Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (fifth edition)

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ABSTRACT

Hemorrhagic complications associated with regional anesthesia are extremely rare. The fifth edition of the American Society of Regional Anesthesia and Pain Medicine's Evidence-Based Guidelines on regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy reviews the published evidence since 2018 and provides guidance to help avoid this potentially catastrophic complication.

The fifth edition of the American Society of Regional Anesthesia and Pain Medicine's Evidence-Based Guidelines on regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy uses similar methodology as previous editions but is reorganized and significantly condensed. Therefore, the clinicians are encouraged to review the earlier texts for more detailed descriptions of methods, clinical trials, case series and pharmacology. It is impossible to perform large, randomized controlled trials evaluating a complication this rare; therefore, where the evidence is limited, the authors continue to maintain an 'antihemorrhagic' approach focused on patient safety and have proposed conservative times for the interruption of therapy prior to neural blockade. In previous versions, the anticoagulant doses were described as prophylactic and therapeutic. In this version, we will be using 'low dose' and 'high dose,' which will allow us to be consistent with other published guidelines and more accurately describe the dose in the setting of specific patient characteristics and indications. For example, the same 'high' dose may be used in one patient as a treatment for deep venous thrombosis (DVT) and in another patient as prophylaxis for recurrent DVT. Due to the increasing ability to obtain drug-specific assays, we have included suggestions for when ordering these tests may be helpful and guide practice. Like previous editions, at the end of each recommendation the authors have clearly noted how the recommendation has changed from previous editions.

Hemorrhagic complications may occur after any neuraxial (spinal or epidural) or peripheral/plexus regional anesthetic technique. However, when the bleeding occurs within fixed, non-compressible, and/or concealed sites, such as the spinal canal or psoas compartment, the result may be catastrophic.[1] The development and evolving status of standards for the prevention of perioperative venous thromboembolism (VTE), as well as the introduction of increasingly more potent antithrombotic medications, resulted in concerns regarding the heightened risk of neuraxial bleeding after neuraxial and deep plexus or deep peripheral blocks. In response to these ongoing patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA PM) has published four previous sets of evidence-based recommendations for the management of regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. The 1998 and 2003 editions focused on *neuraxial* blocks and anticoagulants in *surgical* patients,[2–7] while the 2010 publication[8] also addressed, for the first time, the risk of significant bleeding in patients undergoing plexus and peripheral techniques. The fourth edition, published in 2018,[9] included a comprehensive review of the management of thromboprophylaxis in the parturient and also acknowledged the need for separate recommendations for patients undergoing interventional pain procedures while receiving antithrombotic therapy. Portions of the material presented here in the fifth edition were included in the 1998, 2003, 2010, and 2018 ASRA PM Consensus Documents.[2–9] The fifth edition uses similar methods but is significantly condensed from previous versions, and therefore the clinician is encouraged to review the earlier texts for more detailed descriptions of methods, clinical trials, case series and pharmacology.

In previous versions of the guidelines, the anticoagulant doses were described as prophylactic and therapeutic. In this version, we will be using 'low dose' and 'high dose,' which will allow us to be consistent with other published guidelines and more accurately describe the dose in the setting of specific patient characteristics and indications. For example, an identical 'high' dose of a direct oral anticoagulant (DOAC) is therapeutic in one patient and prophylactic in another patient depending on the individual patient's characteristics and indications for the DOAC (table 1).

Deviation from suggestions or recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. The recommendations are designed to encourage safe and quality patient care but cannot guarantee a specific outcome. They are also subject to timely revision as justified by evolution of information

Table 1 Direct oral anticoagulants

	Apixaban[86]	Edoxaban[87]	Rivaroxaban[89]	Dabigatran[90]
Low dose				
Indications and dosing	Reduction in the risk of recurrent DVT and PE following initial therapy: 2.5 mg two times per day Prophylaxis of DVT following THA or TKA: 2.5 mg two times per day	N/A	Reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE In patients with a CrCl >15 mL/min: 10 mg once per day In patients with a CrCl <15 mL/min: avoid use Prophylaxis of DVT following THA or TKA: In patients with a CrCl >15 mL/min: 10 mg once per day In patients with a CrCl <15 mL/min: avoid use Prophylaxis of VTE in ill medical patients at risk for thromboembolic complications, not at high risk of bleeding In patients with a CrCl >15 mL/min: 10 mg once per day In patients with a CrCl <15 mL/min: avoid use Reduction of risk of major cardiovascular events (CV death, MI, and stroke in CAD) No dose adjustment needed based on CrCl 2.5 mg two times per day plus aspirin (75–100 mg once per day) Reduction of risk of major thrombotic vascular events in PAD, including patients after recent lower extremity Revascularization due to symptomatic PAD No dose adjustment needed based on CrCl 2.5 mg two times per day plus aspirin (75–100 mg once per day)	Prophylaxis of DVT and PE following THA: In patients with CrCl >30 mL/min: 110 mg once per day first day, then 220 mg once per day In patients with CrCl <50 mL/min and concomitant use of P-gp inhibitors (ie, dronedarone or systemic ketoconazole): avoid coadministration
High dose				
Indications and dosing	Reduction of risk of stroke and systemic embolism in NVAF: 5 mg two times per day In patients with at least two of the following characteristics: age ≥80 years, body weight <60 kg, or serum creatinine ≥1.5 mg/dL: 2.5 mg two times per day Treatment of DVT and PE: 10 mg two times per day for 7 days, followed by 5 mg two times per day In patients receiving 5 mg or 10 mg two times per day and concomitant use of P-gp and strong CYP3A4 inhibitors (ie, ketoconazole, itraconazole, ritonavir): reduce the dose by 50%	Reduction of risk of stroke and systemic embolism in NVAF: In patients with CrCl >50 to ≤95 mL/min: 60 mg once per day Do not use in patients with CrCl >95 mL/min In patients with CrCl 15–50 mL/min: 30 mg once per day Treatment of DVT and PE: 60 mg once per day In patients with one or more of the following clinical factors: CrCl 15–50 mL/min or body weight ≤60 kg, or the concomitant use of P-gp inhibitors: 30 mg once per day	Reduction of risk of stroke and systemic embolism in NVAF: In patients with CrCl >50 mL/min: 20 mg once per day In patients with CrCl 15–50 mL/min: 15 mg once per day Treatment of DVT, PE, and reduction in the risk of recurrent DVT and of PE: In patients with a CrCl >15 mL/min: 15 mg two times per day for the first 21 days of the initial treatment 20 mg once per day for the remaining treatment	Reduction of risk of stroke and systemic embolism in NVAF in adult patients: In patients with CrCl >30 mL/min: 150 mg two times per day In patients with CrCl 30–50 mL/min and concomitant use of P-gp inhibitors (ie, dronedarone or systemic ketoconazole): 75 mg two times per day In patients with CrCl 15–30 ml min^{-1}: 75 mg two times per day In patients with CrCl <30 mL/min and concomitant use of P-gp inhibitors (ie, dronedarone or systemic ketoconazole): avoid coadministration Treatment of DVT and PE in adult patients: In patients with CrCl >30 mL/min: 150 mg two times per day Reduction in the risk of recurrent DVT and PE in adult patients: In patients with CrCl >30 mL/min: 150 mg two times per day

CAD, coronary artery disease; CrCl, creatinine clearance; CV, cardiovascular; CYP3A4, cytochrome P450 3A4; DVT, deep venous thrombosis; MI, myocardial infarction; N/A, not available; NVAF, non-valvular atrial fibrillation; PAD, peripheral artery disease; PE, pulmonary embolism; P-gp, P-glycoprotein; THA, total hip arthroplasty; TIA, transient ischemic attack; VTE, venous thromboembolism.

and practice. These recommendations are intended for use by anesthesiologists and other physicians and healthcare providers performing neuraxial and deep plexus/peripheral regional anesthetic/analgesic blockade. However, these recommendations may also serve as a resource for other healthcare providers involved in the management of patients who have undergone or will undergo similar procedures (eg, myelography, lumbar puncture).

METHODS AND DEVELOPMENT PROCESS

Once again, ASRA PM has convened a panel with international (AP and EV) and multidisciplinary representation, including experts in thrombophilia (RM) and obstetric anesthesia (LL). In order to avoid conflicting recommendations, we have compared the current ASRA PM recommendations with those of the Society for Obstetric Anesthesia and Perinatology (SOAP), National Partnership for Maternal Safety,[10] the European Society of Anaesthesiology and Intensive Care (ESAIC), and the European Society of Regional Anaesthesia (ESRA).[11] Based on their expertize, authors were assigned to review and update certain sections of these guidelines. The authors performed a literature search using MEDLINE (OvidSP), EMBASE (OvidSP), and Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and specific keywords for each topic and updated the 2018 recommendations if there was new evidence. There were no limitations on language or types of articles considered, given the rarity of neuraxial hematoma and the primary keywords used were determined by the authors based on their assigned topic or medication. The updated recommendations are clearly denoted

within the document as 'new recommendations.' All authors met several times to review the recommendations, discuss concerns, and ultimately reached a consensus based on the limited existing evidence and published guidelines.

In the past, for each of the antithrombotic agents, ASRA PM has recommended that clinicians follow the Food and Drug Administration (FDA)-approved dosing and American College of Chest Physician (ACCP) management guidelines. However, over time, ACCP recommendations for the perioperative management of antithrombotic therapy have become increasingly more 'antithrombotic'—with shorter time intervals between discontinuation and procedures and earlier reinstitution of antithrombotic and antiplatelet therapy. In some cases, the recommended time interval between the last dose of drug and surgery is shorter than the FDA-approved labeling. For example, the ACCP recommends that ticagrelor be discontinued 3–5 days prior to non-cardiac surgery.[12] However, labeling states, 'when possible, interrupt therapy for 5 days prior to surgery that has a major risk of bleeding.' Conversely, ASRA PM recommendations remain more 'antihemorrhagic,' and more pharmacologically based, with the intent to have near-complete resolution of the antithrombotic effect at the time of regional blockade for high-risk (neuraxial and deep plexus/peripheral) procedures. As a result, there are several instances where the ACCP and ASRA PM recommendations differ (eg, antiplatelet medications and apixaban). These will be discussed in detail within the respective sections. It is important to recognize that the intent of these guidelines is to prevent hemorrhagic complications and are therefore conservative compared with guidelines developed to prevent thrombosis.

STRENGTH AND GRADE OF RECOMMENDATIONS

The suggestions and recommendations presented are based on a thorough evaluation of the available information for this very rare outcome. In order to clearly delineate the recommendation changes in this edition, we used the same evidence classification that had been used in previous editions, which does not precisely follow the new Grading of Recommendations, Assessment, Development, and Evaluations recommendations. This will be updated in the next edition. The level of evidence classification combines an objective description of the types of studies and/or expert consensus supporting the recommendation. Unfortunately, with a complication as rare as neuraxial hematoma, randomized clinical trials (RCTs) and meta-analyses, the highest (I) level of evidence, are not available. Numerous observational and epidemiological series level of evidence (II) have documented the conditions for safe performance of neuraxial anesthesia and analgesia in the anticoagulated patient. However, high-quality evidence may come from well-done observational series yielding very large risk reduction and depending on the risk reduction, recommendations from these sources may be categorized as level of evidence I or II. Recommendations derived from case reports or expert opinion is based on a level of evidence III. Often, recommendations involving the anesthetic management of new antithrombotic agents (where data involving safety and/or risk are sparse) are based on the pharmacology of hemostasis-altering drugs, risk of surgical bleeding, and expert opinion—level of evidence III.

The strength of recommendation also indicates the strength of the guideline and the degree of consensus agreement. For example, grade A represents general agreement in the efficacy, grade B notes conflicting evidence or opinion on the usefulness, and grade C suggests that the procedure may not be useful (possibly harmful). In the case of regional anesthesia and anticoagulation, a grade A recommendation would allow safe performance in patients who benefit from the technique, while grade C may represent performance of the technique in a patient at unacceptably high risk for bleeding (eg, epidural analgesia in the patient receiving twice-daily low molecular weight heparin (LMWH)) or withholding the technique from a patient who would likely benefit from its performance (eg, thoracic epidural analgesia following thoracotomy with thromboprophylaxis using twice-daily low-dose unfractionated heparin (UFH)). The phrase 'we recommend' is used for strong recommendations (grades IA, IB, and IC) and 'we suggest' for weaker recommendations (grades IIA, IIB, and IIC). In cases where the evidence is scant (such as with the new oral anticoagulants), the authors maintained an 'antihemorrhagic' approach focused on patient safety and proposed conservative (ie, longer) times for interruption of therapy prior to neural blockade. These will likely be revised as additional information regarding blood levels and anticoagulant effect is presented.

Table 2 VTE risk scoring tools: medical patients

Risk factor	Points	
	PADUA score[14]	IMPROVE score[26]
Active cancer	3	2
Prior VTE	3	3
Reduced mobility	3	Limb paresis (2 points)
		Immobility ≥ 7 days (1 point)
Thrombophilia	3	2
Recent trauma/surgery (≤1 month)	2	–
Age ≥70 years	1	1 (age >60 years)
Heart or respiratory failure	1	–
Acute MI or ischemic stroke	1	ICU stay (1 point)
Acute infection/rheumatological disorder	1	–
Obesity (BMI >30)	1	–
Hormonal therapy	1	–
High thrombosis risk	≥4 points	≥4 points

BMI, body mass index; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; MI, myocardial infarction; PADUA, from University of Padua, Padova Italy; VTE, venous thromboembolism.

CURRENT RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

VTE is an important healthcare problem and a significant source of morbidity and mortality. Nearly all hospitalized patients have at least one risk factor for thromboembolism and approximately 40% have three or more risk factors (table 2).[13] Consequently, the majority of hospitalized patients are candidates for thromboprophylaxis.

In 2012, the ACCP published guidelines for VTE prophylaxis for medical, surgical, and orthopedic surgical patients.[14–16] Recent updates published in 2016 and 2021 provide no additional guidance on this topic.[17 18] The agent, dosing regimen, and duration of thromboprophylaxis is based on identification of risk factors, both individual (eg, age, gender, history of thromboembolism) and group-specific (eg, primary reason for hospitalization, surgery, medical illness) (table 3).[13 16] Depending on the risks of thromboembolism and bleeding, thromboprophylaxis may be achieved with intermittent compression devices, with medications, or a combination of both.[15 16] Since an

Table 3 Suggested risk stratification for patient-specific periprocedural thromboembolism*

Risk category	Mechanical heart valve	Atrial fibrillation	VTE
High (>10%/y risk of ATE or >10%/mo risk of VTE)	Mitral valve with major risk factors for stroke† Caged ball or tilting disc mitral valve in mitral/atric position Recent (<3 mo) stroke or TIA	$CHADS_2VASc$ score ≥7 or $CHADS_2$ score of 5 or 6; recent (<3 mo) stroke or TIA; rheumatic valvular heart disease	Recent (< 3 month and especially < 1 month) VTE Severe thrombophilia (deficiency of protein C, protein S, or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation, multiple thrombophilias) Antiphospholipid antibodies Active cancer associated with high VTE risk‡
Moderate (4%–10%/y risk of ATE or 4%–10%/mo risk of VTE)	Mitral valve without major risk factors for stroke Bileaflet AVR with major risk factors for stroke	$CHA2DS_2$ score of 5 or 6 or $CHADS_2$ score of 3 or 4	VTE within past 3–12 mo Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene G20210A mutation) Active cancer or recent history of cancer
Low (<4%/y risk of ATE or <2%/mo risk of VTE)	Bileaflet AVR without major risk factors for stroke†	CHA_2DS_2 Vasc score of 1–4 or $CHADS_2$ score of 0–2 (and no prior stroke or TIA)	VTE >12 mo ago

Adapted from Douketis *et al*[284]
*Empiric risk stratification that is a starting point for assessing perioperative thromboembolism risk; should be combined with clinical judgment that incorporates individual patient-related and surgery/procedure-related factors.
†Includes: AF, prior stroke/TIA during anticoagulant interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, congestive heart failure, age ≥75 y.
‡Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.
AF, atrial fibrillation; ATE, arterial thromboembolism; AVR, aortic valve replacement; $CHADS_2$, congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, prior stroke or TIA; CHA_2DS_2VASc, congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, prior stroke or TIA, vascular disease history, age ≥65 y, female sex; mo, months; TIA, transient ischemic attack; VTE, venous thromboembolism; y, years.

individualized approach to thromboprophylaxis is complex, most recommendations are group-specific, with modifications based on the presence/absence of additional risk factors.

Hospital-acquired VTE is defined as VTE occurring from the time of admission until 3 months following hospital dismissal.[19–21] Hospital-acquired VTE after discharge accounts for nearly half of all thromboembolic events occurring in our communities.[20] A number of societies have adopted and published guideline recommendations for VTE prevention for patients hospitalized with medical or surgical indications.[14–16 21–24] Adoption of thromboprophylaxis has been less than adequate for this otherwise preventable disease.[21]

A logical approach to VTE prophylaxis begins with individualized risk assessment. Several well-validated risk assessment tools are available for individualized patient-specific guidance including both medical and surgical indications. For patient's hospitalized with a medical condition, the PADUA[25] and IMPROVE[26] risk tools provide a well-validated framework for assessing which patients will most benefit from VTE prophylaxis (table 2). Recently, fibrin D-dimer has been added to the IMPROVE tool (so-called IMPROVEDD score), further refining risk assessment.[27] Thereafter, a bleeding risk assessment can be performed using the IMPROVE bleeding tool,[28] which helps to determine which patient should receive pharmacological VTE versus mechanical DVT prophylaxis. Patients at increased risk for thrombosis (PADUA score ≥4) with low bleeding risk (IMPROVE score <7) should be given pharmacological VTE prophylaxis. The minority of patients (<10% of those hospitalized) with high bleeding risk (IMPROVE score ≥7) should receive mechanical prophylaxis alone.[28] In general, combining pharmacological and mechanical DVT prophylaxis among critically ill patient has not been shown to add benefit.[29] Conversely, for trauma patients, combined use of pharmacological and mechanical VTE prophylaxis appears to reduce DVT and symptomatic pulmonary embolism (PE).[30] The agent, dosing, regimen, and duration of thrombophophylaxis is based on identification of risk factors, both individual (eg, age, gender, history of thromboembolism) and group specific (eg, primary reason for hospitalization, surgery, medical illness) (table 3).[13 16]

Similar risk assessment tools are available for the surgical patient population. The Caprini and Rogers tools assign risk based on a number of surgery-specific and other clinical variables.[31 32] The Caprini risk calculator has been validated for a number of specific surgical indications.[33–37] In addition to providing risk categorization from low to very high, this easy to implement tool provides guidance for both type and duration of prophylaxis delivery.

Patients with cancer pose a unique and challenging set of clinical variables, whereas these patients are both at risk of VTE as well as major bleeding.[38] The risk of VTE depends on tumor type, stage, duration, and is treatment specific. Several risk assessment tools have been developed for VTE prophylaxis among ambulatory patients with cancer. The Khorana score is a popular and well-validated example.[39] This score considers cancer type, prechemotherapy hemoglobin, body mass index, leukocyte, and platelet counts to determine the risk of acute VTE over the ensuing 2.5 months. Following the publication of two RCTs of DOACs, guideline recommendations include consideration of outpatient VTE prophylaxis among high-risk patients (Khorana score ≥2).[40–43] For patients with cancer undergoing surgery or hospitalized for medical indications, inpatient VTE prophylaxis is guideline endorsed.

As with previous advisories, ASRA PM recommendations incorporate the medication dosing regimen approved by the FDA.

Administration of thromboprophylaxis

For each of the antithrombotic agents, we suggest that clinicians follow the FDA-approved dosing guidelines (grade IIA)

Remarks: there is no change in this recommendation.

Perioperative anticoagulant management

More than 6 million Americans are managed with chronic anticoagulation therapy for treatment of primary or secondary prevention of thromboembolism in the context of atrial fibrillation, mechanical heart valve prosthesis, or VTE.[44 45] Of these, approximately 20% will undergo an invasive procedure each year, for which decision-making regarding anticoagulant interruption will be required of their healthcare team.[46 47] More than 34 million Americans have an indication for antiplatelet therapy such as aspirin or a thienopyridine for the indications of coronary heart disease, prior stroke, or peripheral artery disease (PAD).[45] Like anticoagulants, perioperative management of antiplatelet agents also require thoughtful decision-making.

Goals of management include a strategy to minimize periprocedural thrombosis, bleeding, mortality, inconvenience, and economic burden. Formal guidelines have been provided by the ACCP in 2012, with a recent update in 2022.[12 48] The periprocedural period has been defined as beginning 1 week prior to the procedure and ending 4 weeks following the procedure. This 5-week interval encompasses the time frame when most thrombotic and hemorrhagic complications relative to this encounter occur.[49] In preparation for the invasive procedure, the oral anticoagulant is often discontinued for several days to allow for adequate hemostasis during the proposed procedure. A strategy of periprocedural 'bridging' leverages the short-acting pharmacology of LMWH to shorten the time of anticoagulant interruption, thereby reducing the risk of periprocedural thromboembolism. Over the nearly two decades since concept inception, much has been learned which has led to a temporized enthusiasm for bridging heparin therapy.[50] While risks of thromboembolism have not always been improved, rates of perioperative bleeding have increased.[51] Balancing the risk of bleeding and clotting during this 5-week interval can be challenging and requires a judicious approach.

INCIDENCE, RISK FACTORS, AND NEUROLOGICAL OUTCOME OF NEURAXIAL HEMATOMA

Neuraxial hematoma, defined as symptomatic bleeding within the spinal neuraxis, is a rare and potentially catastrophic complication of spinal or epidural placement. The actual incidence of neurological dysfunction resulting from hemorrhagic complications associated with central neuraxial blockade is unknown; traditional estimates prior to the implementation of routine perioperative thromboprophylaxis were approximated to be <1 in 150 000 epidural and <1 in 220 000 spinal anesthetics.[3] However, case series and epidemiological surveys suggest that the risk has increased[3 52 53] and may be as high as 1:3000 in certain patient populations, such as elderly women undergoing total knee replacement under epidural anesthesia.[3 52]

It is impossible to conclusively determine risk factors for the development of neuraxial hematoma in patients undergoing spinal or epidural anesthesia solely through a review of case series, which represent only patients with the complication and do not define those who underwent uneventful neuraxial analgesia. However, large inclusive surveys that evaluate the frequencies of complications (including neuraxial hematoma), as well as identify subgroups of patients with higher or lower risk, enhance our ability to risk stratify. Moen *et al* investigated serious neurological complications among 1 260 000 spinal and 450 000 epidural blocks performed in Sweden over a 10-year period.[52] Twenty-four of the 33 spinal hematomas occurred in the last 5 years of the decade surveyed. Among the 33 spinal hematomas, 24 occurred in females; 25 were associated with an epidural technique. A coagulopathy (existing or acquired) was present in 11 patients; two of these patients were parturients with hemolysis, elevated liver enzymes, and low platelets syndrome. Pathology of the spine was present in six patients. The presenting complaint was typically lower extremity weakness, rather than radicular back pain. Only five of 33 patients recovered neurologically (due to delay in the diagnosis/intervention). These demographics, risk factors, and outcomes confirm those of previous series.[53] Importantly, the methodology allowed for calculation of frequency of spinal hematoma among patient populations. For example, the risk associated with epidural analgesia in women undergoing childbirth was significantly less (one in 200 000) than that in elderly women undergoing knee arthroplasty (one in 3600, $p<0.0001$). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (one in 22 000) compared with all patients undergoing spinal anesthesia (one in 480 000).

The relatively hypercoagulable state of pregnancy may be protective and offers one possible reason for the lower rate of neuraxial hematomas in the obstetric population. The normal anatomic changes that occur in the aging spine may provide another explanation for the differing incidence. Both Moen *et al* and Pöpping *et al* cited osteoporotic deformities as likely contributing to the risk of symptomatic vertebral canal bleeding after epidural blockade in elderly women.[52 54]

Overall, these series suggest that the risk of clinically significant bleeding varies with age, associated abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during continued anticoagulation (particularly with standard heparin or LMWH), perhaps in an additive versus synergistic multifactorial manner. They also consistently demonstrate the need for prompt diagnosis and intervention.

PHARMACOLOGICAL-BASED RECOMMENDATIONS FOR PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY

As previously mentioned, recommendations involving the anesthetic management of new antithrombotic agents are once again based on the pharmacology of hemostasis-altering drugs, using the ESAIC/ESRA methodology[11] as was done with the previous fourth edition.[9] In contrast to the fourth edition,[9] the terms 'low' and 'high' doses will be used instead of the terms 'prophylactic' and 'therapeutic.' Depending on the indication, a 'prophylactic dose' may actually be what is also considered a 'therapeutic dose.' For example, the same 'high' dose may be used in one patient as a treatment for DVT and in another patient as prophylaxis for recurrent DVT. Also, the presence of reduced kidney function, a low body weight, advanced age, and/or the concomitant use of drugs such as permeability glycoprotein inhibitors such as ciclosporin, dronedarone, erythromycin, or ketoconazole may also cause a 'prophylactic' dose to be a 'high' dose. When calculating the timing of discontinuation of an anticoagulant, the pharmacokinetics for healthy populations were used (eg, compared with those at the extremes of age, weight, and with compromised renal function). For the patient on a low (previously 'thromboprophylactic') dose, a time interval of twice $t_{1/2}$ was required. A high (previously 'therapeutic') dose necessitates a time interval of five times $t_{1/2}$ for performance of neuraxial or deep plexus blocks. Likewise, the $t_{1/2}$ for patients with renal insufficiency would be used to determine the timing of the last dose. Finally, the timing of the first dose after block or catheter removal is also based on the pharmacology of the

drug, taking into account the time to clot formation and peak anticoagulant effect (8 hours–t_{max}).[55 56] Relevant pharmacological parameters such as time to peak effect, $t_{1/2}$ and mode of excretion are included in each section. This methodology allows for an individualized approach, considering patient, anesthetic, and surgical factors.

DIRECT ORAL ANTICOAGULANTS

Currently, the medications known as DOACs consist of the oral direct Xa antagonists (DXA) apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto). Dabigatran (Pradaxa) is an oral direct thrombin inhibitor (DTI). They have similar indications (table 1) and are generally prescribed to reduce the risk of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF), for treatment of DVT and PE, to reduce the risk of recurrence of DVT or PE, and the prophylaxis of DVT, which may lead to PE in patients undergoing knee and/or hip replacement surgery. Rivaroxaban may also be used in the prophylaxis of VTE in acutely ill medical patients, while only rivaroxaban has the indication to reduce the risk of major cardiovascular events in patients with coronary artery disease (CAD), and/or to reduce the risk of major thrombotic vascular events in patients with PAD. Depending on individual patient characteristics and indications, the same 'high' dose of a DOAC is considered therapeutic when used in a patient for the treatment of DVT and inversely as prophylactic when used in another patient for the prevention of recurrent DVT. Therefore, a table showing the 'low' and 'high' doses of the various DOACs and their indications are shown in table 1. Betrixaban was taken off the market in the USA in April 2020 and therefore will not be discussed. Finally, as the pharmacology of apixaban, edoxaban, rivaroxaban, and dabigatran was extensively discussed in the previous fourth edition of the ASRA PM anticoagulation guidelines on regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy,[9] it will not be repeated in the present update, but a summary of the pharmacokinetics can be found in table 4.

The anticoagulant effect of DXAs can be reliably measured using drug-specific, calibrated anti-X activity (aXa) assays.[57–60] A non-detectable anticoagulant effect is defined as a drug-specific threshold plasma level <30 ng/mL.[57 59] If drug-specific calibrated aXa assays are not available, a clinically relevant DXA effect can be ruled out by the use of UFH-calibrated or LMWH-calibrated chromogenic aXa assays.[58 61] In these cases, an aXa activity of 0.1 IU/mL or less is considered to be an undetectable anticoagulant effect.[57–60] Chromogenic drug-specific calibrated aXa assays are very sensitive to the presence of DXA, especially at therapeutic plasma levels, but do not allow assessment of plasma levels lower than or around 30 ng/mL. Using sample dilution and an appropriate calibrated assay may overcome this.[60 62]

The anticoagulant effect of a DTI (ie, dabigatran) can be monitored using the thrombin time (TT). The TT is highly sensitive to dabigatran, and a normal TT predicts the absence of dabigatran or the presence of low plasma concentrations.[57] However, due to this high sensitivity, dabigatran plasma levels lower than or close to 30 ng/mL may cause the TT to still be significantly prolonged.[63] Hence, a prolonged TT is not necessarily linked to a high dabigatran level, which makes the TT not suited to correctly quantify low dabigatran plasma levels.[64] In contrast, the diluted TT (dTT) overcomes the high sensitivity of the TT and has a linear dose response-relationship with clotting times inversely proportional to the dabigatran plasma levels.[60 65–67] Recent studies and guidelines have defined an undetectable

Table 4 Pharmacokinetics of direct oral anticoagulants

	Apixaban[86]				Betrixaban[285–287]				Edoxaban[87]				Rivaroxaban[89]				Dabigatran[90]			
Tmax (hours)	2				3								2				2			
Renal clearance	27%				5%–11%								35%				≥80%			
CrCl (mL/min)	≥80	50–79	30–49	15–29	≥90	60–89	30–59	15–29	<15 (off-dialysis)	≥80	50–79	30–49	<15 (off-dialysis)	≥80	50–79	30–49	15–29	<15 (off-dialysis)	≥80	50–79	30–49	15–29	<15 (off-dialysis)
Elimination half-life $t1/2_{\beta}$ (hours)	15.1[85 288]	14.6[288]	17.6[288]	17.3	37 Effective 19–27	No data	No data	No data	No data	10–14[289]	8.4[290]	9.4[290]	16.9[290]	No data	5–9 (young) 11–13 (elderly)	8.7[291 292]	9.0[291 292]	9.5[291 292]	13.2[292]	12–17[293]	16.6[294]	18.7[294]	27.5[294]	No data
Patient exposure (AUC_{0-24})	N/A				1.0[88]	1.89[88]	2.27[88]	2.63[88]	No data	N/A														

AUC, area under the curve; CrCl, creatinine clearance; N/A, not available.

anticoagulant effect with a dTT-specific threshold value of <30 ng/mL.[57 59]

The availability of these tests throughout the USA and the rest of the world is presently unreliable. We provide recommendations and threshold values with the hope that these tests become more routine and the results more immediate. The use of routine coagulation tests such as the prothrombin time (PT) or the activated partial thromboplastin time (aPTT) should not be used to assess the degree of anticoagulation produced by the DOACs, as there is a large variability in the sensitivity of the reagent used in the different tests.[60 63 68]

At the time of submission, there are no RCTs specifically studying the correlation between low and high doses of DOACs and the occurrence of neuraxial block-related subarachnoid or epidural hematoma in patients. In addition, most of the published cases of neuraxial hematomas associated with a DOAC were either spontaneous or traumatic in origin and involved apixaban, dabigatran, or rivaroxaban.[9 69–75] Only a limited number of these case reports were associated with a neuraxial block,[9 76 77] and involved potentially confounding risk factors such as the concomitant use of other antithrombotic drugs (eg, enoxaparin and/or warfarin), the removal of the epidural catheter after a shorter time interval than recommended by the manufacturer or resuming therapeutic (high) dose dabigatran 24 hours after the neuraxial intervention. In the previous guidelines, the pharmacokinetic properties (table 4) and expert opinion were key elements to recommend therapy-free time intervals to enable the safe performance of a neuraxial or deep plexus intervention in patients treated with a DOAC. A neuraxial anesthetic intervention is considered a high bleeding risk procedure as bleeding would have important consequences not so much in terms of blood loss, but mainly in terms of a neurological deficit caused by bleeding into a confined space.[78 79] It is therefore recommended that a complete return of normal hemostasis is required before any neuraxial or deep plexus/peripheral block is performed.

In healthy patients (young and old) treated with a low-dose DOAC, twice the half-life ($T_{1/2}$) (correlating to when only 25% of the drug is remaining in circulation) was used to determine therapy-free time intervals after the last ingestion,[80] while in patients treated with a high dose, five times the $T_{1/2}$ (correlating to when only 6.2% to 3.1% of the drug remains in circulation) was recommended.[81] The same principle was applied to patients with renal insufficiency.

Still, the use of the $T_{1/2}$ carries the inherent risk of (inter) individual variability, which becomes more important when high doses are used. In these cases, the use of customized clotting tests to determine any residual anticoagulant activity may be a valuable addition or alternative to the $T_{1/2}$-based calculations. As already mentioned and although never clinically validated,[58 59] most experts and international anesthesiology societies consider a DOAC plasma level <30 ng/mL as a safe hemostatic threshold[82–84] to avoid bleeding. Recent prospective data have become available on the residual anticoagulant effect following a standardized preoperative interruption of high doses of DOACs. In a substudy of a prospective cohort study of adults (creatinine clearance (CrCl) >50 mL/min), aged ≥18 years, with NVAF who were taking dabigatran, 110 mg or 150 mg two times per day, and required treatment interruption for an elective surgery/procedure, Douketis *et al* reported the residual anticoagulant effect in 59 dabigatran-treated patients.[85] If the planned procedure had a high bleeding risk (including a neuraxial intervention), the last dose was to be taken 3 days (minimum 60–72 hours from last dose) preprocedure.[78] No detectable anticoagulant effect (ie, a plasma level <20 ng/mL) measured by the dTT was found in 95.5% of the patients at the time of the procedure. In 2017, Godier *et al* studied 422 patients (CrCl >50 mL/min) treated with a high dose of apixaban, rivaroxaban, or dabigatran, and found that a 49–72 hours preprocedural discontinuation of these DOACs resulted in apixaban, rivaroxaban, and dabigatran plasma levels >30 ng/mL in only 5% of the patients.[59] These results supported guidelines that the dabigatran-free time interval before a procedure should also be based on renal function. In the presence of a CrCl of 30–50 mL/min 4–5 days would be needed to ensure a minimal anticoagulant effect in patients receiving dabigatran undergoing a high bleeding risk procedure. Finally, the recent large international, multicenter The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) trial reported the residual DOAC plasma levels after high doses of apixaban, dabigatran, and rivaroxaban, in 3007 patients with NVAF, immediately prior to an invasive procedure.[57] Patients in this trial were separated in three cohorts depending on the specific DOAC used (apixaban, dabigatran, or rivaroxaban). Patients were included if the indication for anticoagulation was atrial fibrillation, their age was >18 years, they were taking one of three DOACs, and were scheduled for an elective invasive procedure. Exclusion criteria included severe renal impairment (CrCl <25 mL/min for apixaban or <30 mL/min for dabigatran or rivaroxaban). The mean CHA2DS2 Vascular score was approximately 3.5 and nearly 20% of subjects had a history of stroke or TIA. Approximately one-third of each group underwent a high bleeding risk procedure, whereas two-thirds underwent low bleeding risk procedures. All DOACs had been omitted for 2 days (last dose taken 3 days or 60–68 hours prior) before a high bleeding-risk procedure (apixaban, rivaroxaban if CrCl ≥30 mL/min, and dabigatran if CrCl ≥50 mL/min), and 4 days (ie, last dose taken 5 days prior, dabigatran if CrCl 30–50 mL/min). Overall, 30-day major bleeding rates ranged from 0.9% to 1.85%. Major bleeding rates were higher for high bleeding risk procedures (0.88%–2.90%) compared with low bleeding risk procedures (0.59%–1.27%). The 30-day arterial thromboembolic event rates were low between 0.16% and 0.6% after a mean apixaban-free time interval of 63.8 hours, residual aXa plasma levels were <30 ng/mL in 93.1% of the patients. A mean rivaroxaban-free time interval of 72 hours resulted in residual aXa plasma levels <30 ng/mL in 85.3% of the patients. The residual anticoagulant plasma levels were <30 ng/mL (measured by the dTT) in 98.9% for all dabigatran patients after 63.2 hours (cohort with CrCl ≥50 mL/min) or after 110.2 hours (cohort with CrCl <50 mL/min).[57] No spinal hematomas were reported in the 230 patients (7.6 %) that had a neuraxial block. Similar data for edoxaban are lacking, and therefore the recommendations are based on the pharmacokinetic profile and expert opinion.

The FDA-approved labeling of apixaban and edoxaban states that the (prolonged) use of indwelling neuraxial catheters may increase the risk of a spinal or epidural bleeding.[86–88] Moreover, all manufacturers emphasize the risk of a neuraxial bleed associated with the removal of a neuraxial catheter.[86–90] If a DOAC were to be inadvertently administered in the presence of an indwelling neuraxial catheter, a therapy-free interval identical to the ones recommended prior to a neuraxial intervention should be observed, or the absence of any residual anticoagulant activity should be documented using an appropriate hemostatic assay.

The most recent guidelines on VTE prophylaxis from the ACCP,[12] and the ESAIC,[55 56] were helpful to recommend the timing to resume a DOAC treatment after a neuraxial intervention (ie, the removal of the neuraxial catheter). VTE prophylaxis (ie, low dose) should be resumed/started 6 hours postoperatively,

while therapeutic anticoagulation should be restarted ≥24 hours postoperatively.[55 56] In 2007, Rosencher *et al* recommended that the next/first postoperative dose of an antithrombotic agent to be administered ≥6 hours (ie, 8 hours (the time needed for an initial platelet plug to solidify) minus T_{max} (the onset time of a drug, which is 2–3 hours for the DOACs)) after surgery.[80] Both the ACCP and European Heart Rhythm Association (EHRA) recommend that the postoperative resumption of DOAC therapy, irrespective of the dose used, be delayed for 24 hours after a procedure with a low/moderate bleeding risk, and for 48–72 hours after a procedure with high bleeding risk, and only to be administered when adequate surgical hemostasis has been accomplished.[12 79] In the interim, a prophylactic/low-dose anticoagulant, such as LMWH or UFH, can be considered in patients at high thrombotic risk.[12 79 91]

Finally, the manufacturers recommend that in case of a traumatic neuraxial puncture the administration of the next dose of apixaban and rivaroxaban should be delayed for 48 hours and 24 hours, respectively.[86 88 89] There is no such recommendation for dabigatran and edoxaban.[87 90]

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING A HIGH DOSE OF APIXABAN

We suggest that a high dose of apixaban be discontinued at least 72 hours prior to neuraxial block or deep plexus/peripheral block. Consider checking apixaban or aXa plasma level if <72 hours (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that a residual apixaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL is acceptable prior to neuraxial block or deep plexus/peripheral block (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels and aXa levels.

We suggest that needle placement/catheter removal occurs at least 24 hours prior to the first postoperative dose (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

With the unanticipated administration of high dose of apixaban with a neuraxial catheter in situ, we suggest that apixaban dosing be withheld for at least 72 hours, or a residual apixaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL before the catheter is removed (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration and recommendations for acceptable plasma levels and aXa levels.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING A LOW DOSE OF APIXABAN

We suggest that a low dose of apixaban be discontinued for at least 36 hours prior to neuraxial block or deep plexus/peripheral block. Consider checking apixaban or aXa plasma level if <36 hours (grade IIC)

Remarks: this is a new recommendation in the setting of low-dose administration.

We suggest that a residual apixaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL is acceptable prior to neuraxial block or deep plexus/peripheral block (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels and aXa levels.

We suggest that needle placement/catheter removal occurs at least 6 hours prior to the first postoperative dose (grade IIC)

Remarks: there is no change in this recommendation.

With the unanticipated administration of low dose of apixaban with a neuraxial catheter in situ, we suggest that apixaban dosing be withheld for at least 36 hours, or a residual apixaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL before the catheter is removed (grade IIC)

Remarks: this is a new recommendation in the setting of low-dose administration and recommendations for acceptable plasma levels and aXa levels.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING A HIGH DOSE OF EDOXABAN

We suggest that a high dose of edoxaban be discontinued for at least 72 hours prior to neuraxial block or deep plexus/peripheral block. Consider checking edoxaban or aXa activity plasma level if <72 hours (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that a residual edoxaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL is acceptable prior to neuraxial block or deep plexus/peripheral block (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels and aXa levels.

We suggest that needle placement/catheter removal occurs at least 24 hours prior to the first (postoperative) dose (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

With the unanticipated administration of high dose of edoxaban with a neuraxial catheter in situ, we suggest that edoxaban dosing be withheld for at least 72 hours, or a residual edoxaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL before the catheter is removed (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration and recommendations for acceptable plasma levels and aXa levels.

MANAGEMENT OF THE PATIENT RECEIVING A LOW DOSE OF EDOXABAN

There is no FDA-approved medical indication for low-dose edoxaban.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING A HIGH DOSE OF RIVAROXABAN

We suggest that a high dose of rivaroxaban be discontinued for at least 72 hours prior to neuraxial block or deep plexus/peripheral block. Consider checking rivaroxaban or aXa activity plasma level if <72 hours (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that a residual rivaroxaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL is acceptable prior to neuraxial block or deep plexus/peripheral block (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels and aXa levels.

We suggest that needle placement/catheter removal occurs at least 24 hours prior to the first postoperative dose (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

With the unanticipated administration of high dose of rivaroxaban with a neuraxial catheter in situ, we suggest that rivaroxaban dosing be withheld for at least 72 hours, or a residual rivaroxaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL before the catheter is removed (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration and recommendations for acceptable plasma levels and aXa levels.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/ PERIPHERAL BLOCK IN THE PATIENT RECEIVING A LOW DOSE OF RIVAROXABAN

We suggest that a low dose of rivaroxaban be discontinued for at least 24 hours (30 hours if CrCl <30 mL/min) prior to neuraxial block or deep plexus/peripheral block. Consider checking rivaroxaban or aXa activity plasma level if <24 hours (grade IIC)

Remarks: this is a new recommendation in the setting of low-dose administration.

We suggest that a residual rivaroxaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL1 is acceptable prior to neuraxial block or deep plexus/peripheral block (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels and aXa levels.

We suggest that needle placement/catheter removal occurs at least 6 hours prior to the first postoperative dose (grade IIC)

Remarks: there is no change in this recommendation.

With the unanticipated administration of low dose of rivaroxaban with a neuraxial catheter in situ, we suggest that rivaroxaban dosing be withheld for at least 24 hours (30 hours if CrCl <30 mL/min), or a residual rivaroxaban plasma level <30 ng/mL or a residual aXa activity plasma level ≤0.1 IU/mL before the catheter is removed (grade IIC)

Remarks: this is a new in the setting of low-dose administration and recommendations for acceptable plasma levels and aXa levels.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/ PERIPHERAL BLOCK IN THE PATIENT RECEIVING A HIGH DOSE OF DABIGATRAN

We suggest that a high dose of dabigatran be discontinued for at least 72 hours in patients with a CrCl ≥50 mL/min prior to neuraxial block or deep plexus/peripheral block. Consider checking dabigatran plasma level if <72 hours (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

We suggest that a high dose of dabigatran be discontinued for 120 hours in patients with a CrCl 30–49 mL/min prior to neuraxial block or deep plexus/peripheral block. Consider checking dabigatran plasma level if <120 hours (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

We suggest against the performance of neuraxial or deep plexus/peripheral blocks in patients with a CrCl <30 mL/min unless a dabigatran plasma level is obtained and <30 ng/mL (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

Prior to neuraxial block or deep plexus/peripheral block we suggest that a residual dabigatran plasma level <30 ng/mL is acceptable (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels and aXa levels.

We suggest that needle placement/catheter removal occurs at least 24 hours prior to the first postoperative dose (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration.

With the unanticipated administration of high-dose dabigatran with a neuraxial catheter in situ, we suggest that dabigatran dosing be withheld for at least 72 hours (120 hours if CrCl 30–49 mL/min) or a residual dabigatran plasma level <30 ng/mL before the catheter is removed (grade IIC)

Remarks: this is a new recommendation in the setting of high-dose administration and recommendations for acceptable plasma levels and aXa levels.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/ PERIPHERAL BLOCK IN THE PATIENT RECEIVING A LOW DOSE OF DABIGATRAN

We suggest that a low dose of dabigatran be discontinued for at least 48 hours prior to neuraxial block or deep plexus/peripheral block. Consider checking dabigatran plasma level if <48 hours (grade IIC)

Remarks: this is a new recommendation in the setting of low-dose administration.

We suggest that a residual dabigatran plasma level <30 ng/mL is acceptable prior to neuraxial block or deep plexus/peripheral block (grade IIC)

Remarks: this new recommendation includes acceptable plasma levels.

We suggest against the performance of neuraxial or deep plexus/peripheral blocks in patients with a CrCl <30 mL/min unless a dabigatran plasma level is obtained and <30 ng/mL (grade IIC)

Remarks: this is a new recommendation in the setting of low-dose administration.

We suggest that needle placement/catheter removal occurs at least 6 hours prior to the first postoperative dose (grade IIC)

Remarks: there is no change in this recommendation.

With the unanticipated administration of low dose of dabigatran with a neuraxial catheter in situ, we suggest that dabigatran dosing be withheld for at least 48 hours, or a residual dabigatran plasma level <30 ng/mL before the catheter is removed (grade IIC)

Remarks: this is a new recommendation in the setting of low-dose administration and recommendations for acceptable plasma levels.

REVERSAL OF THE DIRECT ORAL ANTICOAGULANTS

Andexanet alfa (Andexxa) is a recombinant protein that is indicated in patients treated with rivaroxaban or apixaban, where reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.[92–94] A multicenter, prospective, open-label, single-group study evaluated 67 patients who had an acute major bleed within 18 hours after the administration of apixaban or rivaroxaban. Andexanet alfa substantially reduced apixaban and rivaroxaban with effective hemostasis occurring in 79% of the patients and reducing aXa activity by 92% for both DXAs, at 15–30 min from the end of bolus administration.[95] A full study report followed in 2019 including 227 and 90 patients with intracranial or gastrointestinal bleeding, respectively.[96] In both the apixaban and rivaroxaban cohorts, the median aXa activity decreased by 92% after the andexanet alfa bolus. Although excellent or good hemostasis was found in 82% of the patients, there was no significant relationship between hemostatic efficacy and a reduction in aXa activity. Hence, it remains unclear whether the remaining plasma levels of aXa activity after andexanet alfa administration are predictive of the risk of a neuraxial bleeding. The Annexa-4 trial reported similar results: in apixaban-treated and rivaroxaban-treated patients, andexanet alfa reduced the median aXa activity by 93.8% and 92.6%, respectively.[97] Finally, in a prospective single-arm cohort study of 36 patients with acute major bleeding while treated with edoxaban, andexanet alfa significantly decreased aXa activity, but to a lesser extent (median 68.9%) than in apixaban-treated or rivaroxaban-treated patients.[98] Whether or not the remaining plasma levels of aXa activity after andexanet alfa administration are predictive of the risk of a neuraxial bleeding still remains unclear. In addition, current commercial aXa assays are unsuitable for measuring the remaining factor Xa activity following administration of andexanet alfa.[94] Finally, re-elevation or incomplete reversal of anticoagulant activity may occur because of andexanet alfa's short terminal half-life (ie, 5–7 hours) and its ability to displace DXAs from the extravascular to the intravascular compartment.[93]

A US FDA approval, under accelerated approval regulations pending further investigations, followed in 2018.[99] Andexanet alfa is approved to reverse the anticoagulant effect of apixaban and rivaroxaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexanet alfa is not approved for reversal of anticoagulation prior to emergency surgery/procedures or neuraxial interventions. There are no contraindications to its use. However, a black box warning was included mentioning the association of andexanet alfa with serious and life-threatening adverse events, including: (1) arterial and venous thromboembolic events; (2) ischemic events, including myocardial infarction and ischemic stroke; (3) cardiac arrest, and (4) sudden death.[94] The warning recommends monitoring for thromboembolic events and symptoms/signs that precede cardiac arrest and to initiate anticoagulation when medically appropriate and to provide treatment as needed. Other warnings include the re-elevation or the incomplete reversal of the aXa activity and the inhibition of the anticoagulant effect of UFH by andexanet alfa. The most common adverse reactions in healthy or bleeding subjects receiving andexanet alfa were infusion-related reactions (≥3%) or urinary tract infections and pneumonia (≥5%), respectively.[94]

In case of life-threatening or uncontrolled bleeding, the recommended dosing consists of an initial intravenous bolus dose of 400 mg (low dose) or 800 mg (high dose). Because of andexanet alfa's short half-life and the ability to displace DXAs from the extravascular to the intravascular compartment, it must be followed by a 120 min intravenous infusion of 480 mg (low dose) or 960 mg (high dose), respectively.[94] The choice of the low-dose versus the high-dose regimen of andexanet alfa is determined based on the specific DXA ingested, the dose of the DXA, and time since the patient's last dose of the DXA.

Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment. In October 2015, idarucizumab was approved by the FDA to be used in adult patients treated with dabigatran, when rapid reversal of its anticoagulant effects is required in situations of emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding.[100] This decision was mainly based on a clinical trial in patients with bleeding or requiring urgent surgery that demonstrated the complete reversal of the anticoagulant effect of dabigatran and decreased dabigatran plasma levels below the lower detection threshold of 20 ng/mL within 30 min.[101] Although there are no contraindications to the use of idarucizumab, it is not FDA-approved for the reversal of dabigatran prior to neuraxial interventions. Also, there are no controlled investigations on the use of reversal agents specifically aimed at neuraxial anesthetic techniques. Still, a French Working Group on Perioperative Haemostasis recommended the use of idarucizumab to restore normal hemostasis prior to an urgent diagnostic lumbar puncture, in a context of infectious cerebral disease or a spinal anesthetic, in patients in whom a general anesthetic is best avoided.[102] Indeed, two recent case reports describe the successful use of idarucizumab in an emergency lumbar puncture for the possible diagnosis of infectious central nervous disease.[103 104]

An increased thromboembolic risk is possible in patients having an underlying disease predisposing them to thromboembolic events when exposed to idarucizumab. This risk can be reduced by resuming the anticoagulant treatment as soon as medically appropriate. Other possible adverse reactions/complications related to the use of idarucizumab include: (1) the re-elevation of coagulation parameters; (2) hypersensitivity reactions, and (3) serious adverse reactions (ie, hypoglycemia, hypophosphatemia, metabolic acidosis, an increase in uric acid, and acute liver failure with breakdown of excretory and synthetic function) including a fatal outcome in patients with the condition of hereditary fructose intolerance due to the sorbitol excipient.[100]

The recommended dose in case of emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding is 5 g via an intravenous infusion/injection.[100] There is limited data to support administration of an additional 5 g of idarucizumab, but if reappearance of clinically relevant bleeding together with elevated coagulation parameters is observed after administration of 5 g idarucizumab, administration of an additional 5 g dose of idarucizumab may be considered.

The use of procoagulant agents such as prothrombin complex concentrates (PCC) or activated prothrombin complex concentrates (aPCC) may be an option if specific antidotes for the reversal of the DOACs are not available or are too costly.[12 79] However, all procoagulant agents carry the inherent risk of a prothrombotic effect, and thus their use must be carefully considered.

A number of observational studies (some retrospective) have shown the efficacy of PPC or aPCC in DOAC-treated patients who were actively bleeding,[105–109] although studies in patients with intracranial hemorrhage report mixed results.[110 111] There are no data evaluating the use of PCC or aPCC for reversal in patients treated with DOACs and planned for a neuraxial intervention. Therefore, the availability of specific antidotes such as andexanet alfa or idarucizumab does not imply that DOAC treatment should be reversed for the sole purpose of a regional anesthetic technique. If surgery can be postponed allowing spontaneous recovery of normal hemostasis, discontinuation of the antithrombotic drug is the preferred strategy. If waiting is not an option and reversal is needed for the safe conduct of the surgery itself, regional anesthetic techniques may be considered after full dabigatran reversal by idarucizumab.

Use of DOAC antidotes to facilitate placement of neuraxial block or deep plexus/peripheral block

The present available data suggest *against* the use of idarucizumab, andexanet alfa, PCC, or aPCC to reverse DOAC anticoagulant activity to enable the safe performance of a neuraxial intervention in routine patients (grade IIC)

Remarks: this is a new recommendation.

INTRAVENOUS AND SUBCUTANEOUS UNFRACTIONATED HEPARIN

Pharmacology of unfractionated heparin

The major anticoagulant effect of heparin is due to a unique pentasaccharide that binds to antithrombin (AT) with high affinity and is present in approximately one-third of heparin molecules. Binding of this heparin pentasaccharide to AT accelerates its ability to inactivate thrombin (factor IIa), factor Xa, and factor IXa. Anticoagulant activities of UFH depend on both the number of heparin molecules with the pentasaccharide chain and the size of the molecules containing the pentasaccharide sequence. Larger molecular weight heparins will catalyze inhibition of both factor IIa and Xa. Smaller molecular weight heparins will catalyze inhibition of only factor Xa.[112 113] Intravenous injection results in immediate anticoagulant activity, whereas subcutaneous injection results in a 1–2 hour delay. The anticoagulant effect of heparin is both dose-dependent and molecular size-dependent and is not linear but increases disproportionately with increasing doses. For example, the biologic half-life of heparin increases from 30 min after 25 units/kg intravenous to 60 min with 100 units/kg intravenous, and to 150 min with a bolus of 400 units/kg intravenous.[113 114]

When given in high doses (therapeutic), the anticoagulant effect of heparin is typically monitored with the aPTT. However, this test does not directly measure heparin and is affected by physiological and analytic variables. Anti-Xa testing offers improvements over aPTT testing for accurate measurement of heparin levels. Clinical data from the last 10–20 years suggest that aXa monitoring may offer a more predictable dose-response curve, and require fewer blood samples and dosage adjustments.[115] The activated clotting time (ACT) is typically used to monitor higher doses given during cardiopulmonary bypass and other interventional procedures requiring anticoagulation with heparin such as interventional radiology procedures. Adequate therapeutic effect (in patients with VTE or unstable angina) is achieved with a prolongation of the aPTT to between 1.5 and 2.5 times the baseline value,[112] heparin level of 0.2–0.4 U/mL, or aXa level of 0.3–0.7 U/mL.[116]

Administration of low-dose (5000 U) subcutaneous heparin for prophylaxis of DVT does not significantly prolong the aPTT in the majority of patients and is typically not monitored. However, it can result in unpredictable (10-fold variability) and therapeutic blood concentrations of heparin in some patients (non-pregnant, surgical, and medical patients) within 2 hours after administration.[117] There is also a subset of patients who will develop heparin-induced thrombocytopenia (HIT) after being on heparin for >5 days, resulting in a decreased platelet count.[114] For this reason, patients receiving intravenous or subcutaneous UFH for >4 days should have a platelet count assessed prior to neuraxial block or catheter removal. While the typical onset of HIT occurs within 5–14 days following heparin initiation, patients with a recent heparin exposure within the past 30 days may develop rapid-onset HIT on heparin re-exposure.[118–120] This phenomenon has been explained by already present circulating heparin platelet factor 4 antibodies. In contrast, delayed-onset HIT may occur days to weeks after hospital dismissal.[121 122] For these patients, symptomatic venous thrombotic complications bring the patient to clinical attention. Thrombocytopenia, on re-presentation, may be mild to moderate. Importantly, heparin re-exposure may worsen clinical outcomes. As such, awareness of both rapid-onset and delayed-onset HIT may prevent adverse therapeutic outcomes.

One of the advantages of heparin anticoagulation is that its effect may be rapidly reversed with protamine. Each mg of protamine can neutralize 100 units of heparin. Neutralization of subcutaneously administered heparin may require a prolonged infusion of protamine due to the continued absorption.[114] However, the potential risks of thrombosis following protamine administration have to be weighed against the benefits of a neuraxial anesthetic. A careful balance of risks and benefits needs to be considered including the option of performing a general anesthetic.

Risk factors for neuraxial hematoma in the heparinized patients

Spinal or epidural needle insertion in the presence of sustained therapeutic anticoagulation with heparin is associated with increased risk. Much of our information about this association comes from a report of 342 patients who deliberately received systemic therapeutic heparin after lumbar puncture.[123] Three factors associated with the increased risk of hematoma were identified: <60 min time interval between the administration of heparin and lumbar puncture, traumatic needle placement, and concomitant use of aspirin. These risk factors have been verified in subsequent large reviews of case reports of hematomas associated with neuraxial procedures in the presence of UFH.[124–126]

Intravenous unfractionated heparin

Intraoperative heparinization typically involves injection of 5000–10 000 units of heparin intravenously during the operative period, particularly in the setting of vascular surgery to prevent coagulation during cross-clamping of arterial vessels.[113] Neuraxial anesthetic techniques may be considered for these patients, but the increased risk of neuraxial hematoma, as demonstrated by case series, epidemiological surveys, and the ASA Closed Claims database needs to be considered.[52 53 127 128] Maintaining a minimum 1-hour interval between needle placement and heparinization, as well as avoiding other hemostasis-altering medications, decreases the risk of significant bleeding.

Management of a traumatic neuraxial procedure must also be considered. Previous case reports suggest that presence of a

bloody tap or a traumatic regional block was an associated factor in approximately 50% of spinal hematomas.[53] Although some investigators have recommended cancellation of the surgical procedures if these events occur,[126] there are no clinical data to support this recommendation.[129 130] Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is recommended.

Heparinization may be continued into or initiated in the postoperative period. However, the removal of a neuraxial catheter in the presence of heparin therapy increases the risk of hematoma formation. In a series by Vandermeulen *et al*, half of the spinal hematomas associated with intravenous heparinization were detected at the time of catheter removal.[53] Since the latest version of the ASRA guidelines,[9] one additional case report of postoperative epidural hematoma on a patient on intravenous heparin has been published.[9 131] This patient suffered a perioperative myocardial infarction and pump failure requiring full anticoagulation with intravenous heparin and concomitant antiplatelet therapy. An epidural hematoma ensued after the surgeon removed the epidural catheter under full heparin anticoagulation and concomitant thrombocytopenia. The risk of hematoma resulting from catheter removal has led to the recommendation that in patients who have undergone systemic heparinization, the heparin should be discontinued for 4–6 hours and the coagulation status assessed prior to neuraxial catheter manipulation or removal.[8]

Heparinization during cardiopulmonary bypass

Since the publication of the initial ASRA guidelines in 1998,[5] there have been continued discussions regarding the relative risk and benefit of neuraxial anesthesia and analgesia in the patient undergoing heparinization for cardiopulmonary bypass.[132–136] Unfortunately, while there is improved analgesia, pulmonary function, and decreased cardiac arrhythmias, there is no reduction in hospital stay, myocardial infarction, or mortality. To date, there is a single case of spinal hematoma following the full heparinization associated with cardiopulmonary bypass.[137] However, these series involve small numbers of patients. Using a mathematical analysis of the probability of predicting a rare event and based on the total of 4583 epidural and 10 840 spinal anesthetics reported without complications, Ho *et al* estimated the risk of hematoma to be approximately 1:1528 for epidural and 1:3610 for spinal technique.[138] Thus, this analgesic technique remains controversial in that the risk appears too great for the perceived benefits. Neuraxial anesthetics are therefore not recommended in the setting of high-dose anticoagulation and cardiopulmonary bypass.

Subcutaneous unfractionated heparin

Low-dose subcutaneous UFH is commonly used for prophylaxis against development of VTE following major organ surgery including general surgery, colorectal surgery, gynecology, obstetrics, and urology.[139] Administration of 5000 units of heparin subcutaneously two or three times daily has been used extensively and is effective for prophylaxis against DVT. There is often no detectable change in standard coagulation tests, as measured by the aPTT, aXa level, or heparin level. However, approximately 15% of patients may develop measurable changes in coagulation, with the aPTT rarely exceeding 1.5 times the normal level and normalizing within 4–6 hours after administration.[117] There is a smaller subset (2%–4%) of non-pregnant patients who may become therapeutically anticoagulated during subcutaneous heparin therapy.[5]

The widespread use of subcutaneous heparin and the paucity of complications suggest that there is little risk of spinal hematoma associated with this therapy. There are 10 published series totaling over 12 000 patients who have received this therapy without complications. Three recent series, with a combined total of over 7000 patients who received epidural analgesia in the presence of 5000 units of heparin three times a day, reported no spinal hematomas.[140–142] There are only five case reports of neuraxial hematomas: four epidural,[53 143] and one spinal,[144] during neuraxial block with the use of subcutaneous heparin. The latest case report published since the last iteration of the guidelines[5] described an epidural hematoma shortly after removal of an epidural catheter in a non-pregnant patient on 5000 IU of heparin, administered subcutaneously, two times per day. The latest guidelines appeared to have been followed, but the patient had the additional risk factors of being treated with aspirin 325 mg once per day until 1 week preoperatively and of having a difficult epidural insertion with three attempts required.[143]

The safety of high-dose subcutaneous UFH (doses >5000 units or total daily dose >15 000 units) remains controversial due to the marked variability in patient response to these dosing regimens. Specifically, because the anticoagulant effect of heparin is non-linear, and increases disproportionately with increasing doses, administration of >5000 units will increase the intensity and duration of the anticoagulant effect.[113] For example, in one study involving obstetrical patients, six of 11 women receiving high-dose subcutaneous UFH still had an elevated aPTT 12 hours after their last dose.[145] Timing of assessment of coagulation status for residual heparin effect is based on dose and frequency of dosing. For example, for individual heparin dose of 7500–10 000 U two times per day or a daily dose of ≤20 000 U, it is suggested neuraxial block occur 12 hours after subcutaneous heparin administration *and* assessment of coagulation status with a normal aPTT. Likewise, for individual heparin dose >10 000 U subcutaneously per dose, or >20 000 U total daily dose, it is suggested neuraxial block occurs 24 hours after subcutaneous heparin administration *and* assessment of coagulation status with a normal aPTT.[8]

Current recommendations are consistent with recent trends of perioperative thromboprophylaxis, which recommend dosing regimens that minimize residual anticoagulant at the time of surgery as well as allow for a delay in initiation of postoperative thromboprophylaxis until hemostasis is confirmed.[15 16 48 146] These recommendations are based on the pharmacology of a subcutaneous 5000-unit dose of UFH, which results in an onset of anticoagulant effect 1 hour after administration that persists for 4–6 hours.[113 147]

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING UNFRACTIONATED HEPARIN

We recommend daily review of the patient's medical record to determine the concurrent use of medications that affect other pathways of hemostasis. These medications include antiplatelet medications, LMWH, and oral anticoagulants (grade IB)

Remarks: there is no change in this recommendation.

Since heparin-induced thrombocytopenia may occur during heparin administration, we recommend that patients receiving intravenous or subcutaneous UFH for >4 days have a platelet count assessed (grade IC)

Remarks: there is no change in this recommendation.

Intravenous heparin

Discontinue heparin infusion for a minimum of 4–6 hours and coagulation status be assessed and normal prior to neuraxial block or deep plexus/peripheral block (grade IA)

Remarks: there is no change in this recommendation.

Delay intravenous heparin administration for a minimum of 1 hour after needle placement (grade IA)

Remarks: there is no change in this recommendation.

Remove indwelling neuraxial catheters 4 to 6 hours after the last heparin dose (and after assessment of the patient's coagulation status); reheparinize 1 hour after catheter removal (grade 1A).

Remarks: there is no change in this recommendation although it was inadvertently removed from this edition.

Monitor the patient postoperatively to provide early detection of motor blockade and consider use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma (grade 1A).

Remarks: There is no change in this recommendation although it was inadvertently removed from this edition

Although the occurrence of a bloody or difficult neuraxial needle placement may increase the risk of hematoma, there are no data to support mandatory cancellation of a case. Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is recommended (grade IA)

Remarks: there is no change in this recommendation.

It is not suggested to maintain neuraxial or deep plexus/peripheral catheters in the setting of full anticoagulation during cardiac surgery. If unanticipated heparinization occurs, we suggest postoperative monitoring of neurological status and consider use of minimal concentration of local anesthetics to enhance early detection of neuraxial hematoma (grade IIC)

Remarks: this suggestion reflects a change to avoid the use of neuraxial or deep plexus catheters in cardiac surgery patients with full anticoagulation, due to the increased risk of hematoma and the availability of less invasive alternatives.

Subcutaneous heparin

Preoperative low-dose UFH for thromboprophylaxis (5000 U two times per day or three times per day). We suggest needle placement occur a minimum of 4–6 hours after heparin administration or coagulation status be assessed and normal (grade IIC)

Remarks: there is no change in this recommendation.

Preoperative high dose

7500–10 000 U two times per day or a daily dose of ≤20 000 U
We suggest neuraxial block occur a minimum of 12 hours after subcutaneous heparin administration and confirmation of normal coagulation status (grade IIC)

Remarks: there is no change in this recommendation.

>10 000 U subcutaneously per dose, or >20 000 U total daily dose
We suggest neuraxial block occur a minimum of 24 hours after subcutaneous heparin administration and confirmation of normal coagulation status (grade IIC)

Remarks: there is no change in this recommendation.

Postoperative low-dose UFH

There is no contraindication to maintaining neuraxial catheters in the presence of low-dose UFH. We suggest catheter removal occurs a minimum of 4–6 hours after heparin administration. Subsequent heparin administration may occur immediately after catheter removal (grade IIC)

Remarks: there is no change in this recommendation.

Postoperative high-dose UFH

The safety of indwelling neuraxial catheters in patients receiving doses >5000 U at a time or >15 000 U of UFH daily has not been established. We suggest that the risk and benefits be assessed on an individual basis and that techniques to facilitate detection of new/progressive neurological deficits (eg, enhanced neurological monitoring occur and neuraxial solutions to minimize sensory and motor block) be applied (grade IIC)

Remarks: there is no change in this recommendation.

LOW MOLECULAR WEIGHT HEPARIN

Pharmacology, monitoring, and reversal of the anticoagulant effect of LMWH

The biochemical and pharmacological properties of LMWH differ from those of UFH.[148–152] Most relevant are the lack of monitoring required (except with high-dose *therapeutic* applications), prolonged half-life, and inability to reverse with protamine. The aXa levels peak 3–5 hours after administration. The elimination half-life of LMWH is approximately 5 hours after subcutaneous injection in patients with normal renal function and is dose independent. In patients with severe renal insufficiency, the anticoagulant effect is exaggerated and the elimination half-life may be prolonged up to 16 hours.[148]

The anticoagulant effect of LMWH is most readily assessed by the aXa activity. Because of reduced protamine binding to LMWH fractions, only the anti-IIa activity of LMWH is completely reversed; the aXa activity is not fully neutralized. Both anti-IIa and aXa activity may return up to 3 hours after protamine reversal.[148] The aXa level above which is associated with significant bleeding risk remains unknown. An aXa level of ≤0.1 IU/mL is considered an undetectable anticoagulant effect.[57–60]

Management of neuraxial block or deep plexus/peripheral block in the patient receiving LMWH

In 1993, enoxaparin was the first LMWH to be introduced for general use in the USA. In the first 5 years of use, over 40 spinal hematomas were reported through the MedWatch system.[3] The risk of spinal hematoma was estimated to be approximately one in 3000 continuous epidural anesthetics compared with one in 40 000 spinal anesthetics.[153] The frequency was attributed to twice-daily dosing (compared with once-daily dosing as administered in Europe) in the presence of an indwelling neuraxial catheter. However, 20 years later in Sweden, Moen *et al*[52] reported a 1:3600 frequency of spinal hematomas among women undergoing total knee replacement (with once-daily LMWH), which is strikingly similar to the frequency associated with twice-daily administered LMWH calculated by Horlocker and Wedel.[3]

Risk factors for neuraxial hematoma with LMWH thromboprophylaxis

Based on an examination of the published cases, MedWatch reports, and clinical experience in Europe and North America,

specific risk factors have been proposed.[3 4 52] In summary, age and gender appear to be significant patient factors, perhaps due to less vertebral canal compliance (smaller volume need to produce critical ischemic pressure) and/or drug effect (exaggerated response to LMWH, renal insufficiency). Finally, the additive, if not synergistic effect of multiple hemostasis-altering medications cannot be overstated and may elevate the risk of hematoma in once-daily LMWH dosing to that of twice-daily dosing.[52]

Low versus high dosing regimens

Low-dose LMWH regimens administered for prophylaxis include enoxaparin 40 mg/day, enoxaparin 30 mg every 12 hours, dalteparin 5000 IU daily. The target aXa level for prophylaxis (measured 4 hours after a dose) is regarded to be 0.2–0.5 IU/mL.

High-dose LMWH regimens for treatment of VTE or bridging therapy involves administering a much higher dose that is typically weight based, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 IU/kg every 12 hours, dalteparin 200 IU/kg daily, or tinzaparin 175 IU/kg daily. It is advisable to maintain peak aXa levels between 0.5 U/mL and 1 U/mL (measured 3–4 hours after the LMWH dose). With high-dose LMWH, it is recommended that the last dose should occur at least 24 hours preoperatively and the last dose should be halved in patients with moderate (CrCl 30–49 mL/min) to severe (CrCl <30 mL/min) renal insufficiency to avoid an exaggerated or prolonged response.[12 154]

A small quality improvement publication involving 19 patients found that almost 60% of patients taking high-dose enoxaparin still have higher than expected aXa levels a minimum of 24 hours after the last dose. They also suggested that patients with lower CrCl and increased age may be at particular risk.[155] A more recent retrospective study reported 18% of patients had aXa levels >2 IU/mL 24 hours after the last administration of their high-dose regimen.[156] Finally, a 2023 prospective observational trial of 103 patients concluded that the time from the last high-dose administration until the aXa level fell below 0.2 IU/mL was 31.5 hours.[157] Interestingly, unlike their previous quality improvement study, this trial found no correlation between age, renal function, weight, or sex for those taking high-dose enoxaparin despite similar methodology. In addition, 34% of patients failed to accurately follow the instructions with regard to timing of administration.[157]

These observational studies indicate that a significant number of patients will have detectable aXa levels (>0.1 IU/mL) and some may have levels in the prophylactic and possibly therapeutic ranges. It is difficult to know whether this correlates with an increased risk of neuraxial hematoma. North American recommendations have drawn on the extensive European experience in the development of practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. The ESAIC/European Society of Anesthesiology (ESA) recommend that with either low-dose or high-dose LMWH, the time interval be doubled between last dose of LMWH or the dose halved in the presence of severe renal insufficiency (CrCl <30 mL/min).[11] Although we recommend against *routine* testing, assessment of residual aXa activity may be considered in patients who are elderly, morbidly obese,[158] or patients with severe renal insufficiency, noting that the acceptable level of residual aXa level for performance of neuraxial block remains undetermined and therefore a level ≤0.1 IU/mL is suggested.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING LOW MOLECULAR WEIGHT HEPARIN

The aXa level is not predictive of the risk of bleeding, although it may be useful in monitoring efficacy of therapy with high-dose regimens. We recommend against the *routine* use of aXa level monitoring

Remarks: there is no change in this recommendation.

Heparin-induced thrombocytopenia may occur during LMWH administration; therefore, we recommend that patients receiving LMWH for >4 days have a platelet count assessed prior to needle placement (grade IC)

Remarks: there is no change in this recommendation.

The presence of blood during needle and catheter placement does not necessitate postponement of surgery. We suggest that initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively and that this consideration be discussed with the surgeon (grade IIC)

Remarks: there is no change in this recommendation.

Preoperative LMWH

We recommend that needle placement should occur at least 12 hours after low-dose LMWH (grade IC)

Remarks: there is no change in this recommendation.

Consider checking aXa activity level if <12 hours (grade 2C). An acceptable level of residual aXa activity remains undetermined, therefore we suggest aXa value of ≤0.1 IU/mL (grade IIC)

Remarks: this new recommendation includes consideration of measuring aXa and acceptable levels.

In patients receiving high (therapeutic) doses of LMWH, we recommend delay of at least 24 hours prior to needle/catheter placement (grade IC)

Remarks: there is no change in this recommendation

Consider checking aXa activity level if <24 hours particularly in elderly patients (age >75 years) and patients with renal insufficiency (CrCl ≤30 mL/min). An acceptable level of residual aXa activity remains undetermined, therefore we suggest aXa value of ≤0.1 IU/mL (grade IIC)

Remarks: this new recommendation includes consideration of measuring aXa and acceptable levels.

Postoperative LMWH

Antiplatelet or oral anticoagulant medications administered in combination with LMWH increases the risk of neuraxial hematoma. We recommend against concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, regardless of LMWH dosing regimen when there is an indwelling neuraxial catheter (grade IA)

Remarks: there is no change in this recommendation.

Twice-daily low dose. We recommend the first dose of LMWH be administered the following day and at least 12 hours after needle/catheter placement. Indwelling catheters

should be removed *prior* to initiation of LMWH. Administration of LMWH should be delayed for 4 hours after catheter removal (grade IC)

Remarks: there is no change in this recommendation.

Single daily low dose. We recommend the first postoperative LMWH dose should be administered at least 12 hours after needle/catheter placement. The second postoperative dose should occur no sooner than 24 hours after the first dose. Indwelling neuraxial catheters do not appear to represent increased risk and may be maintained. However, no additional hemostasis altering medications should be administered due to the additive effects. The catheter should be removed 12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur at least 4 hours after catheter removal (grade IC)

Remarks: there is no change in this recommendation.

Single or twice-daily high (*therapeutic*) dosing. High-dose LMWH may be resumed 24 hours after non-high-bleeding-risk surgery and 48–72 hours after high-bleeding-risk surgery. We recommend that indwelling neuraxial catheters be removed 4 hours *prior* to the first postoperative dose and the first postoperative dose should be at least 24 hours after needle/catheter placement, whichever is greater (grade IC)

Remarks: there is no change in this recommendation.

ANTIPLATELET MEDICATIONS

Due to the ubiquitous nature of atherosclerotic arterial occlusive disease in the USA, the number of patients receiving long-term antiplatelet therapy numbers in the tens of millions.[159] The recent ACCP guideline on periprocedural antithrombotic management offers recommendations for antiplatelet therapy.[12] Antiplatelet agents include aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), thienopyridine derivatives/platelet adenosine diphosphate (ADP) antagonists (ticlopidine, clopidogrel, prasugrel), platelet glycoprotein (GP) IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban), platelet P2Y12 receptor antagonists (ticagrelor), and platelet phosphodiesterase IIIA inhibitors (cilostazol). It is important to note the pharmacological differences among the drugs with antiplatelet effects.

Aspirin and other non-steroidal anti-inflammatory medications

NSAIDs inhibit platelet cyclooxygenase and prevent the synthesis of thromboxane A2. Platelets from patients who have been taking these medications have normal platelet adherence to subendothelium and normal primary hemostatic plug formation. Depending on the dose administered, aspirin (and other NSAIDs) may produce opposing effects on the hemostatic mechanism. For example, platelet cyclooxygenase is inhibited by low-dose aspirin (60–325 mg/day) while larger doses (1.5–2 g/day) will also inhibit the production of prostacyclin (a potent vasodilator and platelet aggregation inhibitor) by vascular endothelial cells and thus result in a paradoxical thrombogenic effect.[160 161] As a result, low-dose aspirin (81–325 mg/day) is *theoretically* a greater risk factor for bleeding than higher doses. There is consensus that the optimal dose of aspirin for prevention of myocardial infarction, stroke, or vascular death lies within the narrow range of 75–160 mg/day.[162]

Platelet function is affected for the life of the platelet following aspirin ingestion; other non-steroidal analgesics (naproxen, piroxicam, ibuprofen) produce a short-term defect, which normalizes within 3 days.[163] Celecoxib (Celebrex) is an anti-inflammatory agent that primarily inhibits cyclooxygenase-2, an inducible enzyme which is not expressed in platelets, and thus does not cause platelet dysfunction.[164]

Thienopyridines

The antiplatelet effect of the thienopyridine derivatives, clopidogrel (Plavix) and prasugrel (Efient) results from inhibition of ADP-induced platelet aggregation. The two are prodrugs that must undergo metabolic activation through the hepatic CYP450 system to generate the active metabolites that inhibit the platelet P2Y12 receptor.[162] Thienopyridine derivatives demonstrate both time-dependent and dose-dependent effects. For example, steady state is achieved within 7 days for clopidogrel with doses of 75 mg/day. However, steady state levels of clopidogrel are reached within 2–15 hours with 300–600 mg loading doses.[165 166]

No prospective studies have evaluated perioperative management of clopidogrel, prasugrel, or ticagrelor in patients undergoing *non-cardiac* surgery. Retrospective studies suggest an increased risk of bleeding with clopidogrel continued perioperatively.[12] Labeling of the thienopyridine derivatives recommends that if a patient is to undergo an elective procedure and an antiplatelet effect is not desired, therapy with clopidogrel should be interrupted 'for 5 days prior to surgery'[167] and prasugrel discontinued 'at least 7 days prior to any surgery.'[168] Based on expert opinion (recommendation made with 'very low certainty of evidence'), the ACCP recommends 5 days for clopidogrel and 7 days for prasugrel.[12] However, these time intervals are not sufficient to have a return to baseline activity in all patients. In a pharmacological study of recovery of platelet function following discontinuation of prasugrel and clopidogrel (there was no clinical assessment of postoperative bleeding), in the prasugrel group, ≥50% of patients returned to baseline reactivity by day 6, ≥75% by day 7, and ≥90% by day 9; in the clopidogrel group, ≥50% of patients returned to baseline reactivity by day 3, ≥75% by day 5, and ≥90% by day 6.[169] Thus, while the majority of patients returned to baseline platelet reactivity after 5 and 7 days of clopidogrel and prasugrel discontinuation, respectively, patients in both groups displayed residual effects beyond these intervals and 'a longer time interval, such as 7 days for clopidogrel and 9 days for prasugrel may be desirable to further mitigate any potential bleeding risk.'[169] Based on European labeling, the ESAIC/ERSA recommends 5–7 days for clopidogrel and 7 days for prasugrel.[11]

Although it is possible to assess residual antiplatelet effect using assays of platelet function (eg, PFA II, P2Y12 assay), only a normalized value would be useful; an acceptable level of residual antiplatelet effect remains undetermined.

Ticagrelor

Ticagrelor (Brilinta) represents a new class of non-thienopyridine platelet inhibitors designed to address the limitations of current oral antiplatelet drugs. Ticagrelor completely *reversibly* inhibits ADP-induced platelet activation, unlike the thienopyridines. Ticagrelor also acts directly on the P2Y12 receptor and does not require cytochrome P450 biotransformation. After a loading dose, an antiplatelet effect is observed within 30 min, while maximum effect is achieved within 2 hours. After discontinuation, platelet function recovers 70% in 3 days and to baseline in 5 days.[170–172] Labeling recommends to 'interrupt therapy with

ticagrelor for 5 days prior to surgery that has a major risk of bleeding.'[173]

Based on expert opinion (recommendation made with 'very low certainty of evidence'), the ACCP[12] recommends that ticagrelor be discontinued 3–5 days prior to surgery, while the ESAIC/ESRA based on European labeling recommends a 5-day interval.[11]

Cangrelor

Cangrelor (Kengreal) is a direct and reversible intravenous P2Y12 inhibitor. The dosage of the drug is 30 μg/kg bolus followed by a 4 μg/kg/min infusion. Its antiplatelet effect is seen within 2 min of administration and inhibits platelet aggregation by 95%–100%. Its plasma half-life is 3–6 min and platelet recovery is rapid; 80% and 90% of the samples recover in 60 and 90 min, respectively.[174]

Patients given cangrelor for percutaneous cardiac intervention are usually continued on one of the oral P2Y12 inhibitors. Both clopidogrel and prasugrel will not work while cangrelor is being infused as their metabolite cannot bind to the receptor, while it is being occupied by cangrelor. Ticagrelor, on the other hand, has a binding site separate from cangrelor. For these reasons, clopidogrel and prasugrel should be given immediately after discontinuation of cangrelor, while ticagrelor can be given during or immediately after the infusion.[175]

The oral P2Y12 inhibitors are discontinued for 5–10 days before surgery. Cangrelor can therefore be used as a bridge therapy in these situations. It is possible that perioperative anesthesiologists will encounter this scenario more often in the future. In these cases, a 3-hour interval minimum, and preferably longer should be observed. ACCP and ESAIC/ESRA did not include recommendations for cangrelor because the medication is rarely administered to patients undergoing regional anesthesia/surgery.[11 12]

Platelet GP IIb/IIIa receptor antagonists

Platelet GP IIb/IIIa receptor antagonists, including abciximab (Reopro), eptifibatide (Integrilin), and tirofiban (Aggrastat), inhibit platelet aggregation by interfering with platelet-fibrinogen and platelet-von Willebrand factor binding. The majority of clinical trials involving the GP IIb/IIIa antagonists have evaluated their use in the treatment of acute coronary syndrome, and thus the GP IIb/IIIa antagonists are typically administered in combination with aspirin and heparin. Contraindications include a history of surgery within 4–6 weeks.[176] Time to normal platelet aggregation following discontinuation of therapy ranges from 8 hours (eptifibatide, tirofiban) to 24–48 hours (abciximab).[162] Thrombocytopenia is a known side effect.[162] ACCP and ESAIC/ESRA did not include recommendations for platelet GP IIb/IIIa because these medications are rarely administered to patients undergoing regional anesthesia/surgery.[11 12]

Cilostazol

Cilostazol produces a selective inhibition of phosphodiesterase (PDE) IIIA resulting in a weak, reversible inhibition of platelet aggregation. Cilostazol is used in peripheral arterial vascular disease because of its vasodilatory properties (vascular muscle also contains PDE IIIA). It has a half-life of 11 hours, which is prolonged in patients with severe renal impairment.[162] The terminal half-life and the active metabolite is 21 hours. There are limited data on perioperative administration of cilostazol. However, a single case report of spinal hematoma following epidural catheter removal in the presence of cilostazol therapy has been reported.[177] ACCP and ESAIC/ESRA did not include recommendations for cilostazol because the medication is rarely administered to patients undergoing regional anesthesia/surgery.[11 12]

Neuraxial hematoma in patients receiving antiplatelet medications

Several large studies have demonstrated the relative safety of central neural blockade in combination with NSAID therapy, although the total number of patients in this combined series is only 4714.[7] If low-dose aspirin creates the greatest impact on platelet function, patients receiving 60–325 mg aspirin would theoretically represent the greatest risk of significant bleeding. However, this is not noted in the literature.[178] An exception to this are patients undergoing invasive pain procedures.[179–181]

No series involving the performance of neuraxial blockade in the presence of thienopyridine derivatives or platelet GP IIb/IIIa receptor antagonists has been performed. Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving thienopyridines and GP IIb/IIIa antagonists has been noted.[48 182 183] In general, the cardiac surgical[183] and interventional radiology literature recommend that elective surgery be delayed 24–48 hours following abciximab and 4–8 hours following eptifibatide or tirofiban.[184] Surgery performed within 12 hours of abciximab administration would most likely necessitate a platelet transfusion. There have been three spinal hematomas attributed to neuraxial techniques and thienopyridines, including one patient undergoing a series of epidural steroid injections.[185–187]

Combination of antiplatelet medications with anticoagulants and thrombolytics

NSAIDs alone do not significantly increase the risk of spinal hematoma. However, combination therapy with UFH, LMWH, oral anticoagulants, and thrombolytics have been demonstrated to increase the frequency of spontaneous hemorrhagic complications, bleeding at puncture sites, and spinal hematoma.[3 52 117 123]

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING NSAIDS

NSAIDs appear to represent no added risk for the development of major bleeding after regional anesthetic techniques. NSAIDs (including aspirin) do not create a level of risk that will interfere with the performance of neuraxial or deep plexus/peripheral blocks. In patients receiving these medications, we do not identify specific concerns as to the timing of single-injection or catheter techniques, postoperative monitoring, or the timing of neuraxial catheter removal (grade IC)

Remarks: there is no change in this recommendation.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING THIENOPYRIDINES (CLOPIDOGREL, PRASUGREL)

Based on labeling and surgical/procedural experience, the suggested time interval between discontinuation of thienopyridine therapy and needle placement is 5–7 days for clopidogrel, and 7–10 days for prasugrel (grade IIC)

Remarks: the time intervals reflect labeling and pharmacological findings that the majority of patients may have a significant (though partial) recovery of platelet function at the shorter time. However, patients at high risk for bleeding require longer time intervals for complete recovery.

Neuraxial and deep plexus/peripheral catheters should not be maintained with prasugrel due to the rapid onset. However, since the antiplatelet effect is not immediate with clopidogrel, they may be maintained for 1–2 days, provided a loading dose of the antiplatelet agent is not administered (grade IIC)

Remarks: there is no change in this recommendation.

Thienopyridine therapy may be resumed immediately after needle placement/catheter removal, provided a loading dose of the drugs is not administered. If a loading dose is administered, we suggest a time interval of 6 hours between catheter removal and administration (grade IIC)

Remarks: there is no change in this recommendation.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING TICAGRELOR

Based on labeling and surgical/procedural experience, the recommended time interval between discontinuation of ticagrelor therapy and needle placement is 5 days (grade 2C)

Remarks: previous time interval was 5–7 days. The new time interval reflects labeling and pharmacological findings regarding platelet function recovery after ticagrelor discontinuation.

Neuraxial catheters should not be maintained with ticagrelor due to the rapid onset (grade IIC)

Remarks: there is no change in this recommendation.

Ticagrelor therapy may be resumed immediately after needle placement/catheter removal, provided a loading dose of the drug is not administered. If a loading dose is administered, we suggest a time interval of 6 hours between catheter removal and administration (grade IIC)

Remarks: there is no change in this recommendation.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING PLATELET GP IIB/IIA INHIBITORS

The platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. Following administration, the time to normal platelet aggregation is 24–48 hours for abciximab and 4–8 hours for eptifibatide and tirofiban. We recommend that needle placement should be avoided until platelet function—as impacted by the GP IIb/IIIa inhibitor—has recovered. Caution in patients on dual therapy who may still have residual NSAID effect (grade IC)

Remarks: there is no change to this recommendation.

Postoperative. Although GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery, should one be emergently administered in the postoperative period following a neuraxial or deep plexus/peripheral technique, we recommend the neuraxial infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurological function and that the patient be carefully monitored neurologically (grade IC)

Timing of catheter removal is based on ongoing risk of thromboembolism and need for continued antithrombotic therapy and the potential for spinal bleeding during catheter maintenance and removal (grade IIC)

Remarks: there is no change in this recommendation.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING CILOSTAZOL

The risk of serious bleeding in the presence of residual cilostazol effect is unknown. Based on the elimination half-life, we suggest that needle placement be avoided for 2 days after discontinuation of cilostazol (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that neuraxial and deep plexus/peripheral catheters be removed prior to reinstitution of cilostazol therapy postoperatively (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that the first postoperative dose of cilostazol be administered 6 hours after neuraxial or deep plexus/peripheral catheter removal (grade IIC)

Remarks: there is no change in this recommendation.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING CANGRELOR

The risk of serious bleeding in the presence of residual cangrelor effect is unknown. Based on the elimination half-life, we suggest that needle placement be avoided for 3 hours after discontinuation of cangrelor (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that neuraxial and deep plexus/peripheral catheters be removed prior to reinstitution of cangrelor therapy postoperatively (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that the first postoperative dose of cangrelor be administered 8 hours after neuraxial or deep plexus/peripheral catheter removal (grade IIC)

Remarks: there is no change in this recommendation.

PARENTERAL DIRECT THROMBIN INHIBITORS

Argatroban, bivalirudin, and desirudin

Recombinant hirudin derivatives, including bivalirudin (Angiomax), and desirudin (Revasc), inhibit both free and clot-bound thrombin. Argatroban (Acova), an L-arginine derivative, has a similar mechanism of action. These medications are indicated for the treatment and prevention of thrombosis in patients with HIT and as an adjunct to angioplasty procedures.[188 189] Desirudin is approved for prevention of VTE/PE following hip replacement.[190] The anticoagulant effect of thrombin inhibitors is monitored by the aPTT, and is present for 1–3 hours after intravenous administration. Hemorrhagic complications, particularly when combined with thrombolytic or antiplatelet agents, may be life threatening. There is no 'antidote'; therefore, the antithrombin effect cannot be reversed pharmacologically. Although there are no case reports of spinal hematoma related to neuraxial anesthesia among patients

who have received an intravenous thrombin inhibitor, spontaneous intracranial bleeding has been reported. The lack of information available and the approved applications of these agents (typically patients with HIT who will need therapeutic levels of anticoagulation) make patients receiving these medications poor candidates for neuraxial blockade.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT TAKING PARENTERAL THROMBIN INHIBITORS (ARGATROBAN, BIVALIRUDIN, AND DESIRUDIN)

In patients receiving parenteral thrombin inhibitors, we suggest against the performance of neuraxial techniques (grade IIC)

Remarks: there is no change in this recommendation.

PARENTERAL ANTI-XA AGENTS

Fondaparinux

Fondaparinux (Arixtra), an injectable synthetic pentasaccharide approved for the prevention and treatment of venous thromboembolic events in acutely ill patients (including those affected by COVID-19), patients with cancer, or patients undergoing surgery (dose 2.5 mg) as well as the treatment of acute DVT and PE (dose 5–10 mg). The FDA released fondaparinux with a black box warning about neuraxial anesthesia like that of the LMWHs and heparinoids. Fondaparinux produces its antithrombotic effect through factor Xa inhibition and is used when patients are intolerant to LMWH. Advantages of fondaparinux include: 100% bioavailability subcutaneously, instant onset of action, long half-life, and direct renal excretion.[191] This drug is contraindicated in patients with severe renal impairment (CrCl <30 mL/min) and in patients weighing <50 kg. It should be used with caution in patients with moderate renal impairment (CrCl 30–50 mL/min). The plasma half-life of fondaparinux is 17–21 hours (17 hours in healthy, young patients and 21 hours in healthy, elderly patients), allowing for single daily dosing, with the first low (prophylactic) dose administered 6–8 hours postoperatively.[192] The half-life in patients with moderate renal insufficiency (CrCl 30–50 mL/min) was found to be 29 hours, and 72 hours in patients with severe renal impairment (CrCl <30 mL/min). Routine coagulation tests such as PT and aPTT are relatively insensitive measures of fondaparinux and are unsuitable for monitoring. The aXa activity can be measured by aXa assay using the appropriate calibrator (fondaparinux). It is important to note that protamine would not be an effective reversal strategy. There is a paucity of prospective data and the studies that are published included such strict parameters that it is difficult to use them to develop recommendations. One spinal hematoma was reported in the initial dose-ranging study, at a dose that was determined to be twice that required for thromboprophylaxis.[192 193] A series of 1631 patients undergoing continuous neuraxial or deep peripheral block reported no serious hemorrhagic complications. However, the catheters were removed 36 hours after the last dose of fondaparinux and subsequent dosing was delayed for 12 hours after catheter removal.[194]

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING FONDAPARINUX

Low-dose fondaparinux (2.5 mg once per day)

We suggest holding low-dose fondaparinux (2.5 mg once per day) for 36 hours (young patients) to 42 hours (elderly patients) in healthy patients with normal renal function (grade IIC)

Remarks: these are new recommendations in the setting of low-dose administration and aXa level suggestions.

We suggest holding fondaparinux for a minimum of 58 hours in patients with moderate renal insufficiency (CrCl 30–50 mL/min) (grade IIC)

Remarks: these are new recommendations in the setting of low-dose administration and aXa level suggestions.

We suggest not performing neuraxial or deep plexus/peripheral blocks in patients with severe renal impairment (CrCl <30 mL/min) due to the 72 hours half-life (grade IIC)

Remarks: these are new recommendations in the setting of low-dose administration and aXa level suggestions.

We suggest testing aXa activity calibrated to fondaparinux if placing the needle prior to these recommended times is considered (aXa ≤0.1 IU/mL) (grade IIC)

Remarks: these are new recommendations in the setting of low-dose administration and aXa level suggestions.

High-dose fondaparinux (5–10 mg once per day)

We suggest holding fondaparinux for a minimum of 70 hours in young patients with normal renal function (grade IIC)

Remarks: these are new recommendations in the setting of high-dose administration and aXa level suggestions.

We suggest holding fondaparinux for a minimum of 105 hours in elderly patients with normal renal function (grade IIC)

Remarks: these are new recommendations in the setting of high-dose administration and aXa level suggestions.

We suggest testing aXa activity calibrated to fondaparinux if placing needle prior to the recommended times is considered (aXa ≤0.1 IU/mL) (grade IIC)

Remarks: these are new recommendations in the setting of high-dose administration and aXa level suggestions.

We suggest that neuraxial catheters be removed at least 6 hours *prior* to the first postoperative dose (grade IIC)

Remarks: there is no change in this recommendation.

FIBRINOLYTIC AND THROMBOLYTIC THERAPY

Pharmacology of fibrinolytics/thrombolytics

The fibrinolytic system dissolves intravascular clots as a result of the action of plasmin. Plasmin is produced by the cleavage of a single peptide bond of the inactive precursor, plasminogen. The resulting compound is a non-specific protease capable of dissolving fibrin clots and other plasma proteins, including several coagulation factors. Exogenous plasminogen activators, such as streptokinase and urokinase, dissolve thrombus and affect circulating plasminogen as well. Pharmacological t-PA formulations (Alteplase, Tenecteplase) are more fibrin-selective and have less effect on circulating plasminogen. Clot lysis leads to elevation of fibrin degradation products, which themselves have an anticoagulant antithrombotic effect by inhibiting platelet

aggregation. Given the nature of the underlying thrombotic medical conditions being treated, patients who receive fibrinolytic therapy frequently receive intravenous heparin to maintain an aPTT of 1.5–2 times normal. Often an antiplatelet agent such as aspirin or clopidogrel is also added. While the plasma half-life of thrombolytic drugs is only hours, it may take days for the thrombolytic effect to resolve. Fibrinogen and plasminogen are maximally depressed at 5 hours after thrombolytic therapy and remain significantly depressed at 27 hours.[195] Importantly, original contraindications to thrombolytic therapy included surgery or puncture of non-compressible vessels within 10 days.[196]

There are no large series addressing regional anesthesia in the patient receiving fibrinolytic/thrombolytic therapy. The majority of published reports involve *spontaneous* spinal or epidural hematomas after thrombolytic therapy.[130 197–211] Recent cases involve thrombolysis for myocardial infarction and bleeding has been reported at all spinal levels—cervical, thoracic, and lumbar.[149 212–215]

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/PERIPHERAL BLOCK IN THE PATIENT RECEIVING THROMBOLYTIC THERAPY

Patients receiving fibrinolytic/thrombolytic medications are at risk of serious hemorrhagic events, particularly those who have undergone an invasive procedure. Recommendations are based on the profound effect on hemostasis, the use of concomitant heparin and/or antiplatelet agents (which further increase the risk of bleeding), and the potential for *spontaneous* neuraxial bleeding with these medications.

In patients scheduled to receive thrombolytic therapy, we recommend that the patient be queried, and the medical record reviewed for a recent history of lumbar puncture, spinal or epidural anesthesia, or epidural steroid injection to allow appropriate monitoring. Guidelines detailing original contraindications for thrombolytic drugs suggest avoidance of these drugs for 10 days following puncture of non-compressible vessels (grade IA)

Remarks: there is no change in this recommendation.

In patients who have received fibrinolytic and thrombolytic drugs, we recommend against needle placement for at least 48 hours. Documentation of normalization of clotting studies (including fibrinogen) is suggested (grade IA)

Remarks: there is no change in this recommendation.

In those patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy, we recommend that frequent neurological monitoring (eg, every 2 hours) should be continued for at least 48 hours after the last dose. If neuraxial blocks have been combined with fibrinolytic and thrombolytic therapy and ongoing epidural catheter infusion, we recommend the infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurological function (grade IC)

Remarks: there is no change in this recommendation.

There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. We suggest the measurement of fibrinogen level (one of the last clotting factors to recover) to evaluate the presence of residual thrombolytic effect and appropriate timing of catheter removal. Patients should have frequent neurological monitoring for at least 48 hours following catheter removal (grade IIC)

Remarks: there is no change in this recommendation.

VITAMIN K ANTAGONISTS (WARFARIN)

Warfarin pharmacology

Warfarin exerts its anticoagulant effect by interfering with the synthesis of the vitamin K-dependent clotting factors VII, IX, X, and II (thrombin). The effects of warfarin are dependent on clotting factor half-lives and the anticoagulant effect is not apparent until there is a significant amount of biologically inactive clotting factors[216] (table 5). Clinical experience with patients who are congenitally deficient in factors II, IX, or X suggests that a factor activity level of 40% for each factor is adequate for normal or near-normal hemostasis.[217] Bleeding may occur if the level of any clotting factor is decreased to 20%–40% of baseline. The international normalized ratio (INR) is most sensitive to clotting factors VII and X[218] and is slightly prolonged when factor VII is reduced to approximately 55% of baseline. An INR of 1.5 is associated with a factor VII activity of 40%.[218] For this reason, INRs of 1.4 or less in patients who have not been on warfarin are not at increased risk for spinal bleeding.[8] During the first few days of therapy, the PT reflects primarily a reduction of factor VII, the half-life of which is approximately 6 hours (table 5). Discontinuation of warfarin requires normalization of the INR to ensure adequate activities of all the clotting factors.

Clinical use of warfarin

The measured response to anticoagulant therapy at the initiation of treatment varies significantly. Some of the variability may be attributed to age, female sex, pre-existing medical conditions (low patient weight, liver, cardiac, and renal disease), race, genetic polymorphisms, and drug interactions that are associated with an enhanced response to warfarin and/or a lower dose requirement for maintenance anticoagulation.[8 216 219 220] It has been documented that warfarin dose is inversely related to age and strongly associated with gender, with women being more susceptible.[221] In addition, patients with renal insufficiency may have an increased response to warfarin.[222] There are many drugs that interact with warfarin and potentiate the anticoagulant effect, including concomitant administration of antiplatelet medications, heparin, and LMWH.[216 223 224]

For patients taking warfarin, the first step in decision making is to establish the anticipated risk of bleeding with the proposed procedure and to determine whether the procedure can be performed without antithrombotic interruption.[166] For low-to-moderate bleeding risk surgeries where the anticipated 30-day risk of major bleed is <2%, strategies for periprocedural anticoagulation management can include a shorter interruption period with prompt re-initiation. For high-risk procedures where the anticipated 30-day bleeding risk exceeds 2%, a judicious strategy of anticoagulation interruption is necessary to ensure adequate hemostasis. The second decision-making step is to establish the indication(s) for anticoagulant therapy including an assessment

Table 5 Half-lives of vitamin K-dependent clotting factors

Factor half-life, hours	Half-life, hours
VII	6–8
IX	24
X	25–60
II	50–80

of the patient-specific thromboembolism risk. Risk stratification can be assessed as 'low,' 'intermediate,' or 'high' based on a number of clinical variables (table 3). The ACCP guidelines recommend against heparin bridging for patients at low-to-moderate thromboembolic risk. For patients at high risk of thromboembolism defined as a risk of arterial thrombosis of >10% per year or VTE risk exceeding 10% per month, bridging therapy may be used. The general approach to periprocedural warfarin management is to first choose a surgical date and then discontinue warfarin 5 days prior to this anticipated date. For those patients at high risk of thromboembolism, LMWH (enoxaparin 1 mg/kg two times per day) is initiated once the PT INR has fallen below the lower end of the target range. It is important to ensure that the CrCl (≥30 mL/min) and platelet counts ($\geq 100\times10^9$/L) are satisfactory if using LMWH. Alternatively, intravenous UFH can be used for the patient with severe kidney disease. The last dose of LMWH is given in the morning on the day preceding the day of the procedure. For patients at low-to-moderate risk of thromboembolism, no heparin bridging is indicated preprocedure or postprocedure.

Patients with mechanical heart valves receiving warfarin therapy scheduled for an invasive procedure first require an assessment of the bleeding risk of the proposed procedure.[225] The American Heart Association/American College of Cardiology guidelines recommend continued anticoagulant therapy for those procedures associated with a low risk of bleeding or where bleeding would be inconsequential. For higher bleeding risk procedures, patients with a bileaflet mechanical aortic valve prosthesis and no other risk factors, the risk of thromboembolism is sufficiently low such that bridging anticoagulant therapy can be avoided. For patients with a mechanical aortic valve prosthesis and associated thromboembolic risk factors, an older generation mechanical aortic valve prosthesis, or a mitral mechanical heart valve prosthesis, bridging therapy with LMWH is reasonable when the warfarin has been stopped and the INR is subtherapeutic.

For patients receiving warfarin therapy for the indication of VTE, bridging LMWH can be considered if the thrombotic event occurred within 3 months of the anticipated procedure, if there is active cancer, or if the patient has a documented severe thrombophilia.[226] Apart from these variables, warfarin can simply be stopped 5 days prior to the procedure and restarted after the procedure. Appropriate DVT prophylaxis is warranted during the periprocedural time interval prior to therapeutic warfarin resumption.

When there is an elevated INR without major bleeding, the warfarin can be reversed with oral vitamin K. Intravenous vitamin K can be administered when there is active bleeding.[216] When there is life-threatening bleeding, recombinant activated factor VIIa (rFVIIa), three-factor PCC which contain factors II, IX, and X, or four-factor PCC, containing factors II, VII, IX, and X, can be given. Activated rFVIIa and PCCs are better than FFP in reversing warfarin[227]; PCC is better than rFVIIa[228]; and four-factor PCC appears to be more effective than three-factor PCC.[216 229 230]

Neuraxial techniques in relation to the INR and in the chronically anticoagulated patient

Neuraxial injections and removal of epidural catheters appear to be safe when done within 24 hours after warfarin is initiated. This was documented by Parvizi *et al*,[231] who noted the absence of spinal hematoma in over 12 000 patients in whom they removed the epidural catheters within 24–48 hours of initiation of warfarin therapy. The safety of removing epidural catheters was also documented by other investigators.[222 232] No spinal hematoma occurred after removal of catheters 12–14 hours after warfarin therapy, even in the patients with INRs of 1.5–1.9. The mean (±SD) factor VII levels 12 hours after warfarin initiation were noted to be normal in the patients with INRs ≤1.4 and acceptable in the patients with INRs of 1.5–1.9.[233] Another group of investigators showed no spinal hematoma in 4365 patients when epidural catheters were removed while on warfarin; the mean duration of warfarin treatment was 2.1±0.6 days and the INRs at the time of removal was 1.9±0.4 (range 1.5–7.1).[232] In this study, no other anticoagulant was given except NSAIDs and the patients were closely monitored. A closer look at this study showed that most catheters (4090 patients) were removed on postoperative day (POD) 2 (day of surgery is POD 0); 140 were removed on POD 3. While it does not appear to increase risk to remove epidural catheters 12–24 hours after warfarin was initiated, the risk of removing epidural catheters at 48 hours is not guaranteed to be lower. This is because adequate activity of clotting factor VII is not certain, and activities of factors IX and X are starting to decline.

Warfarin should be discontinued for at least 5 days and the INR should be measured and normalized (per local laboratory) prior to performance of a neuraxial block. This is consistent with ESAIC/ESRA guidelines. Recommendations are based on warfarin pharmacology, the clinical relevance of vitamin K coagulation factor levels/deficiencies, case series, and the case reports of spinal hematoma among these patients. Websites are available to assist clinicians with warfarin dosing.[234]

Table 6 Three herbal medications with the greatest impact on hemostasis*

	Important effects	Perioperative concerns	Time to normal hemostasis after discontinuation
Garlic	Inhibition of platelet aggregation (may be irreversible) Increased fibrinolysis Equivocal antihypertensive activity	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	7 days
Ginko	Inhibition of platelet-activating factor	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	36 hours
Ginseng	Lowers blood glucose Increased prothrombin and activated partial prothrombin times in animals Other diverse effects	Hypoglycemia Potential to increase risk of bleeding Potential to decrease anticoagulant effect of warfarin	24 hours

Adapted from Horlocker *et al*.[9]
*At this time, it is not deemed necessary to discontinue herbal medications and allow resolution of their effects on hemostasis prior to surgery or anesthesia.

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/ PERIPHERAL BLOCK IN THE PATIENT ON WARFARIN

We recommend that the anticoagulant therapy be stopped 5 days prior to the planned procedure, and the INR be measured and normalized (normal range of the local laboratory) prior to needle placement (grade IB)

Remarks: there is no change in this recommendation.

In patients receiving an initial dose of warfarin prior to surgery, we suggest the INR should be checked prior to needle placement if the first dose was given >24 hours earlier, or if a second dose of oral anticoagulant has been administered (grade IIC)

Remarks: there is no change in this recommendation.

In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored daily (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that neuraxial catheters be removed when the INR is <1.5 (grade IIC)

Remarks: there is no change in this recommendation.

In patients with INR >1.5 but <3, the increased risk of maintaining a neuraxial catheter remains unknown. We suggest indwelling catheters may be maintained or removed with caution, closely following the INR and duration of warfarin therapy (grade IIC)

Remarks: there is no change in this recommendation.

In patients with an INR >3, we recommend that the warfarin dose be held or reduced in patients with indwelling neuraxial catheters (grade IA)
We can make no definitive recommendation regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion (grade IIC)

Remarks: there is no change in this recommendation.

We suggest that neurological assessment be continued for at least 48 hours following catheter removal (grade IIC)

Remarks: there is no change in this recommendation.

Neurological testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. To facilitate neurological evaluation, we recommend that the type of analgesic solution be tailored to minimize the degree of sensory and motor blockade (grade IC)

Remarks: there is no change in this recommendation.

HERBAL MEDICATIONS

There is a widespread use of herbal medications in surgical patients. Most patients do not volunteer information regarding herbal medication use and obtaining such a history may be difficult.[235–237] Morbidity and mortality associated with herbal use may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur. Such complications include bleeding from garlic, ginkgo, and ginseng, and potential interaction between ginseng-warfarin (table 6). There have been case reports of spontaneous neuraxial bleeding following ingestion of garlic[238] and gingko biloba.[239–242]

Despite the widespread use of herbal medications, there are few controlled clinical trials of the efficacy (or adverse effects) and few outcome studies of the effects of herbal medications on surgical patients; a prospective study including over 600 patients found no differences in surgical outcomes, including bleeding, in patients reporting recent herbal therapy.[243] However, while overall there does not appear to be a clinically significant increase in surgical bleeding or spinal hematoma in patients receiving herbal medications, data on the combination of herbal therapy with other forms of anticoagulation are lacking. The concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants or heparin, may increase the risk of bleeding complications in these patients. Thus, it is often recommended that these medications be discontinued in anticipation of surgery, but there is no reason for cancellation of the procedure if patients have not done so.[244]

MANAGEMENT OF NEURAXIAL BLOCK OR DEEP PLEXUS/ PERIPHERAL BLOCK IN PATIENTS USING HERBAL THERAPY

The use of herbal medications does not create a level of risk that will interfere with the performance of neuraxial blocks. We recommend against the mandatory discontinuation of these medications or avoidance of regional anesthetic techniques in patients on these medications (grade IC)

Remarks: there is no change in this recommendation.

ANTITHROMBOTIC THERAPY IN PREGNANCY

VTE is one of the most common causes of maternal morbidity and mortality, especially in high-resource countries.[245 246] Some of the risk factors that increase the incidence of thrombosis in pregnant and postpartum people include a personal history of VTE, thrombophilia, prolonged immobilization, and cesarean delivery.[247 248] The 6-week period following delivery is associated with a higher rate of thrombosis and PE than pregnancy itself.[249 250] For this reason, pharmacological thromboprophylaxis for pregnant people at high risk for VTE is often recommended, particularly in the postpartum period.[248]

The American College of Obstetricians and Gynecologists (ACOG), California Quality Maternal Care Collaborative, American Society of Hematology, and ACCP have each published obstetric thromboembolism guidance that has increased the likelihood that pregnant people requesting analgesia or needing urgent cesarean delivery will have recently received an anticoagulant which can potentially restrict their analgesic and anesthetic options. It is therefore critical that proactive, multidisciplinary planning takes place, incorporating the relative risks and benefits of neuraxial and general anesthesia to determine appropriate anticoagulant dosing and cessation times.

Physiological changes in pregnancy affecting thromboprophylaxis

Pregnancy is a hypercoagulable state in which platelet aggregation is enhanced, several coagulation factor levels rise, and protein C and S levels are decreased.[251] Physiological changes during pregnancy include an increased volume of distribution, clearance, bioavailability, and metabolism of many drugs.[252] Available data from studies examining the pharmacokinetics and pharmacodynamics of UFH suggest that, compared with non-pregnant people, aPTT response and duration of action of UFH in pregnancy may be decreased.[253 254] Similarly, for LMWH,

Box 1 Advantages of neuraxial versus general anesthesia for cesarean delivery in the obstetric patients

Mental benefits

Associated with decrease in anesthesia-related adverse events [295]

Reduces the risk of gastric aspiration.[296–298]

Avoids hypertensive response to intubation in vulnerable population (eg, pre-eclampsia).[298]

Avoids awareness under general anesthesia.[299]

Associated with less intraoperative blood loss and uterine atony.[300–302]

Associated with fewer surgical site infections.[303]

Provides superior quality with systemic opioid-sparing cesarean analgesia.

Reduces the risk of chronic postdelivery pain.[304 305]

Enables benefits of immediate postdelivery skin-to-skin bonding and breastfeeding.[306 307]

Improves maternal and paternal participation in birth.[307]

Fetal benefits

Associated with more favorable Apgar scores and umbilical venous pH.[308 309]

Avoids in utero exposure to induction/inhalational agents with potential developmental neurotoxicity.[310]

Enables benefits of immediate postdelivery skin-to-skin bonding and breastfeeding.[306 307]

peak aXa levels, duration of action, and the total exposure to the drug over time (area under the plasma activity vs time curve) are lower in pregnant patients versus non-pregnant or postpartum people.[253 255 256]

Neuraxial hematoma in the obstetric patient

The incidence of neuraxial hematoma after spinal or epidural blockade in the obstetric population is difficult to determine, although it is widely reported that these patients have a significantly lower incidence of this complication than older populations.[52] Moen *et al*[52] reported two spinal hematomas in obstetric patients with apparent coagulopathy (incidence 1:200 000); one after a subarachnoid block and one following the removal of an epidural catheter. This incidence was significantly lower than the incidence of 1:3600 in elderly females undergoing total knee arthroplasty. Bateman *et al*[257] confirmed the substantially lower risk of neuraxial hematoma in obstetric patients documenting seven epidural hematomas among 142 287 patients undergoing epidural anesthesia/analgesia (1:20 326) and none in obstetric patients. These findings are particularly notable since bloody taps, a reputed risk factor for neuraxial hematoma, are more common in the obstetric than in the general surgical population.[258]

A systematic review of English language publications (1952–2016) revealed no cases of neuraxial hematoma *due to neuraxial anesthesia and low dose (thromboprophylaxis) in obstetric patients*, although the denominator (total number of cases) was unknown.[259] The two patients that developed a hematoma had confounding issues: one had relevant symptoms before receiving the anticoagulant and the other developed symptoms after high-dose (therapeutic) anticoagulation for a PE. A subsequent publication reported the development of a neuraxial hematoma after spinal anesthesia for cesarean delivery when a larger dose of LMWH was administered post partum, earlier than the time interval recommended by ASRA guidelines.[260] Potential explanations for the lower incidence of neuraxial hematoma in obstetric compared with older, orthopedic patients include the hypercoagulable state and a more compliant epidural space, unimpeded by osteoporotic deformities, which can accommodate larger volumes of blood before symptomatic neural compression occurs.[52 54]

Neuraxial and general anesthesia in the obstetric patient

Neuraxial analgesia and anesthesia are particularly vital to the care of the obstetric patient. For labor, neuraxial analgesia provides superior pain relief to other modalities. Neuraxial labor analgesia also provides an in situ neuraxial catheter that can be converted to an anesthetic for cesarean delivery, and decreases circulating catecholamine levels which may be particularly beneficial for patients with pre-eclampsia or other comorbidities. Although the risk of death from neuraxial versus general anesthesia for cesarean delivery is not statistically different, avoidable (non-emergent) general anesthesia is associated with an increased odds of severe overall complications (aOR 2.9; 95% CI 1.6 to 5.2) and severe anesthetic complications (aOR 1.6; 95% CI 1.4 to 1.9).[261] These include surgical site infection, postoperative VTE, and hemorrhage (box 1).

Peripartum management of the obstetric patient

The peripartum management of the obstetric patient that receives anticoagulant medications presents a significant clinical challenge.[10 262] ACOG and the SOAP recommendations support every labor unit having a protocol for when anticoagulants should be stopped, and if short-term strategies such as converting to UFH, due to its shorter half-life, in anticipation of delivery should be considered.[262] In the event of unforeseen labor or urgent cesarean delivery, the choice of analgesia and/or anesthesia should balance the risks of general anesthesia and benefits of neuraxial anesthesia given the anticoagulant, dose, time of administration, and pertinent laboratory values. The plan for reinitiating anticoagulation post partum must also incorporate the anesthetic management and hemostasis after delivery.

MANAGEMENT OF NEURAXIAL BLOCK IN THE ANTICOAGULATED PARTURIENT

Given the limited pharmacological data on antithrombotic agents in pregnancy and in the absence of a large series of neuraxial techniques in the pregnant population receiving prophylaxis or treatment for venous thromboembolism, we suggest that the recommendations included in this document be applied to parturients (grade IIC)

Remarks: there is no change to this recommendation

However, in circumstances involving select high-risk parturients receiving VTE prophylaxis, and requiring urgent interventions for maternal or fetal indications, the risk of general anesthesia may be greater than neuraxial anesthesia, and exceptions/modifications of these recommendations may be appropriate (grade IIC)

Remarks: there is no change to this recommendation.

PLEXUS AND PERIPHERAL BLOCKADE IN THE ANTICOAGULATED PATIENT

Although neuraxial hematoma is the most concerning hemorrhagic complication of regional anesthesia due to the catastrophic

nature of bleeding into a fixed and non-compressible space, the associated risk following plexus and peripheral techniques remains undefined. The fear of bleeding, specifically in a deep, non-compressible site can deter providers from performing peripheral nerve blockade, even in patients who would likely benefit. Unfortunately, there continues to be a lack of investigations examining the frequency and severity of hemorrhagic complications following plexus or peripheral blockade in anticoagulated patients. In addition, there continues to be case reports of significant morbidity related to hematomas following peripheral nerve blockade in coagulopathic patients.[263–267] All published cases of clinically significant bleeding/bruising after plexus or peripheral techniques in patients with normal hemostasis were published in the previous edition.[263–266 268–281] A recent practice advisory published by the Regional Anesthesia and Acute Pain Section of the Canadian Anesthesiologists Society sought to stratify the bleeding risk into 'low risk,' 'intermediate risk,' or 'high risk' for peripheral nerve blocks and interfascial plane blocks.[282] Hemorrhagic complications following the deep plexus/deep peripheral techniques (including but not limited to those listed as high risk, eg, stellate ganglion, infraclavicular, lumbar sympathetic, lumbar plexus, and paravertebral), particularly in the presence of antithrombotic therapy, are often serious and a source of major patient morbidity.[282] These cases continue to suggest that significant blood loss, rather than neural deficits, may be the most serious complication.

MANAGEMENT OF DEEP PLEXUS/PERIPHERAL BLOCK IN THE ANTICOAGULATED PATIENT

For patients undergoing deep plexus or deep peripheral block, we recommend that guidelines for neuraxial block be similarly applied (grade IC)

Remarks: there is no change in this recommendation.

For patients undergoing other plexus or peripheral techniques, we suggest performance, catheter maintenance, and catheter removal be based on site compressibility, vascularity, and consequences of bleeding, should it occur (grade IIC)

Remarks: there is no change in this recommendation.

RECOMMENDATIONS OF THE ESAIC/ESRA

The previous European Society of Anaesthesiology guidelines on 'regional anesthesia and antithrombotic agents' were published in 2010.[280] In the same year, ASRA also published its third edition of similar guidelines.[8] The fourth edition of the ASRA guidelines in 2018 were the result of a collaboration with ESA to construct a single set of guidelines.[9] As a result, the differences were only minimal. The most recent European guidelines were a collaborative effort of both the ESAIC and the ESRA and were published in February 2022.[11]

In the resulting recommendations, the wording 'prophylactic' or 'therapeutic' doses was replaced by 'low' and 'high' for the DOACs, the LMHWs, UFH, fondaparinux, and aspirin, as both the dose used and the indication, along with the presence of risk factors, influence the pharmacokinetics in the individual patient.

The present ESAIC/ESRA guidelines now recommend a complete resolution of the VKA effect (similar to the ASRA recommendation) and a return of the INR to the normal range of the local laboratory (eg, ≤1.1). The low-dose DOAC-free time intervals were based on the half-lives of the drugs in the presence of mild/moderate renal insufficiency (CrCl ≥30 mL/min) and/or advanced age but were prolonged in the case of severe renal insufficiency (CrCl 15–29 mL/min) for edoxaban and rivaroxaban. A high-dose DOAC-free time interval of 72 hours was recommended for all DOACs, while laboratory testing was recommended in the presence an impaired kidney function (DXA's CrCl <30 mL/min; dabigatran CrCl <50 mL/min). The time intervals to resume DOAC treatment after removal of the neuraxial catheter now consider the planned DOAC dose. In contrast, the management of patients receiving low-dose UFH, low-dose LMWH, low-dose fondaparinux, and antiplatelet therapy have remained quite similar to the ASRA guidelines. Therapy-free time intervals are recommended in the presence of high-dose UFH and LMWH treatment, but so is the use of target laboratory values, especially in the presence of a CrCl <30 mL/min. Like ASRA, superficial nerve blocks can be performed without any therapy-free time interval and irrespective of the dose of the antithrombotic drug used. In contrast, deep nerve blocks should be performed according to the more stringent recommendations for neuraxial procedures. Finally, in obstetric patients requiring a neuraxial block for delivery or cesarean section, the same recommendations as those advocated for the non-pregnant population should be followed. However, a deviation from the current guidelines may be considered in selected cases (eg, a parturient with high thrombotic risk who requires an unplanned or urgent fetal or maternal intervention, in whom the risk of general anesthesia outweighs the risk of a neuraxial technique), following a multidisciplinary discussion and a careful risk-benefit analysis.

UNPLANNED ANTICOAGULATION DURING NEURAXIAL ANALGESIA

Occasionally, patients require emergent antithrombotic therapy (vascular graft thrombosis, acute coronary syndrome/myocardial infarction), or a breakdown in communication results in unanticipated anticoagulation in the presence of indwelling epidural catheters. It is critical that the acute pain medicine service be aware of alterations in the degree and timing of anticoagulation. Increasing centralization and computerization make it possible for hospital pharmacy services to assist with patient management. Since all medication orders are filled by pharmacists using a central computer, patients who receive an epidural infusion are identified within the pharmacy database. Any subsequent order for an antithrombotic agent is flagged as a drug 'interaction' during entry, and the pharmacist receives an alert notice to contact the pain service. The pain service is then able to consult in a multidisciplinary manner with other services involved in the patient's care. The timing of catheter removal will be based on the ongoing risk of thromboembolism, the need for continued antithrombotic therapy, and the potential for neuraxial bleeding during catheter maintenance and removal. This 'pharmacy failsafe' allows the anesthesia acute pain service to participate proactively in the timing of catheter removal and subsequent anticoagulation, as well as closely monitor the patient's neurological status.[281]

SUMMARY

Practice guidelines or recommendations summarize evidence-based reviews. However, the rarity of spinal hematoma defies a prospective-randomized study, and there is no current laboratory model. As a result, these *consensus statements* represent the collective experience of recognized experts in the field of neuraxial anesthesia and anticoagulation. They are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding with appropriate grading of the level of evidence and strength of the

recommendations. An understanding of the complexity of this issue is essential to patient management and this consensus statement cannot be applied universally to the complex scenarios that may confront clinicians. Rather, the decision to perform spinal, epidural, or deep plexus/peripheral anesthesia/analgesia, as well as the timing of catheter removal in a patient receiving antithrombotic therapy, should be made on an individual basis. This decision should weigh the small, though definite, risk of neuraxial hematoma against the benefits of regional anesthesia for the specific patient, as well as the risks of withholding these benefits. Alternative anesthetic and analgesic techniques exist for patients whose risk of regional anesthesia exceeds the expected benefit. The patient's coagulation status should be optimized at the time of spinal or epidural needle/catheter placement, and the level of anticoagulation must be carefully monitored during the period of epidural catheterization. Indwelling neuraxial catheters should not be removed in the presence of therapeutic anticoagulation, as this appears to significantly increase the risk of spinal hematoma. Identification of risk factors and establishment of guidelines will not completely eliminate the complication of spinal hematoma.[283] In the series by Vandermeulen *et al*, although 87% of patients had a hemostatic abnormality or difficulty with needle puncture, 13% had no identifiable risk factor.[53] Vigilance in monitoring is critical to allow early evaluation of neurological dysfunction and prompt intervention. Protocols must be in place for urgent MRI and hematoma evacuation, if there is a change in neurological status. We must focus on the prevention of neuraxial hematoma and on rapid diagnosis and treatment to optimize neurological outcomes. Anesthesiologists need to further weigh the risks and benefits in settings where imaging and surgical decompression are not options. Documentation of the risks, benefits, and alternatives is also recommended.

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