currently, we are not aware of direct pharmacokinetic interactions between anticoagulant and antiplatelet drugs. For example, VKA do not seem to have an influence on platelet reactivity, when added to clopidogrel[129] and rivaroxaban does not seem to be influenced by aspirin.[130] Therefore, we believe that there is no necessity to increase time intervals longer than that of the drug with the longest time interval.

If a platelet inhibiting drug is to be continued (e.g. low-dose Aspirin), we need to consider an increased bleeding rate.[131–133] The American Society of Regional Anesthesia and Pain Medicine (ASRA) suggest that NSAIDs in combination with unfractionated heparin, low molecular weight heparin, oral anticoagulants and thrombolytics increases the frequency of spontaneous haemorrhagic complications, bleeding at puncture sites and spinal haematoma.[38] Vela Vasques *et al.*[104] and ASRA suggest an increase in haematoma risk if aspirin is combined with heparin.

Peri-operative combinations with drugs exerting side effects on haemostasis increase the bleeding risks of blocks.[134,135] We therefore suggest avoiding combinations of antithrombotic drugs with drugs such as NSAIDs and tricyclic antidepressants peri-operatively, particularly for neuraxial procedures and deep peripheral blocks.

**Clinical situation: urgent antiplatelet and anticoagulant therapy with a neuraxial/deep nerve catheter in situ**

> ***Recommendation 20***
> If urgent administration of combinations of antithrombotics is necessary when a neuraxial catheter is already in situ interdisciplinary management is suggested, together with laboratory drug measurements and neurological monitoring after neuraxial procedures. 2C
> With loading doses of aspirin and clopidogrel, a neuraxial catheter could be removed immediately, before the clopidogrel reaches full effect. 2C
> In cases of combined antiplatelet and anticoagulant drug treatment, a neuraxial catheter could be removed after reducing the anticoagulant dose or replacing the antiplatelet drug by a short acting antiplatelet drug (e.g. tirofiban, eptifibatide, cangrelor). 2C

**Evidence Summary:** Removing an epidural catheter in a patient receiving urgent antiplatelet and anticoagulation therapy for acute coronary syndrome is challenging. Currently, 11 case reports are available describing successful management. The cases describe myocardial infarctions during or within 3 days after surgery.[116,136–145] Key factors to successful management is an interdisciplinary approach and measures of platelet and plasma function.

If dual platelet inhibition with clopidogrel and/or aspirin and anticoagulant treatment has not yet been started after the diagnosis, one may consider removing the catheter immediately [142,145] and implement close neurological monitoring, because clopidogrel needs 12 to 24 h to reach full effectivity after a loading dose.[146]

If dual platelet inhibition and anticoagulant treatment is fully effective and the thromboembolic or ischaemic risk is high, one may consider tapering down the anticoagulant (e.g. low-dose UFH then pause 4 h or low-dose LMWH and pause 12 h before catheter removal), leave or pause aspirin at low dose (e.g. 100 mg) and replace the second platelet inhibitor with the short acting tirofiban or cangrelor as a bridge. Tirofiban can be stopped 8 h before catheter removal.[141,147] Cangrelor can be stopped 3 h before catheter removal.[147]

Platelet and plasma function measurements should ensure normalisation of thrombocyte function and plasma coagulation for the shortest period achievable during which the catheter can be removed.[116,137–140]

**Clinical situation: critical illness and parenteral urgent antiplatelet and/or anticoagulant therapy with a neuraxial or deep nerve catheter in situ**

***Recommendation 21***

In the case of urgent indications for parenteral direct thrombin inhibitors (argatroban, bivalirudin, desirudin), prostaglandins (prostacyclin, epoprostenol) or glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), when a neuraxial or deep nerve catheter is already in situ, interdisciplinary management is recommended, together with laboratory drug measurements and neurological monitoring after neuraxial procedures. 2C

The catheter could be removed after pausing short acting drugs for four to five half-lives (e.g. argatroban 4 h, prostacyclin 1 h). 2C

**Evidence Summary:** Regional anaesthesia is rarely indicated in severe illness, but if this develops postoperatively with an epidural or deep nerve catheter in situ, special considerations have to be taken for well tolerated catheter management in these patients. Patients who are sedated will not complain of symptoms related to nerve damage by haematoma compression or infection and there is no perfect option in such complex situations. The catheter could be removed before administration of parenteral antithrombotic agents to simplify management. It could also be removed before hirudins reach full effectivity, and shortly after pausing short acting argatroban or prostaglandins. For deep nerve catheters, haematoma formation at the puncture site may be monitored using close neurological assessment as well as ultrasound.

**Clinical question 3**

**3.1 Is there a difference in time intervals between patients with and without bleeding risk score assessment?**

***Recommendation 22***

Bleeding risk scores have no influence on the time interval from last drug intake to intervention or to next drug dose following a procedure. 2C

**Evidence Summary:** There are no studies available which tested whether bleeding risk scores have any influence on the rate of wound haematoma after PNBs or the rate of spinal or epidural haematoma after neuraxial puncture/catheter insertion/removal.

Tsui[148] proposed a scoring system using three categories of consideration to classify any regional procedure and to determine bleeding risk. Nevertheless, this classification has never been assessed.

**Clinical question 4**

**4.1 Is there a difference in time intervals between patients with and without drug measurements?**

There are no controlled studies in patients on any antithrombotic drug before and after neuraxial blockade and catheter removal that investigated whether drug measurements and consequently laboratory threshold values reduce the neuraxial bleeding risk. Similarly, there are no controlled studies available that tested whether drug measurement or laboratory threshold values have any influence on the rate of wound haematoma after deep nerve blocks or superficial nerve blocks.

***Recommendation 23***

In patients on VKA, a normal INR is targeted for neuraxial and deep nerve procedures, irrespective of the time the drug is withheld for (R1). 1C

**Evidence Summary:** In patients treated with VKAs, factor activity levels can fall below 40% when the INR is 1.3 or above and therefore bleeding becomes possible.[5] Regarding general bleeding risk, an INR more than 1.0 was found to be associated with increased bleeding and mortality after cholecystectomy[27] and major surgery,[26] while an INR more than 1.25 was associated with increased bleeding after major orthopaedic surgery.[6,25] However, Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine suggest that, where there is potential benefit of neuraxial blocks in term of mortality reduction, INR levels of 1.4 or less, less than 1.8, less than 2.2 for single shot spinal anaesthesia and INR levels of 1.2 or less, less than 1.6, less than 1.8 for epidural analgesia for weak, strong, vital indications, respectively, may be acceptable.[38,149]

***Recommendation 24***

In patients on high-dose UFH, an aPTT or an anti-Xa activity or an ACT within or below the normal range of the local laboratory is the necessary target for neuraxial and deep nerve procedures, irrespective of the time interval after the last dose (R10). 1C

**Evidence summary:** The anticoagulant effect of heparin is typically monitored using the widely available aPTT. Some authors suggest that anti-Xa testing is superior to aPTT testing in order to determine measurement of heparin activity more accurately. Activated clotting time (ACT) is typically used to monitor higher doses given during cardiopulmonary bypass.[47]

***Recommendation 25***

In patients on high-dose LMWH or fondaparinux, an anti-Xa activity of 0.1 IU $ml^{-1}$ or less is targeted for neuraxial or deep nerve procedures and this may shorten or increase the time interval after administration is withheld (R7). 2C

Anti-Xa activity of residual LMWH anticoagulant effect, either from high-dose or low-dose regimens, may be considered in the presence of renal insufficiency (CrCl <30 ml $min^{-1}$) and in older, frail or very low body weight patients to guide the timing of neuraxial and deep nerve procedures. 2C

**Evidence summary**: It must be recognised that the plasma anti-Xa level above which the bleeding risk becomes significant is unknown. In patients on LMWH, when there is a risk of elevated plasma anti-Xa levels, and anti-Xa activity is monitored, an activity value of 0.1 IU $ml^{-1}$ or less is considered a nondetectable anticoagulant effect. If deciding to monitor LMWH anti-Xa activity before a neuraxial procedure, it is generally accepted to proceed with a level of 0.1 or less.[63]

With regard to fondaparinux, German S1-Guidelines suggest that, where neuraxial block is indicated, an anti-Xa activity of 0.1 IU $ml^{-1}$ or less should be targeted.[150] In patients on fondaparinux wherein there may be a risk of elevated plasma anti-Xa levels, if anti-Xa activity can be monitored, an activity value of 0.1 IU $ml^{-1}$ or less can be considered a nondetectable anticoagulant effect. Whether this is applicable to neuraxial procedures or deep nerve blocks remains uncertain.

***Recommendation 26***

In patients on high doses of direct Xa inhibitors (DXA), calibrated DXA levels less than 30 ng $ml^{-1}$ or an anti-Xa activity of 0.1 IU $ml^{-1}$ or less is targeted for neuraxial or deep nerve procedures and this may shorten or increase the time interval after the DXA is withheld (R4). 2C

Drug measurement of residual DXA anticoagulant effect may be considered in the presence of renal insufficiency (CrCl <30 ml $min^{-1}$) to guide the timing of neuraxial or deep nerve procedures. 2C

**Evidence summary**: In patients on oral direct Xa inhibitors, when time of last dose is uncertain, but calibrated drug-specific plasma levels are not available, heparin or LMWH-calibrated chromogenic anti-Xa assays can be used to rule out the presence of clinically relevant DXA effect.[45] An anti-Xa activity of 0.1 IU $ml^{-1}$ or less is considered a nondetectable anticoagulant effect. Where calibrated drug-specific plasma levels assays are available, recent studies and guidelines have defined a nondetectable anticoagulant effect with a specific threshold value of less than 30 ng $ml^{-1}$.[46,47] Nevertheless, anti-Xa activity is very sensitive to the presence of DXA and, thus, could increase even when concentrations are less than 30 ng $ml^{-1}$.

Whether this is applicable to neuraxial procedures or deep nerve blocks remains uncertain.

***Recommendation 27***

In patients on high doses of dabigatran, a thrombin time (TT) within or below the normal range of the local laboratory or a dabigatran level less than 30 ng $ml^{-1}$ is targeted for neuraxial or deep nerve procedures and may shorten the time interval after the last dose (R4). 2C

Drug measurement of any residual dabigatran anticoagulant effect may be considered in the presence of renal insufficiency (CrCl <50 ml $min^{-1}$) for guiding the timing of neuraxial or deep nerve procedures. 2C

**Evidence summary**: In patients on dabigatran, when the time of last dose is uncertain and calibrated drug-specific plasma levels are not available, a normal TT excludes the presence of dabigatran with a high negative predictive value.[45] A normal TT is considered a nondetectable anticoagulant effect. If calibrated drug-specific plasma levels are available, recent studies and guidelines have defined a nondetectable anticoagulant effect with a specific threshold value of less than 30 ng $ml^{-1}$.[46,47] Whereas a normal TT is highly reliable in excluding residual dabigatran activity, the TT is very sensitive to the presence of dabigatran and thus could increase even when concentrations are less than 30 ng $ml^{-1}$.

Whether this is applicable to neuraxial procedures or deep nerve blocks remains uncertain.

***Recommendation 28***

In patients on low doses of anticoagulants, no routine laboratory tests are suggested for neuraxial, deep or superficial nerve procedures. 2C

Drug measurements may be considered in the presence of impaired anticoagulant elimination (e.g. renal insufficiency). 2C

***Recommendation 29***

In patients on high doses of anticoagulants, no routine laboratory tests are suggested for superficial nerve procedures.2C

Specific laboratory values within or below the patient's individual therapeutic range of VKA, UFH or LMWH are targeted for superficial nerve blocks. 2C

Therapeutic ranges for DOACs have not been defined yet. C

**Evidence summary:** No recommendation can be made on any upper laboratory threshold values for superficial nerve blocks, as laboratory threshold values are limited by the surgical indication to operate. However, it is of interest that a recent study on rivaroxaban by Kaserer *et al.*[151] on 308 surgical interventions in 298 patients showed calculated rivaroxaban concentrations only greater than 100 ng ml$^{-1}$ to be associated with a significant increase in red blood cell loss.

### *Recommendation 30*

No recommendation can be proposed on monitoring aspirin and $P2Y_{12}$ inhibitors, before neuraxial, deep or superficial nerve procedures. Specific platelet function tests in the normal range of the local laboratory could be considered as targets for neuraxial and deep nerve procedures. 2C

**Evidence summary:** Although platelet function tests may be used to assess whether patients respond to antiplatelet therapy, no evidence or clinical guidance exists to decide on invasive procedures based on using those tests.[152]

**Clinical question 5**

**5.1 Is there a difference in time intervals between patients with and without reversal of VKA and DOAC?**

The term 'reversal' relates to direct and specific antidote treatment only and not to nonspecific enhancement of the haemostatic potential. In general, anticoagulant treatment must not be reversed only for the sole purpose of a regional anaesthetic technique. If reversal is required for the well tolerated conduct of the surgical procedure, time intervals are suggested below, after which regional anaesthetic techniques may be performed.

### *Recommendation 31*

From a pharmacological point of view, neuraxial or deep nerve procedures may be performed in emergency situations following an individual risk–benefit evaluation once the anticoagulant activity of VKA is fully reversed by prothrombin complex concentrate (PCC), INR-dependent dose adjusted and combined with vitamin K (10 mg). 2C

### *Recommendation 32*

Neuraxial or deep nerve procedures may be performed in emergency situations once the anticoagulant activity of dabigatran is fully reversed by the specific antidote idarucizumab. 2C

Nonspecific haemostatic agents (PCC or activated PCC) do not affect time intervals for dabigatran. 2C

Andexanet alpha does not affect time intervals. 2C

Nonspecific haemostatic agents (PCC or activated PCC) do not affect time intervals for DXA. 2C

**Evidence Summary:** Reversal of VKA with PCC and vitamin K is recommended peri-operatively.[153,154]

There are no controlled data investigating the use of reversal agents, such as idaruzicumab, andexanet alpha or PCC, in the setting of planned neuraxial anaesthesia. However, in patients on dabigatran, the urgent need for a diagnostic lumbar puncture for infectious reasons or spinal anaesthesia where contraindications to general anaesthesia exist, a French guideline recommends the use of idarucizumab to normalise coagulation before the neuraxial technique is performed.[155] Of note, the approval study for idarucizumab, the mAb fragment neutralising the anticoagulant effect of dabigatran, investigated the reversal agent in an uncontrolled study. This did not include patients requiring reversal of anticoagulation for the purposes of a neuraxial block or insertion or removal of a neuraxial catheter.[156] In this study, the administration of 5 g of idarucizumab decreased dabigatran plasma levels below the lower detection of level of 20 ng ml$^{-1}$ within 30 min in 100% of patients who were either actively bleeding or scheduled for emergency surgery. So far, however, it is not known whether low levels of dabigatran (<20 ng ml$^{-1}$) are well tolerated or may increase the risk of haematoma formation during neuraxial block, catheter insertion and removal, or after these procedures.[157]

For patients on apixaban and rivaroxaban, the direct reversal agent andexanet alpha has been approved and is recommended to reverse the anticoagulant effect of these direct factor Xa inhibitors.[158] In the uncontrolled approval study of andexanet alpha, the administration of a low or high-dose bolus decreased anti factor Xa activities by 92% for both oral Xa inhibitors, with residual plasma levels of 11.1 ng ml$^{-1}$ for apixaban and 14.2 ng ml$^{-1}$ for rivaroxaban, respectively, at 15 to 30 min from the end of bolus administration.[159] Following these results, the EHRA recommends the administration of andexanet alpha for life-threatening bleeding under medication with oral factor Xa inhibitors but approved for apixaban and rivaroxaban only. Reversal of DXA by andexanet alpha may not be complete after bolus administration followed by a continuous infusion for 2 h; conventional calibrated anti-Xa activity assays may not be reliable in detecting residual DXA anticoagulant effects in the presence of andexanet alpha. The EHRA recommendation does not apply to the situation of the reversal of factor Xa inhibitors prior to neuraxial block or catheter insertion or removal for which no data are available as yet. Furthermore, it remains unclear whether the remaining plasma levels after andexanet alpha reversal may influence the risk of spinal epidural haematoma formation.

Although there are results from observational studies of the successful use of PCC in patients with life-threatening haemorrhages due to direct factor Xa-inhibitors

(mainly intracranial bleeds),[160,161] there are no data that support its use in patients planned for neuraxial block or neuraxial catheter placement or removal while on treatment with factor Xa inhibitors.

**5.2 Is there a difference in time intervals between patients with and without reversal of LMWH, UFH, fondaparinux?**

***Recommendation 33***

From a pharmacological point of view, neuraxial or deep nerve procedures may be performed in emergency situations once the anticoagulant activity of UFH is fully reversed by protamine (sulfate or chloride) and protamine overdose is avoided. 2C

No recommendation can be proposed in emergency situations for LMWH reversal and for fondaparinux reversal.

**Evidence Summary:** Apart from UFH which is effectively neutralised by equimolar doses of protamine (either sulphate or chloride) within minutes,[162,163] current national guidelines (including the last ESAIC guideline) neither mention nor recommend the reversal of anticoagulation with LMWH or fondaparinux (FPX) to facilitate neuraxial block, catheter insertion or removal.[38,97,150,164,165] In contrast, the Scandinavian Practice Advisory[149] lists protamine as a reversal agent for LMWH in a Table, but does not mention it in a specific recommendation. Of note, protamine per se has anticoagulant properties.

To date, there are no prospective randomised trials investigating the effect of reversal agents for heparins and fondaparinux in the setting of planned neuraxial anaesthetic procedures. From a pharmacological point of view, the effect of protamine in reversing anticoagulation induced by LMWH is incomplete, as it is mainly the anti-thrombin (factor IIa) effect of LMWH that is neutralised, while the anti-factor Xa effect remains unchanged.[166] The remaining anticoagulant effect of factor Xa inhibition of the LMWHs is unclear and therefore recommendations to use protamine as a reversal agent for LMWH anticoagulation in the context of neuraxial anaesthesia are not possible.

Recently, an uncontrolled study of andexanet alpha, a synthetic molecule with a high structural similarity to the activated clotting factor X, investigated the reversal effect in patients with bleeding due to the factor Xa inhibitors apixaban, rivaroxaban and enoxaparin.[158] However, in patients with enoxaparin-induced bleeding ($n = 20$), the antifactor Xa activity was also reduced by 75% with a remaining activity of 0.15 IU $ml^{-1}$. Although this study did not include patients with a spinal or epidural haematoma due to enoxaparin medication, these results do provide some clinical proof of concept that andexanet alpha inhibits the antifactor Xa effect of enoxaparin. Uncertainty remains however whether even low levels of antifactor Xa activity are well tolerated in the setting of neuraxial anaesthetic procedures and, also, what dose of andexanet alpha may be regarded as effective.

Ciraparantag, which may have the potential to inhibit the anticoagulant effect of LMWH, is currently under clinical development,[167] but has not yet gained market approval.

The synthetic pentasaccharide fondaparinux has been approved for years for thromboprophylaxis as well as treatment of deep vein thrombosis and pulmonary embolism[168] but as yet no direct reversal agent is available,[169] nor have controlled clinical data been published on how the anticoagulant effect of fondaparinux can be effectively reversed in the setting of neuraxial anaesthetic procedures. Andexanet alpha as a specific reversal agent of factor Xa inhibitors, and ciraparantag as a more unspecific pro-haemostatic agent may have the pharmacological potential to reverse the effect of fondaparinux, but no controlled clinical data have been published in the context of neuraxial anaesthetic procedures and therefore uncertainties regarding their clinical applicability in this scenario remain.

**5.3 Is there a difference in time intervals between patients with and without reversal of aspirin or $P2Y_{12}$ inhibitors?**

***Recommendation 34***

In peri-operative patients who are on low-dose aspirin neuraxial or deep nerve procedures are not contraindicated; reversal cannot affect time intervals. 1C

Emergency situations (e.g. acute coronary syndrome) usually require loading doses of antiplatelet agents. Consequently, neuraxial or deep nerve procedures should not be performed. 1C

No recommendation can be made for $P2Y_{12}$ inhibitor reversal.

**Evidence summary.** Aspirin is recommended for secondary prevention of cardiovascular disease and must not be discontinued during the peri-operative period of most procedures without critical assessment of the individual bleeding and ischaemic risk[170] given that discontinuation of aspirin may increase the risk of ischaemic complications such as stent thrombosis, myocardial infarction or stroke.[171] Weighing the relatively small risk of bleeding after a neuraxial technique with ongoing low-dose aspirin treatment against the ischaemic risk of aspirin discontinuation, most guidelines recommend maintaining low-dose aspirin throughout the peri-operative phase in patients undergoing neuraxial anaesthetic procedures.[38,97,150]

In patients undergoing moderate and high-risk neuraxial pain interventions, it is recommended that aspirin be discontinued after individual assessment and risk stratification.[164]

The Nordic Practice Advisory for Central Neuraxial Blocks or Spinal Pain Procedures recommends to pause the aspirin on the day of the neuraxial anaesthetic procedure only.[149] With the clear and unequivocal recommendations of several guidelines and long years of clinical experience of continuing low-dose aspirin in most elective surgical settings, there is no need for a reversal agent. Most guidelines do not mention or recommend the reversal of aspirin before neuraxial procedures.[38,97,149,150] Although there is no specific agent that reverses aspirin-induced inhibition of platelet cyclooxygenase, desmopressin is mentioned in one recommendation as a reversal agent for aspirin. No further explanation however is provided in the manuscript.[149] The beneficial effect of desmopressin was mainly shown in patients on prophylactic aspirin undergoing cardiac surgery, in whom the intra-operative blood loss was significantly reduced.[172] A recent systematic review confirmed the reduction in blood loss and transfusion requirements[173] with an underlying low to moderate quality of evidence. However, the evidence for the interaction of desmopressin and aspirin-induced platelet inhibition remains unclear. Platelet transfusion corrects the effects of aspirin.[174]

The group of $P2Y_{12}$ inhibitors mainly comprise clopidogrel and the newer substances prasugrel and ticagrelor, which either irreversibly (clopidogrel and prasugrel) or reversibly block adenosine diphosphate from binding to the $P2Y_{12}$ receptor on the platelet surface.[137,175] For the combination of each $P2Y_{12}$ inhibitor with aspirin, a beneficial effect on ischaemic outcomes in patients with acute coronary syndromes has been shown compared with aspirin alone.[176–178]

Apart from secondary prevention with low-dose aspirin alone, all national guidelines advise against neuraxial techniques in patients receiving combined antiplatelet therapies (e.g. aspirin as well as $P2Y_{12}$ inhibitors) unless the $P2Y_{12}$ inhibitor is interrupted according to guideline recommendations.[38,97,149,150,164]

Platelet transfusion has been proposed to correct the effects of $P2Y_{12}$ inhibitors.[179–182]

So far, no direct reversal agent has been approved for the $P2Y_{12}$ inhibitors, although recently a specific antibody was successfully found in a phase 1 trial to completely reverse the platelet inhibiting effect of ticagrelor.[183] Further clinical evaluation of this drug is needed.

National guidelines do not mention the reversal of the effect of $P2Y_{12}$ inhibitors, but instead recommend an interruption of 3 to 10 days[38,97,149,150,164] depending on the duration of the drug-specific platelet inhibition and the production of a sufficient number of active platelets by the bone marrow.

**Clinical question 6**

**6.1 Is there a difference in time intervals between patients with and without ultrasound guidance?**

***Recommendation 35***

Ultrasound reduces vascular puncture and therefore its use is recommended in patients on anticoagulants and antiplatelet drugs. 1C

Ultrasound guidance has no influence on the time interval from last administration of antithrombotic drugs (VKA, DOAC, LMWH, UFH, fondaparinux and $P2Y_{12}$ inhibitors) prior to superficial or deep PNBs, or to timing of the subsequent drug dose after the block. 1C

In peri-operative patients who are on low-dose aspirin (<200 mg), superficial or deep PNBs are not contraindicated, and therefore, ultrasound guidance does not affect time intervals. 1C

**Evidence Summary:** There is good evidence that using ultrasound for PNBs reduces vascular puncture and local anaesthetic systemic toxicity.[184] There is no evidence, however, that ultrasound reduces the incidence of haematoma or postoperative neurological symptoms in any group of patients who take anticoagulants.[184] Although ultrasound used by an appropriately trained individual should in theory reduce the incidence of perineural haematomas secondary to vessel puncture, there is no direct evidence that ultrasound improves safety in patients taking anticoagulants.

Surveys, and some national guidelines, suggest ultrasound should be used when a superficial or deep peri-operative nerve block is necessary in a patient taking either antiplatelet or anticoagulant medication.[152,185] This is pragmatic opinion based on indirect evidence about vessel puncture rather than direct evidence of neurological complications in these patients. Nerve damage is so rare that clearly it is difficult to obtain accurate figures for nerve damage in all patients, and so, it would be even more difficult to study in patients on antiplatelet or anticoagulants.

There are a number of observational studies and case series of patients on VKA, and other APA or anticoagulants, who have had both superficial and deep ultrasound-guided nerve blocks. These are summarised in a systematic review that concluded the overall incidence of bleeding was 0.82%, but the nerve localisation technique did not influence this complication rate.[39] In another case series of 498 patients undergoing ultrasound-guided pectoralis and serratus plane nerve blocks (PECS), there were eight haematomas.[186] In five of these eight cases, the patients were on APA or anticoagulants confirming that ultrasound-guided fascial plane blocks are not without risk.

Ultrasound is not used during catheter removal for continuous PNBs, and therefore, this part of the PICO question is not relevant.

There are no large case series or any higher levels of evidence that ultrasound influences the rate of haematoma in the group of patients on DOAC and fondaparinux.

There are only small case series wherein some of the patients have been administered LMWH and have had PNBs. In one series, six out of the 70 patients had an uncomplicated ultrasound-guided lumbar plexus block whilst taking LMWH.[187] The dose of heparin however was unclear. As before, the above recommendation is based on indirect evidence that ultrasound reduces the rate of vascular puncture and therefore may be safer in this group of patients who are at a higher risk.

In a case series of 141 patients all undergoing ultrasound-guided continuous catheter thoracic paravertebral block, 15 of the patients had an aPTT of between 40 and 80 s.[188] Despite paravertebral block being regarded as a higher risk block, and all patients receiving intra-operative unfractionated heparin, most within 100 to 200 min, there were no cases of haematoma in this small group. There is little other evidence about the use of ultrasound for PNB in patients receiving unfractionated heparin. As before, the above recommendation is, therefore, based on indirect evidence that ultrasound reduces the rate of vascular puncture and so may be safer in this group of patients who are at a higher risk.

Guidance has changed over recent years whereby it is now accepted that superficial plexus blocks can be achieved safely in patients on anticoagulants and antiplatelet agents, due to site compressibility, and lesser vascularity and consequences of bleeding.[38] There is no direct evidence, however, that ultrasound reduces complications compared with other nerve localisation techniques in patients on $P2Y_{12}$ inhibitors and so, as before, the above recommendation is therefore based on indirect evidence that ultrasound reduces the rate of vascular puncture and so may be safer in this group of patients who are at higher risk.

**Clinical question 7**

**7.1 Is there a difference in time intervals between needle and catheter insertion *versus* catheter removal?**

> ***Recommendation 36***
> Similar time intervals should be respected for insertion of a needle with or without a catheter and for removal of a catheter at neuraxial, deep or superficial nerve block sites. 1C

**Evidence Summary:** The management of indwelling neuraxial and peripheral nerve catheters in the perioperative period can be divided into four relevant scenarios. After a last dose, the time interval before both catheter insertion and for catheter removal; then, the time interval for restarting anticoagulation after catheter removal, and, lastly, the time period for catheter removal after an unanticipated administration of anticoagulant with an indwelling catheter (Table 3).

Regarding the time interval for catheter insertion, current evidence suggests that the risks of bleeding and haematoma formation is similar for catheter insertion as for single injection techniques, and thus, the same recommended time intervals should be respected for neuraxial and deep PNBs. Clinicians appreciate that catheter needles are generally of a larger gauge and that there is direct relationship between potential tissue damage and needle size. A smaller single shot needle may pose less of a risk for haematoma formation compared with a larger needle for catheters. This may be a factor to consider when weighing up the risk–benefit ratio for an individual patient for superficial PNB sites. Unfortunately, there is insufficient evidence to quantify this risk, because of a multitude of variables, including clinician's expertise, regional anaesthesia technique used, use of ultrasound and the complexity of individual patient characteristics that may result in haematoma formation. It is also difficult to predict when bleeding may occur as demonstrated by a case series of continuous thoracic paravertebral catheters (considered a deep block) in 141 cardiac surgery patients who all received intra-operative unfractionated heparin, with no reports of haematoma formation.[188]

Cases and registry data demonstrate that haematoma formation can occur after any catheter insertion or removal. The risks are similar and therefore recommended time intervals are also similar.

Regarding the time interval for catheter removal after the last dose, catheter removal may seem like an innocuous intervention, but cases and registry data confirm that it poses a significant intervention and thus a bleeding risk if not managed appropriately. Catheter removal should therefore be considered as an intervention and consequently the appropriate time intervals should apply for each anticoagulant (Table 3).

Nevertheless, perineural lower limb nerve catheters were safely removed from 1029 patients receiving prophylactic rivaroxaban without complications.[57]

A vitamin K antagonist, warfarin at therapeutic level, was involved in one patient who developed local bleeding after lumbar plexus catheter removal without haematoma formation or neurological compromise.[38]

No bleeding or neurovascular complications were reported in a case series by Horlocker with the removal of peripheral nerve catheters in patients receiving prophylactic or therapeutic doses of DOACs.[38]

Starting prophylactic rivaroxaban after femoral, sciatic and lumbar catheter removal did however result in local

haematoma formation at the puncture sites and some minor bleeding as reported by Joubert *et al.*[39]

**Clinical question 8**

**8.1 Is there a difference in time intervals between superficial and deep peripheral nerve blocks?**

***Recommendation 37***

Superficial nerve blocks may be performed in the presence of anticoagulant or antiplatelet drugs. 1C
Deep nerve blocks should be performed according to the recommendations for neuraxial procedures (R3, R6, R9, R12, R16, R18). 1C

***Recommendation 38***

Consequences of local bleeding caused by blocks should be considered and monitored.1C
The lowest bleeding risk technique should be chosen and performed by an operator with experience in ultrasound guidance. 1C

**Evidence Summary:** The exact frequency and severity of haemorrhagic complications associated with PNBs remain poorly defined compared to neuraxial blockade. Although peripheral haematomas can compress nerves and cause nerve palsy, severe neurological complications due to neural ischaemia are scarce.[189] Still, reports of morbidity and mortality secondary to severe haemorrhagic complications do exist and can occur in patients with coagulopathies, or receiving thromboprophylaxis/anticoagulation who have not had a regional anaesthesia procedure; patients undergoing PNB with normal coagulation status; and patients undergoing PNB on thromboprophylaxis/anticoagulation.[189]

In a systematic review,[39] the estimated bleeding complication incidence related to PNB was 0.67% (95% CI: 0.51 to 0.83), rising to 0.82% (95% CI: 0.64 to 1.0) if case reports were accounted for. Examining 32 severe haemorrhagic complications, with one death, associated with PNB, 18 were associated with coagulation abnormalities and 14 with normal haemostasis.[38] None used ultrasound guidance (USG). Vascular trauma occurs in 11% of cases of neurostimulation-guided infraclavicular block.[190] Although USG can reduce the rate of vascular injection almost eight-fold, operator experience, probe choice and needle-probe alignment are also important, whilst it is recognised ultrasound is more challenging in deeper nerve blocks.[127] Indeed in children, there are two cases of delayed presentation haematomas after USG quadratus lumborum block demonstrating that USG is not a panacea.[92] The most significant haemorrhagic complications are related to deep, noncompressible site blocks such as lumbar sympathetic, lumbar plexus and paravertebral blocks. Although a very low incidence of block-related haematoma in the absence of anticoagulation has been described in a large series of patients (0.01%; 95% CI 0.00 to 0.05),[191] the incidence in patients on antithrombotic therapy is unknown. In a retrospective analysis of 6935 blocks, continuous or single PNB performed prior to the initiation of aspirin thromboprophylaxis [325 mg twice daily (b.i.d.)] and catheter removal under LMWH, warfarin, and aspirin thromboprophylaxis were considered safe.[192] The risk of minor bleeding was calculated as 0.7% (95% CI 0.2 to 4.1) in a study wherein no haematoma was associated with paravertebral thoracic blocks, even though more than 90% of catheter procedures were performed in the presence of a bleeding risk.[193] When examining continuous or single shot PNB in hip or knee arthroplasty patients receiving prophylactic rivaroxaban, there was no increased risk of major bleeding after one or two doses of rivaroxaban administered postoperatively. Although 80% of minor haemorrhages occurred at the puncture site prior to the administration of thromboprophylaxis in superficial continuous blocks (femoral), no major haemorrhages were observed in deep continuous blocks (lumbar and sciatic). Minor hemorrhage risk was estimated to be 1.3%, with 0.2% attributed to the PNB.[194] The association of femoral and sciatic blocks has been advocated as a well tolerated alternative to neuraxial blocks in anticoagulated patients for lower limb anaesthesia.[195,196] Continuous peripheral catheters were also considered well tolerated in combat casualties prescribed LMWH.[197] Fascial plane blocks can be deep and/or in the vicinity of blood vessels but may still be a safer alternative to neuraxial blocks. Case series of single shot or continuous fascial plane blocks[198,199] in patients with coagulation abnormalities did not report haemorrhagic sequelae. Conversely, in a series of 498 consecutive cases of USG PECS block, eight patients presented with haematoma around the injection site. Five of these patients were under the effect of haemostasis inhibitors.[186]

Generating a definitive, stratified list of the bleeding risk of different blocks is difficult.[200] Risk is likely to be related to proximity to blood vessels, block depth (which influences needle visibility), if bleeding or haematoma is easy or not to assess, site compressibility and how easy or not an intervention may be applied to prevent or treat bleeding. In addition, other factors must be considered. Patient factors[201] such as body habitus[200]; peri-operative anticoagulation status (therapeutic versus prophylactic anticoagulation plan, acquired anticoagulation disorders); type and size of the needle used; technical difficulties, multiple attempts, needle passes and bloody tap;[202] use of catheters and type of nerve location technique (USG *versus* 'blind' techniques), and operator experience.[36,200,202] The HAS-BLED score may be a useful tool to predict major bleeding in anticoagulated patients.[165]

Regardless of the anaesthetic technique, it has been proposed to continue haemostasis inhibitors for many ophthalmic procedures.[203] Most cataract procedures are

performed with topical anaesthesia, where it is generally agreed that anticoagulants should be maintained.[204,205] Utilising a peribulbar or retrobulbar block in such circumstances is more controversial as a retrobulbar haematoma, albeit rare, is an ocular emergency with devasting consequences given the risk of retinal ischaemia and blindness. In two prospective studies, each involving 1000 patients, continuing antiplatelet agents[206] was not associated with a significant increase in the bleeding risk when peribulbar anaesthesia was performed. However, in another retrospective study including 206 patients (30% of whom were taking anticoagulants), whilst the overall incidence of haemorrhagic complications did not differ the more severe complications occurred in the antiplatelet (clopidogrel) group.[207] In a large series of nearly 160000 patients, three cases of retrobulbar haematoma occurred under dual antiaggregation and the other one under warfarin.[208] The authors recommended against performing retrobulbar blocks in patients on dual antiplatelet treatment. In a systematic review however, the very low incidence of severe haemorrhagic complications meant that the data were not powerful enough to provide a reliable evaluation of the true effects of antithrombotics.[209]

**Clinical question 9**

**9.1 Is there a difference in time intervals between patients with and without blood in the neuraxial needle or catheter?**

***Recommendation 39***

Manifestation of vessel puncture with a bloody tap may increase the time interval to the next drug dose, based on an interdisciplinary clinical assessment of the patient's thrombotic risk, the presence of peri-operative coagulopathies, the adequacy of postoperative haemostasis and pharmacological profile of the antithrombotic. 2C

**Evidence Summary:** A bloody tap (free backflow of blood, blood tinted cerebrospinal fluid) is a risk factor for neuraxial haematoma formation. This was demonstrated in a number of case series of spinal haematoma after a neuraxial procedure, wherein a bloody tap was reported in 10 to 40% of cases.[103,210–212] The ACCP recommends that thromboprophylaxis should be delayed if a haemorrhagic aspirate ('bloody tap') is encountered during the initial spinal needle placement.[213] In its 2010 guideline, the European Society of Anaesthesiology (ESA) recommended that low-dose anticoagulation (5000 IU heparin i.v.) should be avoided for 1 to 2 h.[97] This recommendation was also supported by the DGAI (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin).[150] Full intra-operative heparinisation should be avoided for 6 to 12 h, with the cardiac operation being postponed to the next day, if necessary.[97] Alternatively, epidural catheter placement could be carried out the evening before surgery to avoid any delays. In contrast, American Society of Regional Anesthesia (ASRA) does not recommend mandatory cancellation of a cardiac surgical intervention after a bloody tap, as there are no data to support such a strategy, but rather direct communication with the surgeon and a patient-specific risk-benefit decision in each case.[38]

**Clinical question 10**

**10.1 Descriptive information on spinal or epidural haematoma after neuraxial block or catheter procedures**

***Recommendation 40***

For patients receiving any anticoagulant or antiplatelet drug in the peri-operative period and undergoing a neuraxial or deep block technique, we recommend postinterventional vigilance by the multidisciplinary healthcare team for signs and symptoms related to any new or progressive neurological defect (e.g. new or increasing back pain, numbness or weakness of the legs, bowel or bladder dysfunction, duration or extension of the motor or sensory block that cannot be explained by the pharmacodynamic properties of the local anaesthetic used). 1C

Patients should be informed pre and postoperatively to report such symptoms as early as possible (especially in ambulatory surgery). 2C

Regular patient assessments by trained personnel should be performed for a minimum of 24 h after intervention and longer in high-risk patients. 2C

A neurological deficit that may indicate a spinal or epidural haematoma should prompt a specialist neurological examination, if available, and/or immediate imaging (preferably magnetic resonance imaging as the gold standard) for the diagnosis of a spinal or epidural haematoma. 1C

If indicated, surgical decompression should be performed within 6 h to optimise neurological recovery. 2C

**Evidence Summary:** Spinal or epidural haematoma (SEH) is an uncommon but devastating complication of neuraxial puncture and it may be defined as bleeding within the spinal neuraxis.[38,214] Two categories of SEH exist: traumatic and nontraumatic (spontaneous) SEH. As this ESAIC Guideline is related to the performance of a neuraxial technique, all the recommendations are made in the context of preventing a traumatic SEH.

Most SEHs occur in the epidural space because the vascular plexus is more prominent here. In the majority of cases however, the reports do not distinguish if bleeding is in the epidural or subarachnoid space. This difference is not clinically important however because bleeding in each area results in similar signs and symptoms, diagnostic steps and treatment. The source of the

bleeding can be from either a damaged artery or a damaged vein.

## Clinical signs and symptoms

When the SEH compresses the spinal cord, common typical early signs or symptoms include new or increased back pain, progressive leg weakness or paraesthesia, bladder or bowel disturbances and sensory loss unrelated to the block.[98,135,149,215] The symptomatology is similar in obstetric patients.[76]

Atypical presentations with unilateral pain and isolated sensory or motor blocks have been also reported.[216–219]

The onset of symptoms has been described any time from a few hours to several days after the neuraxial puncture (spinal or epidural) or the catheter removal. In the latter scenario, most patients have begun to receive an anticoagulant drug at the recommended time interval.[220,221]

In patients receiving continuous local anaesthetic infusions, unexpected progressive motor block should increase the level of suspicion, avoiding attributing the increasing motor and sensory blockade to the action of the local anaesthetic agent. In order to detect any new or progressive neurologic symptom, these patients should be examined at least b.i.d.[220]

Where bleeding is minimal, the small volume of blood may be insufficient to compress the spinal cord and thus the haematoma could be asymptomatic. It is possible therefore that the true incidence of SEH could be higher.[77]

## Diagnosis

Repeated evaluation of neurological status is crucial to diagnose a SEH early, and all patients should be carefully monitored for signs of a developing SEH, both after neuraxial puncture and after removal of the neuraxial catheter.[222]

Close neurological monitoring for signs of SEH after a neuraxial puncture is recommended.[223] Although there are no strong recommendations regarding the duration of neurological monitoring, it should continue at least for 24 h from the puncture or the removal of the neuraxial catheter,[224] considering the latter as critical as catheter insertion.[97] In all patients receiving anticoagulants or antiplatelet agents after the performance of a neuraxial technique, we suggest extending this monitoring period until after having received two or three doses.

There is general agreement that when the clinical symptoms lead to suspect a haematoma, magnetic resonance imaging must be performed as soon as possible to confirm the diagnosis.[76,220]

## Conclusion

Specific time intervals related to the adminstration of antithrombotic drugs both prior to and after neuraxial procedures or high bleeding risk (deep) PNBs should be observed. The time intervals vary according to the type and dose of anticoagulant drugs, renal function, and whether a traumatic puncture has occurred. Drug assays may be used to guide individual time intervals whilst specific reversal for vitamin K antagonists and dabigatran may also influence time intervals. Ultrasound guidance, drug combinations and bleeding risk scores do not modify time intervals. In low risk of bleeding PNBs (superficial, compressible), the time intervals generally do not apply.

The safety of patients undergoing regional anaesthesia techniques requires consideration of haemostatic competence both before and after nerve blockade and catheter removal. General considerations include patient-specific bleeding risks such as inherited bleeding disorders, perioperative acquired bleeding disorders, a history of significant bleeding, renal failure, hepatic failure, extreme body weight, advanced age, female sex, malignancy and concomitant use of medications that may influence haemostasis or anticoagulant medications (e.g. thrombolytic drugs, nonsteroidal anti-inflammatory drugs, steroids, diuretics, verapamil, diltiazem, nicardipine, amiodarone and so on). An individual risk–benefit analysis must always be made, ideally in conjunction with the patient, before any regional anaesthesia procedure. Where the bleeding risk is high, alternative techniques should be considered (general anaesthesia or low bleeding risk regional anaesthesia techniques if possible). Where the risk of thromboembolism or ischaemia is high, it may be preferable to continue antithrombotic drugs perioperatively without withdrawal.

Healthcare teams managing patients undergoing regional anaesthesia techniques must also be aware of any possible haematoma and be competent in detecting and managing these. Postprocedure assessment should be mandatory in all patients, particularly those taking APA and anticoagulant drugs. Persistent pain at the block site, a drop in haemoglobin level, morphological skin changes, cardiovascular instability and any neurologic deficits (prolonged or new motor/sensory block in a regressing block without recent bolus or continuous infusion of local anaesthetic) should raise suspicion of a haemorrhagic complication associated with the regional technique and should immediately trigger diagnostic measures and rapid treatment.

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