Periprocedural management of patients on oral anticoagulation: focus
on regional anesthesia

Authors: Jinlei Li, Adriana D. Oprea

Article type: Review article

Received: May 19, 2020.

Accepted: June 1, 2020.

Published online: June 3, 2020.

ISSN: 1897-9483

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.
Periprocedural management of patients on oral anticoagulation: focus on regional anesthesia

Jinlei Li, MD PhD¹, Adriana D. Oprea, MD¹

¹ Associate Professor of Anesthesiology, Yale School of Medicine, New Haven CT

Name of Department(s) and Institution(s)

From the Department of Anesthesiology, Yale School of Medicine, New Haven, CT, United States of America

Disclaimers

None

Corresponding author

Adriana D. Oprea, MD

Department of Anesthesiology

333 Cedar St, TMP 3

PO Box 208051

New Haven, CT 06520-8051

United States of America

Tel: +1 203 785 2802

Fax: +1 203 785 6664

E-mail: adriana.oprea@yale.edu

Reprints
None applicable

Financial support
None

Conflicts of interest
None

Running title:
Regional anesthesia in patients on oral anticoagulants
Abstract

Management of anticoagulant medications in patients undergoing regional anesthesia procedures remains an evolving topic. As with all procedures, the goal is maintaining a balance between bleeding and thrombotic risks when interrupting oral anticoagulants. In contrast with operating room procedures, where the blood loss volume is probably the most important concern, for regional anesthesia procedures it is the location of the bleeding event that takes precedence. For neuraxial anesthesia and deep plexus and peripheral nerve blocks, a lower volume bleed in an enclosed, deep, and noncompressible area can result in transient or permanent neuronal damage. Differences exist between current guidelines for management of oral anticoagulants, likely due to patients’ anatomy, practitioner experience and standardized use of imaging modalities for different procedures.

Key words: direct oral anticoagulants, regional anesthesia, vitamin K antagonists
Periprocedural Management of Patients on Oral Anticoagulation: Focus on Regional Anesthesia

Introduction

An increasing number of patients receive chronic oral anticoagulant (OAC) therapy to mitigate the risk of thromboembolic complications due to atrial fibrillation (AF), mechanical heart valves or history of venous thromboembolism (VTE). Internists, cardiologists, hematologists, anesthesiologists, and surgeons often care for such patients who need to undergo elective or emergent medical procedures. The balance between the risk of thromboembolism and the risk of bleeding should be carefully maintained and fine-tuned perioperatively in order to maximize benefits and minimize risks.[1,2] This review discusses the commonly used anticoagulants prescribed during the periprocedural period with a focus on appropriate considerations for regional anesthesia. Several societies have recently updated their guidelines on the subject, including the American Society of Regional Anesthesia and Acute Pain (ASRA) and the European Society of Anaesthesiology (ESA).[3-5]

Oral Anticoagulants Pharmacology

Vitamin K antagonists (VKA) - warfarin and acenocumarol - block the synthesis of the vitamin K–dependent clotting factors (II, VII, IX, and X). Rapidly absorbed from the gastrointestinal tract, their blood levels peak a few hours after administration. As compared to warfarin, which has a long half-life of 36–42 h, acenocumarol has a half-life of 8-11 h.[6,7] The anticoagulant effect is monitored by the prothrombin time (PT) or
target international normalized ratio (INR) values. An INR of <1.1 is considered normal in healthy patients, however some data point towards almost normal coagulation factor levels with an INR close to 2 (30% clotting factor activity).[8]

It should be noted that the INR may not reflect a decrease in all vitamin K dependent clotting factors simultaneously. When starting or stopping warfarin, the INR value mirrors initially the activity of factor VII (half-life 6-8 h), with 5 days being necessary for all coagulation factors to decrease to < 40% or increase to >40%, respectively. Moreover, at the start of warfarin therapy, there is an initial prothrombotic state (conferred by decreases in levels of vitamin K dependent natural anticoagulation factors protein C and S). Therefore, in patients who need to be therapeutically anticoagulated rapidly with warfarin, a bridging agent may be necessary for the first few days. For most indications, an INR of 2.0–3.0 is recommended. Patients at high thrombotic risk, such as patients with mechanical mitral valves, older generation aortic mechanical valves (Starr Edwards or ball-in-cage) and mechanical valves having suffered a recent stroke (< 6 months) should be maintained at a higher INR 2.5–3.5.

In the past decade, direct oral anticoagulants (DOACs) have been introduced to the market and have increasingly replaced VKAs for many indications. These include the direct thrombin inhibitor, dabigatran, as well as several anti-Xa agents such as: rivaroxaban, apixaban, edoxaban and betrixaban (Table 1). As compared to warfarin, all DOACs have a rapid onset of action and peak serum level achieved within 1-4 hours. Moreover, all DOACs have a component of renal excretion, which affects the drugs’ half-life. In addition to the traditional indications, the anti-Xas (with the exception of betrixaban) have also been studied in patients with cancer, where they were found to be
non-inferior in comparison to LMWH.[9-11] All DOACs with their clinical indications and relevant pharmacokinetic properties are presented in Table 1.[12-18]

**Periprocedural Management of Oral Anticoagulants**

Periprocedural management of OACs relies on balancing the risk of thrombosis while temporarily stopping the OAC with the risk of bleeding incurred by the medication. While some procedures can be performed continuing the OAC, for most procedures (especially for patients undergoing neuraxial blocks (NBs)), the medication needs to be stopped in advance, as to allow for normalization of the coagulation process. For patients and/or procedures that require temporary interruption of the OAC, the risk of thrombosis could be mitigated through bridging therapy (UFH or LMWH). This is of particular importance in patients on VKA when long half-lives of VKA and factors II and X require the OACs to be discontinued more than a few days prior to the procedure.

**Procedural Bleeding Risk Assessment**

Periprocedural bleeding can be frequently categorized into two types, major and minor, based on the amount and location of blood loss, with major being defined as greater of 2g/dl drop on hemoglobin, or requiring transfusion of at least 2 units of packed red blood cell, or hemodynamically instability or bleeding into a critical site.[19] More recently, the International Society of Thrombosis and Haemostasis classifies bleeding risk (BR) based on a 48 h periprocedural time frame, with 2-4% as high BR and less than 2% as low BR.[20] With the exception of procedures at very high BR in enclosed spaces (such as intracranial, intrathecal, epidural space, and posterior chamber of the eye), the
volume of blood loss is the most common factor contributing to negative consequences in operating room procedures. In contrast, for regional anesthesia techniques, clinically relevant heavy bleeding is only occasionally seen in a small subset of procedures, where a large amount of blood loss may occur in anatomically deep, non-expandable and non-compressible locations. For example, lumbar plexus blockade has been reportedly associated with rare, yet significant, retroperitoneal bleeding.

More commonly, a major concern for regional anesthesia procedures is due to the close proximity to vital structure, such as spinal cord (spinal anesthesia), spinal nerve and nerve root (epidural anesthesia, paravertebral block), nerve plexus (cervical, brachial, lumbar and sacral plexus block) and nerve (major peripheral nerve such as sciatic nerve, femoral nerve). In this context, the location of bleeding is more important than the volume of blood loss. Similar to intracranial bleeding, a relatively small bleed can result in devastating consequences.[21] Neurological injury due to bleeding is mostly a secondary ischemic event, due to either hematoma compression of a vital structure and/or its feeding vessels, and/or direct injury to the feeding vessels to the vital structure.

Another difference between surgery versus regional anesthesia-related bleeding is that regional anesthesia patients are frequently symptomatic before a critical blood loss is reached. The major differences between typical surgical bleeding where volume blood loss is more important and regional anesthesia bleeding where location is more relevant may explain the major differences in anticoagulation guidelines issued by American College of Cardiology [19,22] and ASRA.[3,5]

The assessment of the BR in a particular patient while planning for an invasive surgical procedure should start with the severity of surgical bleeding.[23] Once the risk of
surgical bleeding is deemed acceptable, the second step would be determining specific regional anesthesia options, with their BR and planning for mitigation of bleeding, should it occur. As discussed above, NBs are considered high BR procedures by ASRA Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy (Fourth Edition) (ASRA regional).[3] Also ASRA regional considers superficial easily compressible plexus or peripheral nerve blocks (PNBs) as low risk, whereas deep blocks pose the similar BR as NB.[3] (Table 2)

There are differences in the Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition) (ASRA pain) and ASRA regional guidelines, with the similar or the same procedure being assessed differently in the two publications (Table 2).

In addition, rating of BR is not necessarily linked with guidelines. ASRA pain classifies epidural steroid injection, sympathetic, and paravertebral blocks as intermediate risk procedures, and all PNB as low risk. [21] In contrast, ASRA regional deems NB (including epidural) and deep PNB/plexus blocks (such as paravertebral) as high risk, and only superficial and compressible nerve blocks are ranked as low risk. [3] Despite lower BR rating for similar procedures, most pain procedures call for longer duration before resumption of oral anticoagulation agents or agents with anticoagulation effects. These discordances between ASRA pain and ASRA regional for the same procedure may be explained by a different patient population, with interventional pain (IP) procedures usually performed in post-surgical patients where changes and less forgiving anatomy as well as a much higher rate of direct visualization during procedure performance and less diversity in proceduralists requiring board certification or at least special credentialing.
Although the assessment and categorization of bleeding risk in regional anesthesia, especially severe bleeding with clinically relevant consequences, has not yet been established, a systemic approach has been recently proposed and named CIA (Critical, Intervention, Assess).[24] CIA is based on the sum of three factors: the proximity of the regional anesthesia location to critical structures, whether an invasive intervention is need in the event of bleeding, and whether there can be quick and easy identification of bleeding. Each contributing factor is scored from 0 (if absent) to 1 (if present), with the resultant CIA score ranging from 0 to 3, with 0 as low risk, 1 as intermediate risk, 2 and 3 as high risk for bleeding in regional anesthesia specifically.[24] It should be pointed out that, with the introduction of ultrasound, many regional anesthesia procedures can be performed under direct visualization. As such, the risks of venous and arterial puncture have significantly decreased. However, the risk of postoperative neurological deficits remains the same, leading to the assumption that the major risks of perioperative nerve injury may be unrelated to regional anesthesia.[25,26] Controversy exists as to BR classification in regional anesthetic techniques. While ASRA’s regional anesthesia bleeding risk assessment of PNBs is mostly based on anatomical considerations and data from NB, the expert consensus from the Regional Anesthesia and Acute Pain Section of the Canadian Anesthesiologists Society (CAS) takes into account of the above mentioned CIA score and the absolute number of reported bleeding events for the specific plexus and nerve block discussed.[27] One caveat to this classification is that, since the total number of a specific plexus and nerve blocks performed as compared to the reported cases complicated by bleeding is unknown, the prevalence of bleeding for a certain regional procedure remains debatable. In addition, the level of expertise among
proceduralists may vary among different plexus and nerve block, for example an unexperienced proceduralist is more likely to start with a TAP block than an anterior sciatic nerve block, which further complicates the difficulty in precisely predict bleeding risk in regional anesthesia.

Nonetheless, the consensus from CSA is arguably the only available classification specifically focused on PNBs and it recommends ultrasound to be used routinely to prevent complications [28].

**CSA classification of low BR:**

Occipital block and superficial cervical plexus blocks are devoid of serious complications, as bleeding in that location is readily identified, therefore considered at low risk. Axillary brachial plexus block, while in proximity to the axillary artery and veins, is an easily compressible site, therefore considered at low BR as hematomas have been rarely noted in large studies.[29] Suprascapular as well as upper extremity PNBs (radial, median and ulnar) are considered to be at low risk for bleeding, as no bleeding complications have been described. Superficial blocks such as lateral femoral cutaneous, infrainguinal fascia iliaca and ankle block are easily compressible and the BR is low.[27]

**CSA classification of intermediate BR:** Proximal upper extremity blocks such as interscalene, supra- and infraclavicular brachial plexus blocks are considered at intermediate risk with reported vascular injections in 0.63%, 0.4 % and 0.7% of cases in retrospective reviews.[30-32] Retroclavicular brachial plexus block has been recently described and no data are available as to its intravascular puncture risk. Interfascial block such as transverse abdominal plane (TAP), iliohypogastric ilioinguinal nerve, serratus anterior, pectoral nerve (PECS) and rectus sheath are superficial, however complications
such as bleeding and hematomas have been reported.[33,34] These blocks are considered at intermediate BR as well as newer blocks for which data are not available (erector spinae block).[28] Intercostal blocks present concerns similar to paravertebral blocks, although there are few reports of hematomas; as such, this block is deemed to be at intermediate BR. Femoral block, despite its superficial nature, was reportedly associated with retroperitoneal hematoma formation in one report and is considered at intermediate BR.[35] Other intermediate risk lower extremity blocks include adductor canal, sciatic nerve block in most locations (popliteal, transgluteal, subgluteal, and anterior approach), obturator and suprainguinal fascia iliaca, however evidence-based data are not available.[27]

**CSA classification of high BR:** Deep cervical block could result in intravascular injection (vertebral artery, supra or infrascapular artery) and a hematoma could have dire consequences of airway compression.[36] As such, the CAS considers deep cervical block a high risk bleeding procedure, despite no complications reported during cervical block in patients undergoing carotid endarterectomy, who are frequently continued on coagulation altering medications for the procedure[27]. Lumbar plexus block is deeply situated and despite use of nerve stimulators and under ultrasound guidance, hematomas are still occasionally reported especially in patients with multiple passes or on coagulation altering drugs.[37-42] Therefore, lumbar plexus block is deemed to be a high BR procedure as well as the parasacral sciatic nerve block, due to their proximity to vascular structures.[3,27] Quadratum lumborum is a deep block with a needle aiming to a noncompressible space; this is considered at high BR.[43] Paravertebral blocks are generally considered at high BR given the structures (nerves and vessels) present in the
space as well as the lack of access and compressibility of the space and difficulty in
detecting pleural puncture. Though multiple reports have described it as an alternative to
NB in patients deemed at high risk of bleeding (either anticoagulated or
thrombocytopenic), the guidelines call for the same coagulation status requirement.

Classifying procedures into low, intermediate and high risk is only one of the facets
of BR assessment. The other component should take into account patient’s specific BR as
it relates to comorbidities that might increase bleeding as well as concurrent
administration of medications other than OACs that alter coagulation (such as herbal
supplements, NSAIDs or antiplatelet agents). The HAS BLED score is a tool available
for quantifying patient BR, extrapolated from the AF literature. It takes into account
several conditions- Hypertension, Abnormal kidney or liver function, Stroke, Bleeding
history, Labile INR, Elderly (age >65), Drugs or alcohol, each being assigned 1 point
(patients with a HAS BLED score of >3 are considered high risk). When it relates to
anticoagulation management, an OAC interruption time may need to be longer when
patient’s BR is high even if the procedural risk is considered low.

Thromboembolic Risk and Bridging

Thromboembolic risk assessment:

As with traditional surgical procedures, thrombotic risk while interrupting OACs
should be quantified. Historically, the risks has been defined as low, intermediate or high
based on a yearly rate of <5%, 5-10% or >10%, respectively.[44] Patients’ thrombotic
risk depends on the indication for OAC. Traditionally, the CHADS₂ and CHA₂DS₂ VASc
scores have been used in assessing the stroke risk for patients with AF. These scores take
into account certain comorbidities, such as Congestive heart failure, Hypertension, Age >75, Diabetes, Stroke, Vascular disease, Age 65-74 and female Sex (each gets 1 point with the exception of A2 and S2, which are assigned 2 points). CHA2DS2-VASc scores of 7-9 or CHADS2 of 5-6, or a history of recent embolic stroke (<3 months) place patients at high thrombotic risk. Similarly, patients with mechanical valves (mitral, older aortic valves, stroke/ transient ischemic attack < 6 months prior) as well as patient with multiple or very recent VTE events (within 3 months), or severe thrombophilies have traditionally been regarded as at high risk.

**Bridging while on VKA**

Historically, in order to mitigate thrombotic risk, patients on warfarin requiring temporary interruption have been bridged with heparin or low molecular weight heparin (LMWH) in the periprocedural period. Patients at low thrombotic risk- AF with CHA2DS2-VASc scores of 0-4, VTE events >12 months prior or bileaflet aortic valves without risk factors for stroke (low ejection fraction, antiphospholipid antibody syndrome, thrombophilias) do not require bridging with LMWH or UHF. Controversy exists as far as bridging recommendations for patients in the intermediate thrombotic risk category. Traditionally, the decision for bridging has been left to the discretion of the prescribing provider, however, there is mounting evidence describing an increased surgical bleeding risk in patients bridged with LMWH with little benefit pertaining to protection against thrombosis.[45] In patients with AF at low and moderate thrombotic risk (CHADS2 scores of 0-4), the BRIDGE trial has not detected a thrombotic benefit for bridging, which was associated with increased rated of minor and major bleedings.[46] Recently, given bleeding concerns, bridging is not endorsed by recent guidelines published the
American Society for Hematology for patients at intermediate risk for VTE treated with warfarin.[47] Similarly, the PERIOP 2 trial that randomized patients with AF and/or mechanical valves to bridging with dalteparin vs. interrupting warfarin alone detected no difference in the rates of thromboembolism and bleeding between the two groups.[48]

The most commonly used bridging agents for VKAs are subcutaneous LMWHs. (Table 3) Generally, LMWH is started 48 h after warfarin discontinuation, with the last dose given at half dose 24 h prior to the planned surgery. Recent data suggested the dose of bridging LMWH may be decreased in elderly or those with renal impairment as significant anti-Xa activity was present in these patients 24 hours after last therapeutic dose of LMWH. Intravenous UFH infusion could be an alternative, however it requires hospital admission with frequent monitoring of the aPTT.[3] For patients at risk for VTE, while bridging with therapeutic dose LMWH is not generally recommended for the considerations discussed above, different prophylactic (lower dose) regimens of either subcutaneous LMWH or UFH can be prescribed. Considerations for bridging regimens and regional anesthesia are discussed in Table 3.

**Bridging while on DOACs**

In contrast with warfarin, DOACs have short half-lives and predictable pharmacokinetics; bridging therapy is generally not required or indicated.[22,49] Moreover, the recently published international multicenter Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) trial found that, in patients with AF, foregoing bridging therapy was safe. In this study, using a standardized protocol for interrupting the DOAC based on procedural bleeding risk generally resulted in <2% major bleeding rates and <1% stroke rates.[50] At this time, there are no data available as to whether
considerations for no bridging can apply for DOACs in patients at high VTE thrombotic risk, such as those with very recent thromboses or active cancer.

**Temporary Interruption of OAC in Preparation for Regional Anesthesia**

**Temporary Interruption of VKA**

Warfarin and acenocumarol are the most commonly used VKA in the United States and Europe, respectively. Differences exist between their pharmacologic properties and between the ASRA pain and ASRA regional (Table 3) and the recent Canadian Society bleeding risk stratification. It is widely accepted in clinical practice (as well as supported by guidelines and current evidence) that low risk bleeding procedures (whether PNBs or IP procedures) may be performed safely while continuing the VKA with therapeutic INR less than 3.0 after careful consideration of existing comorbidities with specific weighing the risk of bleeding versus thromboembolic events.[5,27,51,52]

For procedures deemed to be at high bleeding risk, such as NB (spinal and epidural), deep plexus (lumbar, sacral) or deep PNBs (paravertebral), the VKA agent is required to be discontinued for 5 day (warfarin) and 3 days (acenocumarol). In addition, a normal INR (<1.1) or at least an INR<1.4 (per 2010 ESA guidelines) should be documented prior to procedure [44] as 7% of patients will still have an INR >1.5 after off warfarin for five days.[53] For those patients with an INR of 1.5 to 1.9 the day prior to surgery, administration of oral vitamin K (as low as 1 mg) could further lower the INR to 1.4 in greater than 90% of cases.[54] For patients at high thrombotic risk, a bridging regimen as described above may be recommended. (Table 3)
Decision-making for intermediate risk IP procedures or PNBs remains a grey zone. A conservative approach would represent following recommendations for high risk bleeding procedures. However, using an ultrasound guidance technique by an experienced provider would allow more leeway when deciding to proceed with some anticoagulant activity on board. Similarly, patients undergoing low risk procedures could, in fact, be at an increased risk if they are elderly, have high HAS BLED scores or take other medications that affect hemostasis (herbal medication, NSAIDs or antiplatelet agents).

**Pearls in periprocedural management of warfarin**

1. Activity level of vitamin K dependent clotting factors (II, VII, IX and X) at 40% or greater are considered adequate for hemostasis [55], whereas activity levels of less than 20% are associated with bleeding.[56]

2. The INR has be to regularly monitored, due to narrow therapeutic index and wide variation among patients due to a variety of factors (e.g. genetics, diet).[57]

3. Given the mechanism of action, while warfarin’s half-life is important, its periprocedural management relies also on its effect on protein synthesis and factors’ II, VII, IX and X half-lives.

4. There is an initial (first several days) dissociation between INR values and the degree of anticoagulation or hemostasis, as INR reflect mostly factor VII activity levels.

5. Approximately 5 days are necessary for all vitamin K dependent coagulation factor activity to increase to >40% and the INR to normalize (required for normal hemostasis especially for high risk bleeding procedures such as NBs)
6. A NB can be performed within 24 h of warfarin administration without checking an INR (as long as only one dose was given). Similarly, postprocedurally, a catheter can be removed within 24 h of warfarin administration without checking an INR.

7. If patients require a bridging regimen, LMWH or UFH are discontinued or restarted postprocedurally as per Table 3.

8. The resumption of warfarin may occur as soon as post-operative hemostasis has been achieved. Patients who require perioperative bridging are frequently restarted on bridging until INR is therapeutic for 48 h. (Table 3)

**Temporary Interruption of DOACs**

While the DOACs are generally safe as far as bleeding profile, the relative risk associated with DOAC vs. warfarin in regional anesthesia has not been systemically studied.

Considerations for management of DOACs prior and after regional procedures as recommended by ASRA pain, ASRA/ESA regional, mostly extrapolated from the existing data on major bleedings such as hemorrhagic strokes and gastrointestinal bleeding, are detailed in Table 3.

**Pearls in periprocedural management of DOACs**

1. DOACs have short half-lives, therefore, in contrast to warfarin they only need to be stopped a few days prior to the regional anesthesia and pain procedures.

2. DOACs are generally not bridged with LMWH or UFH, given their short interruption times, as well as concerns with increased bleeding with bridging.
3. All DOACs have some degree of renal excretion; as such, knowledge of the patient’s renal function (creatinine clearance rather than creatinine level) as well as its impact on the drug’s half-life is necessary when a tailored approach is desired for performing a regional procedure.

4. Differences exist between recommendations for DOAC management from the ASRA regional as compared to ASRA pain or the ESA guidelines.[3,5] However, there is consensus as far as discontinuing DOACs for 5 half-lives prior to high risk bleeding procedures (see section of warfarin management), as less than 3% of residual anticoagulant effect remains.[5]

5. Low risk bleeding procedures such as compressible PNBs, performed by skilled providers and under ultrasound guidance (if applicable) could be performed without stopping the DOAC or after observing a 2 half-life interruption period, which would provide a reasonable balance between thrombosis protection while having ~ 25% residual anticoagulant on board.[5] Similarly, it is prudent for patients at moderate/high risk of bleeding undergoing low/moderate risk procedures to observe a longer interruption period (5 half-lives) as recommended by ASRA regional.

6. Recommendations from ASRA regional regarding DOAC management err towards the conservative side, given their novelty, lack of experience and scarcity of safety data as pertaining to regional procedures with them as compared with warfarin.

7. As compared to warfarin, where bleeding can be easily treated without major side effects, reversal agents for DOACs do not exist for all drugs, they have been
recently made available on the market and their use is not devoid of serious side effects.

8. Standard coagulation testing is not routinely performed or recommended prior to surgical procedures or regional anesthetics, which is one of the advantages of DOACs over VKAs. However, there are clinical situations where clinicians do need to know with certainty whether an anticoagulant effect is present. The aPTT could be a qualitative indicator signaling presence of dabigatran; a normal aPTT excludes above on therapy levels of dabigatran but does not exclude presence of therapeutic levels of the drug.[58,59] The PT is not affected by apixaban. However, a normal PT excludes above on therapy levels of rivaroxaban and edoxaban but not on therapy levels of rivaroxaban or above on therapy levels of edoxaban at trough.[58-60]

9. Direct measurement of DOAC anticoagulant activity is not widely used in clinical practice as tests are expensive, have long turnover times, and not readily available in every laboratory. Moreover, the lowest level at which a surgical or invasive procedure can be safely performed is not known, but most recommendations point towards a <50 ng/ml cut off.[61] The dilute thrombin time and ecarin clotting test correlate linearly with dabigatran activity. Similarly, the anti-Xa activity is ideally measured using an anti-Xa assay calibrated for the specific anticoagulant. If available, they could guide clinical decisions in patients needing regional procedures when less than 5 half-lives have passed since the last dose of DOAC and a regional procedure is desired or an inadvertent administration of the DOAC occurred in the presence of an indwelling epidural catheter.[3,62-64]
Urgent or Emergent Interventions: Reversal of Oral Anticoagulation

While regional procedures are generally elective, occasionally a NB may be desired in patients at very high risk for general anesthesia. Anti-fibrinolytics such as tranexamic acid and epsilon-aminocaproic acid are helpful in minimizing bleeding. Knowledge of options for reversal of commonly used OACs is necessary and could be especially useful when bleeding complications occur with inadvertent administration of OACs very close to neuraxial puncture.

VKA action could be counteracted by administration of vitamin K. Administration of vitamin K 2.5 mg orally or intravenously (higher risk of anaphylaxis) can lead to normalization of the INR within 18-24 h. Reversal of VKAs can be rapidly achieved with administration of fresh frozen plasma (FFP) at rates of 15ml/kg. The infusion of FFP, nonetheless, takes time and is associated with significant volume load that could be concerning in patients with compromised cardiopulmonary status. Moreover, given the short half-life of factor VII, FFP should be administered every 6-8 h, in order to maintain an appropriate level of coagulation factors. In addition to volume overload, patients receiving high volumes of FFP could be at risk for transfusion associated acute lung injury (TRALI). Recent advancement allows for rapid and efficient reversal of warfarin effect (within 30 minutes) following administration of prothrombin complex concentrates (3 or 4 factor PCC). The dose of PCC is calculated based on the INR level and the factor IX content of the product. For INRs of 2-4, 4-6 and >6, 25, 35, and 50 U of factor IX/kg body weight should be, respectively, administered. The advantage of PCC-mediated reversal of warfarin effects is its rapid effect, fast preparation and small volume.
However, at doses of more than 25 U/kg, there is a prothrombotic tendency directly proportional with the dose.

The need for DOAC reversal is rare due to short half-lives, and reversal should be considered only under emergency or life-threatening bleeding circumstances. There are no readily available point-of-care laboratory studies to guide the initiation or monitoring of reversal effects. These are a composite decision based on clinical scenario, pharmacodynamics and laboratory tests.[19]

There are several options for addressing bleeding in the setting of dabigatran use. Hemodialysis is an option, specifically in patients where procedures or the consequences of bleeding are not immediate. When emergent reversal is needed, idarucizumab (Praxbind), a monoclonal antibody and the specific antidote for dabigatran, is the first line treatment administered intravenously at the dose of 5 g divided in 2 vials. It leads to almost complete reversal of dabigatran action, with a low risk of prothrombotic events.[65,66] Occasionally, a second idarucizumab dose is needed, if bleeding and/or a prolongation of clotting time recur within 24 h of reversal, mostly due to redistribution of dabigatran from the extravascular space into the blood vessels.[67,68] In the absence of idarucizumab, activated PCC such as factor eight inhibitor bypassing activity (FEIBA)-50 to 80 IU/kg, 3- or 4-factor PCC- 25-50 U/kg, or recombinant factor VII are viable options for urgent reversal. [69]

For anti-Xa inhibitors, hemodialysis is not an option (high degree of protein binding). Andexanet alfa (Andexxa) has been approved as an antidote for rivaroxaban and apixaban associated bleeding. Andexanet is a decoy Xa protein that binds the anti-Xa, reversing its anticoagulant effect.[70,71] It is administered in high or low dose,
considering the dose of anticoagulant as well as the timing elapsed since the last dose.
Andexanet should be reserved for treatment of life-threatening and neuraxial bleeding
due to rivaroxaban or apixaban, given its cost as well as a high risk of thrombotic events.
The FDA black box cautions as to a high risk of myocardial infarction, strokes, arterial
and thromboses, as well as sudden death with administration of andexanet.[72] 4 factor
PCC 2000 U is suggested as an alternative when andexanet is not available.[69]
Betrixaban and edoxaban related bleeding could be reversed with off label high dose
andexanet or 2000 U of 4-factor PCC.[69] Other options for all anti-Xas include
recombinant factor VIIa (90 μg/kg) and aPCC (FEIBA) can be used at 90 to 100 IU/kg
intravenously, albeit with an increased thrombotic risks.

**Current Status and Future Directions**

Evaluation of a patient’s overall health condition and past medical history is the
critical step to allow providers to stratify the patient’s periprocedural thrombotic and
bleeding risk. Assessing thrombotic risk is a critical step in periprocedural management
of VKA, however all current recommendations and data support a no bridging approach
for the DOACs regardless of thromboembolic risk.

There are a significant amount of clinical data and pharmacodynamic reasoning
backing up the current ASRA pain and ASRA regional guidelines, but there are also
many unknowns. As such, clinicians should use the guideline in a more fluid rather than
rigid way in conjunction with specific clinical scenarios, weighing risks and benefits. For
example, ESRA’s 2010 guideline specifically provided guidelines on DOAC at
prophylactic doses, and recommended these to be held for 2 half-lives before an invasive
procedure. This 2 half-lives requirement is consistent with the ASRA regional recommendation for catheter removal during incidental DOAC administration in the presence of an indwelling catheter. At this moment the DOACs are deemed incompatible with any indwelling catheters based on limited clinical data, yet the removal of catheter only calls for 2 half-lives rather than the 5 half-lives required for the placement of NBs. With accumulating clinical data, one would expect sufficient evidence-based knowledge to back up a differential management of patients on prophylactic vs. therapeutic doses of DOAC.

Less data are available on the safety of various types of PNB than for NBs, which have a much longer history of clinical application. Nonetheless, it is clear that nerve injury in PNB is not the same as in NBs when it comes to bleeding around the neuronal tissues. While bleeding into a neurovascular sheath may result in significant decreases in hematocrit, the expandable nature of peripheral site may decrease the chance of irreversible neural ischemia.[3] Significant blood loss, rather than neural deficits, may be the most serious complication of non-neuraxial regional techniques in the anticoagulated patient. While hemorrhagic complications following the deep plexus/deep peripheral techniques, particularly in the presence of antithrombotic therapy, are often serious and a source of major patient morbidity, most complications occurred in earlier cases with less visualized techniques such as trans-arterial for axillary brachial plexus block, with paresthesia technique and without imaging modalities such as ultrasound or fluoroscopy.[27] This is could be one of the reasons epidural anesthesia is considered intermediate risk of bleeding in ASRA pain guideline as the standard of care in pain practice for epidural injection is under direct imaging-guided visualization, while in
ASRA regional, it is classified as high risk of bleeding as most epidural anesthesia is performed by body landmark blind technique.

Although the current ASRA regional guideline is focused on NB, it does recognize the difference between central and peripheral regional anesthesia and does allow room for adjustment based on clinical judgement for PNBs. In the authors’ opinion, before a universal bleeding risk guideline specifically for PNB is made available by major governing agencies, an institution-specific guideline can be adopted as the interim, taking into considerations of not only ASRA regional guideline, but also the local factors in a specific institution, including but not limited to regional anesthesia expertise levels of proceduralists, history of bleeding prevalence for each plexus and nerve block, and if imaging guidance is readily available. This small-scale guideline based on institutional evidence will help maintain a balance between observance of ASRA guideline principles, taking advantage of the uniqueness of PNB as compared to NB, and optimization of care in practical clinical practice.

References

1. van Veen JJ, Makris M. Management of peri-operative anti-thrombotic therapy. Anaesthesia. 2015; 70: 58-67, e21-23.

2. Eisele R, Melzer N, Bramlage P. Perioperative management of anticoagulation. Chirurg. 2014; 85: 513-519.

3. Horlocker TT, Vandermeuilen E, Kopp SL, et al. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of
4. Gogarten W, Vandermeulen E, Van Aken H, et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol. 2010; 27: 999-1015.

5. Narouze S, Benzon HT, Provenzano D, et al. Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition): Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med. 2018; 43: 225-262.

6. Daniels PR. Peri-procedural management of patients taking oral anticoagulants. BMJ. 2015; 351: h2391.

7. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. Clin Pharmacokinet. 2005; 44: 1227-1246.

8. Dzik WS. Reversal of drug-induced anticoagulation: old solutions and new problems. Transfusion. 2012; 52: 45S-55S.

9. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med. 2020; 382: 1599-1607.

10. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med. 2018; 378: 615-624.
11. Fuentes HE, McBane RD, Wysokinski WE, et al. Direct Oral Factor Xa Inhibitors for the Treatment of Acute Cancer-Associated Venous Thromboembolism: A Systematic Review and Network Meta-analysis. Mayo Clin Proc. 2019; 94: 2444-2454.

12. Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol. 2010; 70: 703-712.

13. Dias C, Moore KT, Murphy J, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis. Am J Nephrol. 2016; 43: 229-236.

14. Chang M, Yu Z, Shenker A, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. J Clin Pharmacol. 2016; 56: 637-645.

15. Mandernach MW, Beyth RJ, Rajasekhar A. Apixaban for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism: an evidence-based review. Ther Clin Risk Manag. 2015; 11: 1273-1282.

16. Ridout G, de la Motte S, Niemczyk S, et al. Effect of renal function on edoxaban pharmacokinetics (PK) and on population PK/PD model. J Clin Pharmacol. 2009:1124

17. Minor C, Tellor KB, Armbruster AL. Edoxaban, a Novel Oral Factor Xa Inhibitor. Ann Pharmacother. 2015; 49: 843-850.

18. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American
College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 63: e57-185.

19. Fabbro M, Dunn S, Rodriguez-Blanco YF, Jain P. A Narrative Review for Perioperative Physicians of the 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. J Cardiothorac Vasc Anesth. 2019; 33: 290-301.

20. Spyropoulos AC, Brohi K, Caprini J, et al. Scientific and Standardization Committee Communication: Guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: Recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. J Thromb Haemost. 2019; 17: 1966-1972.

21. Oprea AD, Noto CJ, Halaszynski TM. Risk stratification, perioperative and periprocedural management of the patient receiving anticoagulant therapy. J Clin Anesth. 2016; 34: 586-599.

22. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017; 69: 871-898.

23. Barnes GD, Mouland E. Peri-Procedural Management of Oral Anticoagulants in the DOAC Era. Prog Cardiovasc Dis. 2018; 60: 600-606.

24. Tsui BCH. A systematic approach to scoring bleeding risk in regional anesthesia procedures. J Clin Anesth. 2018; 49: 69-70.
25. Barrington MJ, Watts SA, Gledhill SR, et al. Preliminary results of the Australasian Regional Anaesthesia Collaboration: a prospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications. Reg Anesth Pain Med. 2009; 34: 534-541.

26. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med. 2013; 38: 289-299.

27. Tsui BCH, Kirkham K, Kwofie MK, et al. Practice advisory on the bleeding risks for peripheral nerve and interfascial plane blockade: evidence review and expert consensus. Can J Anaesth. 2019; 66: 1356-1384.

28. Ueshima H. Pneumothorax after the erector spinae plane block. J Clin Anesth. 2018; 48: 12.

29. Stan TC, Krantz MA, Solomon DL, et al. The incidence of neurovascular complications following axillary brachial plexus block using a transarterial approach. A prospective study of 1,000 consecutive patients. Reg Anesth. 1995; 20: 486-492.

30. Sandhu NS, Manne JS, Medabalmi PK, Capan LM. Sonographically guided infraclavicular brachial plexus block in adults: a retrospective analysis of 1146 cases. J Ultrasound Med. 2006; 25: 1555-1561.

31. Perlas A, Lobo G, Lo N, Brull R, et al. Ultrasound-guided supraclavicular block: outcome of 510 consecutive cases. Reg Anesth Pain Med. 2009; 34: 171-176.
32. Bert JM, Khetia E, Dubbink DA. Interscalene block for shoulder surgery in physician-owned community ambulatory surgery centers. Arthroscopy. 2010; 26: 1149-1152.

33. Long JB, Birmingham PK, De Oliveira GS, et al. Transversus abdominis plane block in children: a multicenter safety analysis of 1994 cases from the PRAN (Pediatric Regional Anesthesia Network) database. Anesth Analg. 2014; 119: 395-399.

34. Ueshima H, Otake H. Ultrasound-guided pectoral nerves (PECS) block: Complications observed in 498 consecutive cases. J Clin Anesth. 2017; 42: 46.

35. Wiegel M, Gottschaldt U, Hennebach R, et al. Complications and adverse effects associated with continuous peripheral nerve blocks in orthopedic patients. Anesth Analg. 2007; 104: 1578-1582.

36. Hakl M, Michalek P, Sevcik P, et al. Regional anaesthesia for carotid endarterectomy: an audit over 10 years. Br J Anaesth. 2007; 99: 415-420.

37. Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. Anesthesiology. 2003; 98: 581-585.

38. Aida S, Takahashi H, Shimoji K. Renal subcapsular hematoma after lumbar plexus block. Anesthesiology. 1996; 84: 452-455.

39. Dauri M, Faria S, Celidonio L, et al. Retroperitoneal haematoma in a patient with continuous psoas compartment block and enoxaparin administration for total knee replacement. Br J Anaesth. 2009; 103: 309-310.
40. Klein SM, D'Ercole F, Greengrass RA, Warner DS. Enoxaparin associated with psoas hematoma and lumbar plexopathy after lumbar plexus block. Anesthesiology. 1997; 87: 1576-1579.

41. Aveline C, Bonnet F. Delayed retroperitoneal haematoma after failed lumbar plexus block. Br J Anaesth. 2004; 93: 589-591.

42. Warner NS, Duncan CM, Kopp SL. Acute Retroperitoneal Hematoma After Psoas Catheter Placement in a Patient with Myeloproliferative Thrombocytosis and Aspirin Therapy. A A Case Rep. 2016; 6: 28-30.

43. Visoiu M, Pan S. Quadratus lumborum blocks: Two cases of associated hematoma. Paediatr Anaesth. 2019; 29: 286-288.

44. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141: e326S-350S.

45. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation. 2012; 126: 1630-1639.

46. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015; 373: 823-833.

47. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018; 2: 3257-3291.
48. Kovacs M, Rodger M, Wells P, et al. Double Blind Randomized Control Trial of Postoperative Low Molecular Weight Heparin Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism (PERIOP 2). Blood. 2018; 132: 424.

49. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39: 1330-1393.

50. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. JAMA Intern Med. 2019; 179: 1469-1478.

51. Ahmed I, Gertner E. Safety of arthrocentesis and joint injection in patients receiving anticoagulation at therapeutic levels. Am J Med. 2012; 125: 265-269.

52. Conway R, O'Shea FD, Cunnane G, Doran MF. Safety of joint and soft tissue injections in patients on warfarin anticoagulation. Clin Rheumatol. 2013; 32: 1811-1814.

53. Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation. 2004; 110: 1658-1663.

54. Woods K, Douketis JD, Kathirgamanathan K, et al. Low-dose oral vitamin K to normalize the international normalized ratio prior to surgery in patients who require temporary interruption of warfarin. J Thromb Thrombolysis. 2007; 24: 93-97.
55. Xi M, Beguin S, Hemker HC. The relative importance of the factors II, VII, IX and X for the prothrombinase activity in plasma of orally anticoagulated patients. Thromb Haemost. 1989; 62: 788-791.

56. Loeliger EA. The optimal therapeutic range in oral anticoagulation. History and proposal. Thromb Haemost. 1979; 42: 1141-1152.

57. Zineh I, Pacanowski M, Woodcock J. Pharmacogenetics and coumarin dosing--recalibrating expectations. N Engl J Med. 2013; 369: 2273-2275.

58. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost. 2018; 16: 209-219.

59. Gosselin RC, Adcock DM, Douxfils J. An update on laboratory assessment for direct oral anticoagulants (DOACs). Int J Lab Hematol. 2019; 41: 33-39.

60. Siegal DM, Konkle BA. What is the effect of rivaroxaban on routine coagulation tests? Hematology Am Soc Hematol Educ Program. 2014; 2014: 334-336.

61. Tripodi A, Braham S, Scimeca B, et al. How and when to measure anticoagulant effects of direct oral anticoagulants? Practical issues. Pol Arch Intern Med. 2018; 128: 379-385.

62. Sarode R. Direct oral anticoagulant monitoring: what laboratory tests are available to guide us? Hematology. 2019; 2019: 194-197.

63. Denny NDR, Keighley L, Siganporia Z, et al. A level-headed approach to measuring direct oral anticoagulants: A 2-year retrospective analysis of DOAC levels from a tertiary UK centre. Int J Lab Hematol. 2019; 41: 200-207.
64. Gu TM, Garcia DA, Sabath DE. Assessment of direct oral anticoagulant assay use in clinical practice. J Thromb Thrombolysis. 2019; 47: 403-408.

65. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015; 373: 511-520.

66. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017; 377: 431-441.

67. Crowther M, Cuker A. How can we reverse bleeding in patients on direct oral anticoagulants? Kardiol Pol. 2019; 77: 3-11.

68. Łopatowska P, Młodawska E, Sobkowicz B, et al. Redistribution of dabigatran after idarucizumab administration in a 90-year-old woman with renal failure due to persistent large intestinal bleeding. Pol Arch Intern Med. 2019; 129: 932-933.

69. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol. 2019; 94: 697-709.

70. Powell J, Taylor J, Garland SG. Andexanet alfa: A Novel Factor Xa Inhibitor Reversal Agent. Ann Pharmacother. 2019: 53: 940-946.

71. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015; 373: 2413-2424.

72. Tao J, Oprea AD. Periprocedural Anticoagulation Management For Nonoperating Room Anesthesia Procedures: A Clinical Guide. Semin Cardiothorac Vasc Anesth. 2019; 23: 352-368
| Drug        | Warfarin, Acenocumarol | Dabigatran | Rivaroxaban | Apixaban | Edoxaban | Betrixaban |
|-------------|-------------------------|------------|-------------|----------|----------|------------|
| Brand name  | (Marevan®)              | (Sintrom®) | (Pradaxa®)  | (Xareto®) | (Eliquis®) | (Savaysa®) |
| Mechanism   | Vitamin K antagonist    | Vitamin K antagonist | Direct thrombin inhibitor | Factor Xa inhibitor | Factor Xa inhibitor | Factor Xa inhibitor |
| Indications | Stroke reduction in valvular and non-valvular AF | Stroke reduction in valvular and non-valvular AF | Stroke reduction in non-valvular AF | Stroke reduction in non-valvular AF | Stroke reduction in non-valvular AF | VTE prophylaxis in adult patients hospitalized for acute illness |
| VTE treatment | VTE treatment        | VTE treatment and prevention | VTE treatment and prevention | VTE treatment and prevention | VTE treatment and prevention | VTE treatment and |
| and prevention | Mechanical valves | Mechanical valves | Mechanical valves | Mechanical valves |
|----------------|-------------------|-------------------|-------------------|-------------------|
| VTE prophylaxis | VTE prophylaxis | VTE prophylaxis | VTE prophylaxis |
| after hip replacement surgery | after hip replacement surgery | after hip/knee replacement surgery | |
| Time to peak effect | 1.5 h | 1-3 h | 2 h | 2-4 h | 1-3 h | 1-2 h | 3-4 h |
| Excretion | Hepatic, oxidative metabolism | Hepatic, oxidative metabolism | 80% Renal | 36% Renal | 25% Renal | 35% Renal | 5-7% Renal |
| Half-life | 12-14 h (CrCl >80) | 8.3 (5-9 h) (CrCl >80) | 15.1 h (CrCl >80) | 10-14 h (CrCl >80) | 19-27 h (normal CrCl) |
| Duration  | 36-42 h | 8-11 h | mL/min) | mL/min) | mL/min) | mL/min) | No data for renal insufficiency |
|-----------|---------|--------|---------|---------|---------|---------|--------------------------------|
| 15 h (CrCl 50-79 mL/min) | 8.7 hours (CrCl 50-80 mL/min) | 14.6 hours (CrCl 50-80 mL/min) | 8.4 hours (CrCl 50-80 mL/min) |
| 18 h (CrCl 30-49 mL/min) | 9 h (CrCl 30-50 mL/min) | 17.6 (CrCl 30-50 mL/min) | 9.4 (CrCl 30-50 mL/min) |
| 27 h (CrCl 15-29 mL/min) | 9.5 (CrCl 15-29 mL/min) | 17.3 (CrCl 15-29 mL/min) | 16.9 (CrCl 15-29 mL/min) |
| 30 h (CrCl) | 13.2 (CrCl) | No data (CrCl) | No data (CrCl) |
### Monitoring of anticoagulant effect

|                     | Required, PT/ INR | Required, PT/ INR | Not required | Not required |
|---------------------|-------------------|------------------|--------------|--------------|
| Specific tests      | Specific tests    | include dilute   | include dilute| ecarin clotting time |
|                     |                   | thrombin time    |              |               |
| Specific test       |                   | Specific test:   |              |               |
|                     |                   | anti-Xa test     |              | calibrated for the specific anti-Xa agent |

### Reversal agents

|                     | Vitamin K | Vitamin K | Idarucizumab | Andexanet alfa | Andexanet alfa | 3- or 4- factor PCC | 3- or 4- factor PCC |
|---------------------|-----------|-----------|--------------|----------------|----------------|---------------------|---------------------|
| 3- or 4- factor PCC | 3- or 4-factor PCC | 3- or 4- factor PCC | 3- or 4- factor PCC | 3- or 4- factor PCC | aPCC (FEIBA) | aPCC (FEIBA) | aPCC (FEIBA) | aPCC (FEIBA) |
| Fresh               | Fresh frozen | aPCC (FEIBA) | aPCC (FEIBA) | aPCC (FEIBA) | Andexanet | Andexanet | Andexanet | Andexanet |
| Periprocedural bridging | frozen plasma | plasma | Recombinant factor VII | Recombinant factor VII | alfa (off label) | alfa (off label) |
|------------------------|--------------|--------|------------------------|------------------------|------------------|------------------|
| Use                    | On the decline | On the rise | Generally not recommended, due to short half-lives, predictable pharmacokinetics and increased bleeding with bridging |

AF, atrial fibrillation; VTE, venous thromboembolism; PT, prothrombin time, INR, international normalized ratio; aPTT, activated thromboplastin time; PCC, prothrombin complex concentrate, aPCC, activated prothrombin complex concentrate; FEIBA, factor eight inhibitor bypassing activity; CrCl, creatinine clearance
| Bleeding risk | Low risk | Intermediate risk | High risk |
|---------------|----------|-------------------|-----------|
| Guideline     |          |                   |           |
| ASRA regional |          |                   |           |
| Superficial and compressible plexus or peripheral nerve blocks | Other procedures based on compressibility, comorbidities, body habitus as well as duration and intensity of anticoagulation | Neuraxial blocks |
| ASRA pain     |          |                   |           |
| Peripheral nerve blocks | Interlaminar ESI | Spinal cord stimulator placement |
| Peripheral joint and musculoskeletal | Transforaminal ESI | Dorsal root ganglion stimulation |
| Injection                                      | Procedure                          | Equipment                          |
|-----------------------------------------------|------------------------------------|------------------------------------|
| Trigger point injection, including piriformis | Cervical facet block               | Intrathecal catheter and pump implant |
| Thoracic and lumbar facet block               | Sympathetic blocks                 | Vertebral augmentation/kyphoplasty |
| Sacroiliac injection                         | Trigeminal ganglion block          | Percutaneous decompression laminectomy |
| Peripheral nerve stimulation and implant      | Sphenopalatine ganglion block      | Epiduroscopy and epidural decompression |
| Pocket revision and implantable pulse generator/intrathecal | | |
| Procedure                        | Block Type                                    | Block Type                                      | Block Type                               |
|----------------------------------|-----------------------------------------------|------------------------------------------------|-------------------------------------------|
| pump replacement                 |                                               |                                               |                                           |
| CAS                             | Occipital nerve block                         | Interscalene block                             | Deep cervical plexus block               |
|                                 | Superficial cervical plexus                   | Supraclavicular brachial plexus                | Paravertebral block                      |
|                                 | Axillary brachial plexus                      | Infraclavicular brachial plexus                | Lumbar plexus block                      |
|                                 | Median nerve block                            | Popliteal sciatic                             | Quadratus lumborum block                 |
|                                 | Radial nerve block                            | Subgluteal sciatic block                       | Parasacral sciatic block                 |
|                                 | Ulnar nerve block                             | Transgluteal sciatic block                     |                                           |
|                                 | Lateral femoral cutaneous nerve block         | Anterior sciatic block                        |                                           |
| Ankle block | Femoral nerve block |
|-------------|---------------------|
|             | Rectus sheath block |
|             | PECS block          |
|             | TAP block           |
|             | Erector spinae      |
|             | blocks              |

PECS, pectoralis nerve; TAP, transversus abdominis; CAS, Canadian Society of Anesthesiologists; ESI, epidural steroid injection
### Table 3. Periprocedural management of antithrombotics

| Drug                  | 2018 Interventional Pain ASRA Guidelines | 2018 Regional ASRA Guidelines | ESA 2010 guidelines |
|-----------------------|------------------------------------------|------------------------------|---------------------|
|                       | When to discontinue                      | When to restart              | When to discontinue | When to restart |
| High and intermediate |                                          |                              |                     |                   |
| Low bleeding risk     |                                          |                              |                     |                   |
|                  | Intravenous heparin | Subcutaneous heparin 5,000 U twice a day | Subcutaneous heparin 5,000 U three |
|------------------|---------------------|----------------------------------------|----------------------------------|
| e bleeding risk  | 6 hours             | 6 hours                                | 24 hours                         |
|                  | 6 hours             | 6 hours                                | 6 hours                          |
|                  | 2 hours             | 2 hrs for low risk                     | 6-8 hrs for intermediate         |
|                  | 4-6 hours           | 4-6 hours                              | 4-6 hours                        |
|                  | before to needle    | immediate                              | 1 hour after nontraumatic needle placement and catheter removal (normal aPTT documented) | 1 hour after nontraumatic needle placement and catheter removal |
|                  | position and catheter removal | 1 hour | 4-6 hours | 1 hour |
| Subcutaneous heparin 7500-10000 U twice a day (< 20000 U/day) | Subcutaneous heparin > 10000U/dose or > 20000 U/day | LMWH Prophylactic dosing |
|-------------------------------------------------------------|------------------------------------------------------|--------------------------|
| NA                                                          | NA                                                   | 12 hours                 |
| NA                                                          | NA                                                   | 12 hours before needle placement or
| NA                                                          | NA                                                   | Single daily dosing       |
| 12 hours                                                    | 12 hours                                             | 12 hours                 |
| 4 hours after a low risk                                    |                                                      | 4 hours                  |
| 12 hours before needle placement or
|                                                            |                                                      | 12 hours before needle placement or
|                                                            |                                                      | Single daily dosing       |
|                                                            |                                                      | 12 hours                 |
|                                                            |                                                      | 4 hours                  |
- **Enoxaparin 30 mg** twice a day
- **Enoxaparin 40 mg** daily
- **Deltaparin 5000 units** daily

| Procedure | Catheter Removal | First Dose | Second Dose | At Least 4 Hours After Catheter Removal |
|-----------|-----------------|------------|-------------|----------------------------------------|
| 12-24 hours after a intermediate or high | | 12 hours after needle placement | 24 hours after the first dose | Twice daily dosing |
| | | | At least 4 hours after catheter removal | Not recommended |
| Risk Procedure | With Catheter in Place |
|----------------|------------------------|
| At Least 12 Hours After Needle/Catheter Placement |
| 4 Hours After Catheter Removal |

**LMWH Therapeutic Dosing**

- **Enoxaparin**
  - **1.5 mg/kg**

| 24 hours | 24 hours | 4 Hours After Catheter Removal if Negligible Procedure | 24 Hours | Epidural Catheter Contraindicated |
|----------|----------|-------------------------------------------------------|---------|---------------------------------|
|          |          |                                                      |         |                                 |
| 24 hours |          |                                                      |         |                                 |
|          |          |                                                      |         |                                 |

| 4 Hours | 24 Hours | 4 Hours After Catheter |
|---------|----------|------------------------|
|         |          |                        |
|         |          |                        |
| Drug                      | Dosage                                  | Bleeding Risk | Time After Procedure |
|---------------------------|-----------------------------------------|----------------|----------------------|
| Dalteparin                | 120 units twice a day or 200 units daily | bleeding risk | 24 hours after    |
| Tinzaparin                | 175 U/kg daily                          | bleeding risk | 24 hours after    |
| Warfarin                  | Stop for 5 days and INR ≤ 1.2 on        | 6 hours        | 48-72 hours after   |
|                           | Discontinuation may not be necessary if |                | a high risk bleeding|
|                           | INR < 1.4                               |                | procedure          |
|                           | INR < 1.4                               |                | After catheter     |
|                           | Remove catheter when INR is < 1.5       |                | removal            |
|                           |                                        |                | INR < 1.4           |
|                           |                                        |                | After catheter     |
|                           |                                        |                | removal            |
| Coumadin | INR <3 | Restart any time after needle placement or catheter removal |
|----------|--------|----------------------------------------------------------|
| If not on coumadin INR ≤ 1.4 in high and intermediate risk | | |

| Dabigatran | 4 days (normal renal function) | 5 days before puncture, catheter manipulation or removal | 6 hours after puncture, catheter manipulation or removal | For prophylaxis 150-220 mg, contraindicated |
|------------|-------------------------------|--------------------------------------------------------|--------------------------------------------------------|----------------------------------------|
|            | 5-6 days (impaired renal function) | 24 hours | 6 hours | 6 hours |
|            | Shared assessment and risk stratification, a 2 half-life interval may be | 24 hours | 6 hours after puncture, catheter manipulation or removal | 6 hours |

*Alternative graded approach if*
| renal function | stable and no additional bleeding risk factors |
|---------------|-----------------------------------------------|
| 72 hours      | If given with catheter in place, wait 34-36 h until removal |
| (CrCl > 80 mL/min) |                                              |
| 96 hours (CrCl of 50 to 79 mL/min) |                                              |
| 120 hours (CrCl of 30 to 49 mL/min) |                                              |
| caution against |                                              |
| Rivaroxaban   | 3 days in all pts | 24 hours | 3 days before puncture, catheter manipulation or removal | 6 hours after puncture, catheter manipulation or removal | For prophylaxis, 10 mg daily 22-26 hours | 4-6 hours |
|---------------|------------------|----------|--------------------------------------------------------|-------------------------------------------------------|------------------------------------------|----------|
|               |                  |          | neuraxial blocks when CrCl < 30 mL/min                 |                                                       |                                          |          |
|               |                  |          | If given with catheter in place, wait 22-26 h until catheter |                                                       |                                          |          |
| Drug    | Dosing Requirements | Time Before Puncture/Catheter Manipulation | Time After Puncture/Catheter Manipulation | Purpose                                                                 | Time Until Catheter Removal |
|---------|---------------------|------------------------------------------|------------------------------------------|-------------------------------------------------------------------------|------------------------------|
| **Apixaban** | 3 days in all pts | 24 hours                                | 3 days before puncture, catheter manipulation or removal | 6 hours after puncture, catheter manipulation or removal | For prophylaxis, 2.5 mg daily 26-30 h If given with catheter in place, wait 26-30 h until catheter removal | 4-6 hours                  |
| **Edoxaban** | 3 days in all pts | 24 hours                                | 3 days before puncture, catheter          | 6 hours after puncture, catheter                                       | NA                           | NA                         |
|            | manipulation or removal | manipulation or removal | If given with catheter in place, wait 22-28 h until catheter removal |
|------------|-------------------------|-------------------------|-------------------------------------------------------------------|
| **Betrixaban** | 5-6 days | 3 days | 24 hours | 3 days before puncture, catheter manipulation or removal |
|            |            |            |          | 5 hours after puncture, catheter manipulation or removal |
|            |            |            |          | Contraindicated if Cr Cl< 30 |
|            |            |            |          | If given with catheter in |
|            |            |            |          | NA |
|            |            |            |          | NA |
| mL/min | place, wait 72 h until catheter removal |

LMWH, low molecular weight heparin; aPTT, activated partial thromboplastin time; INR, international normalized ratio; ASRA, American Society of Regional Anesthesia and Pain Medicine; CrCl, creatinine clearance; NA, not available