SPECIAL ARTICLE

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

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Abstract: The American Society of Regional Anesthesia and Pain Medicine (ASRA) 2012 survey of meeting attendees showed that existing ASRA anticoagulation guidelines for regional anesthesia were insufficient for their needs. Those surveyed agreed that procedure-specific and patient-specific factors required separate guidelines for pain and spine procedures. In response, a guidelines committee was formed. After preliminary review of published complications reports and studies, the committee stratified interventional spine and pain procedures according to potential bleeding risk: low-, intermediate-, and high-risk procedures. The ASRA regional anesthesia anticoagulation guidelines were largely deemed appropriate for the low- and intermediate-risk categories, but the high-risk category required further investigation. The first guidelines specific to interventional spine and pain procedures were published in 2015. Recent reviews evaluating bleeding complications in patients undergoing specific interventional pain procedures, the development of new regional anesthesia and acute pain guidelines, and the development of new anticoagulants and antiplatelet medications necessitate complementary updated guidelines. The authors desired coordination with the authors of the recently updated regional and acute pain anticoagulation guidelines. The latest evidence was sought through extensive database search strategies and the recommendations were evidence based when available and pharmacology driven otherwise. We could not provide strength and grading of these recommendations because there are not enough well-designed large studies concerning interventional pain procedures to support such grading. Although the guidelines could not always be based on randomized studies or on large numbers of patients from pooled databases, it is hoped that they will provide sound recommendations and the evidentiary basis for such recommendations. This publication is intended as a living document to be updated periodically with consideration of new evidence.

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A survey was conducted among participants at the "Anticoagulation/Antiplatelets and Pain Procedures" open forum held at the American Society of Regional Anesthesia and Pain Medicine (ASRA) annual fall meeting in 2012. The purpose of the survey was to determine the safe practice patterns of pain physicians regarding continuance of concurrently administered anticoagulants, timing schedules for cessation and resumption of use, and any use of "bridging" therapies when planning for various interventional pain procedures. The survey items included specific practice characteristics and whether active protocols were utilized. In addition, the survey queried the frequency of adherence to specific elements of the current ASRA practice guidelines for regional anesthesia and/or if respondents incorporated different protocols for different pain procedures.[1]

One hundred twenty-four active participants attended the open forum. Responses were collected using an audience response system. Eighty-four percent of respondents were anesthesiologists, and the remainders were physical medicine and rehabilitation physicians, neurologists, orthopedic surgeons, and neurological surgeons.

The vast majority of respondents (98%) followed ASRA regional anesthesia guidelines for anticoagulants but not for antiplatelet agents. Two-thirds of the participants (67%) had separate protocols regarding aspirin (acetylsalicylic acid [ASA]) or nonsteroidal anti-inflammatory drugs (NSAIDs). Moreover, 55% stopped ASA before spinal cord stimulation (SCS) trials and implants, and 32% stopped ASA before epidural steroid injections (ESIs). However, 17% admitted that they used different protocols for cervical spine injections as compared with lumbar spine injections. Most did not express familiarity with selective serotonin reuptake inhibitors' (SSRIs') effects on platelets. Only 36% knew that SSRIs can lead to a bleeding disorder.

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Based on these results, the need for separate ASRA guidelines, specifically for interventional spine and pain procedures in patients on antiplatelets/anticoagulants, was self-evident. The Board of Directors of the ASRA recommended that the *Regional Anesthesia and Pain Medicine* appoint a committee to develop separate guidelines for pain interventions.[2] The committee has an international representation and was endorsed by the European Society of Regional Anesthesia and Pain Therapy, American Academy of Pain Medicine, the International Neuromodulation Society, North American Neuromodulation Society, and the World Institute of Pain. The recommendations were published in the *Regional Anesthesia and Pain Medicine* in 2015.[1]

These recommendations were timely as there has been a growing interest in this topic spanning several years, as evidenced by the recent publications of cases of epidural hematoma during interventional pain procedures in patients receiving antiplatelet agents (ASA and NSAIDs).[3–5]

The current ASRA guidelines for the placement of epidural and spinal catheters do not recommend cessation of these antiplatelet agents for epidural procedures, nor do the guidelines differentiate between interventional pain procedures and perioperative regional anesthesia blocks.[2]

The development of new anticoagulants and antiplatelet medications as well as the recent publications evaluating bleeding complications in patients undergoing specific interventional spine and pain procedures including facet procedures, ESIs, percutaneous spinal cord stimulator trials and implantations, celiac plexus blocks, and intrathecal drug delivery systems[6–9] necessitates updated guidelines. Hence, the ASRA Board of Directors recommended that the guidelines committee develop updated guidelines for pain medicine interventions.

The latest evidence was sought through extensive database search strategies. Although the guidelines may not always be based on randomized studies or on large numbers of patients from pooled databases, it is hoped that they will provide sound recommendations and the evidentiary basis for such recommendations.

Readers of this article are reminded that these guidelines were created because data on this subject are limited or nonexistent. These guidelines are based on limited clinical and animal data, and as such, the synthesis and interpretation of data by 1 group of experts may differ from conclusions by another set of equally qualified experts. The recommendations contained herein do not define standard of care. They are not intended to replace clinical judgment as applied to a specific patient scenario. Importantly, in this imperfect setting of controversial topics, limited data, and bias inherent to expert opinion, the panel consistently tended toward conservative recommendations. These recommendations are intended to encourage optimal patient care but cannot ensure the avoidance of adverse outcomes. As with any clinical guideline recommendation, these are subject to revision as knowledge of specific complications advances.

DISCUSSION

Pain-specific procedural guidelines are important because the technical and anatomical considerations for pain interventions are significantly different than for peripheral regional anesthesia technique. These factors can be divided into procedure-specific factors and patient-specific factors. The spectrum of interventional spine and pain procedures is far broader than that for regional anesthesia, with diverse targets and objectives. Pain procedures vary from minimally invasive procedures with high-risk targets (eg, percutaneous SCS lead placement, vertebral augmentation, deep visceral blocks, and spine interventions) to low-risk peripheral nerve blocks (Table 1).

The ASRA regional anesthesia and acute pain guidelines may be appropriate for the low- or intermediate-risk category, but the high-risk targets require a more intensive look at the issues specific to patient safety and improved outcomes.

For example, SCS lead placement requires the use of large-gauge needles with a long bevel and stiff styletted leads to enhance directional control. In many cases, the technique is simple with little tissue stress. However, multiple needle and lead insertions can occur, exposing the epidural space to significant trauma.[1,4]

Patients with neck or back pain undergoing ESIs or other spinal interventions may have significant spinal abnormalities including spinal stenosis, ligamentum flavum hypertrophy, spondylolisthesis, or spondylosis, which may compress the epidural venous plexus within tight epidural spaces.[5,10] Moreover, patients, after various spine surgeries, may develop fibrous adhesions and scar tissue, thus further compromising the capacity of the epidural space and distorting the anatomy of the epidural vessels. The risk of bleeding is further increased in pain patients taking several concomitant medications with antiplatelet effects including NSAIDs, ASA, and serotonin reuptake inhibitors (SRIs).[2]

The major update to Table 1 compared with the first publication is the addition of lumbar facet medial branch nerve block (MBNB) and radiofrequency ablation (RFA) to the low-risk procedure category based on a recently published review. Endres et al[8] examined bleeding complications in 4766 interventional pain procedures for which anticoagulants were continued. A majority of the procedures for which the anticoagulants were continued were MBNB patients (2074 patients) in whom a large percentage of patients continued warfarin (1090/2074) and clopidogrel (890/2074). The authors reported no bleeding complications. The procedures were not stratified according to cervical, thoracic, and lumbar segment levels. Therefore, it is unknown how many individuals had lumbar versus cervical procedures.

Based on these new findings, the guidelines committee felt that it is appropriate to move thoracic and lumbar facet MBNB and RFA to low-risk procedures, especially in patients who are at high risk of thromboembolic events. The procedure should be performed with imaging guidance with special attention to the lateral views to ensure that the needle is not advanced into the vicinity of the vascular structures in the neuroforamen. This is especially important with the use of large-gauge needles during RFA procedures.

The Neurostimulation Appropriateness Consensus Committee recommendations formed by the International Neuromodulation Society also published specific measures to reduce the risk of bleeding and neurological injury secondary to impairment of coagulation in the setting of implantable neurostimulation devices in the spine, brain, and periphery. These recommendations are aligned with the recommendations published here.[11]

Anatomical Considerations for Hematoma Development in Spinal and Nonspinal Areas

Although most cases of a spinal hematoma have a multifactorial etiology, certain anatomical features may pose higher risks secondary to the anatomy and vascular supply of that specific spinal location.[12] It is important for interventional pain physicians to apply knowledge of spinal and epidural anatomy during preprocedural planning. Contents of the epidural space include the epidural fat, dural sac, spinal nerves, extensive venous plexuses, lymphatics, and connective tissue (eg, plica mediana dorsalis and scar tissue following previous surgical intervention). The amount of epidural fat in the posterior epidural space is directly related to age and body weight.[13,14] Epidural fat decreases with age. The amount of epidural fat according to spinal location increases with caudal progression,

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TABLE 1. Pain Procedures Classification According to the Potential Risk of Serious Bleeding

High-Risk Procedures	Intermediate-Risk Procedures*	Low-Risk Procedures*
Spinal cord stimulation trial and implant	Interlaminar ESIs (C, T, L, S)	Peripheral nerve blocks
Dorsal root ganglion stimulation	Transforaminal ESIs (C, T, L, S)	Peripheral joints and musculoskeletal injections
Intrathecal catheter and pump implant	Cervical† facet MBNB and RFA	Trigger point injections including piriformis injection
Vertebral augmentation (vertebroplasty and kyphoplasty)	Intradiscal procedures (C, T, L)	Sacroiliac joint injection and sacral lateral branch blocks
Percutaneous decompression laminotomy	Sympathetic blocks (stellate, T, splanchnic, celiac, lumbar, hypogastric)	Thoracic and lumbar facet MBNB and RFA
Epiduroscopy and epidural decompression	Trigeminal and sphenopalatine ganglia blocks	Peripheral nerve stimulation trial and implant‡
		Pocket revision and implantable pulse generator/intrathecal pump replacement

*Patients with high risk of bleeding (eg, old age, history of bleeding tendency, concurrent uses of other anticoagulants/antiplatelets, liver cirrhosis or advanced liver disease, and advanced renal disease) undergoing low- or intermediate-risk procedures should be treated as intermediate or high risk, respectively.

†There is rich neck vascularity in the vicinity of the target structure(s) (refer to the section entitled Anatomical Considerations for Hematoma Development in Spinal and Nonspinal Areas).

‡Peripheral neuromodulation is low to intermediate risk, depending on the location of the targeted nerve in relation to critical vessels and the invasiveness of the procedure.

C indicates cervical; L, lumbar; S, sacral; T, thoracic.

being absent in the cervical spine and highest in the lumbosacral spinal region.[15] Epidural lipomatosis (ie, excessive hypertrophy and abnormal accumulation of epidural fat) may also be seen with long-term exogenous steroid use, obesity, and ESIs. The size of the epidural space also varies based on anatomical level with the posterior epidural space measuring approximately 0.4 mm at C7–T1, 7.5 mm in the upper thoracic spine, 4.1 mm at the T11–T12, and 4 to 7 mm in the lumbar regions.[16]

The epidural space has extensive thin-walled, valveless venous plexi (plexus venous vertebralis interior, anterior, and posterior), which are vulnerable to damage during needle placement and advancement of spinal cord stimulator leads and epidural and intrathecal catheters. These epidural veins are mainly found in anterior and lateral aspects of the epidural space.[17–19] Furthermore, the fragility of these vessels increases with age. Igarashi et al[14] demonstrated blood vessel trauma in 28% of patients who underwent an epidural puncture at L2–L3. The size of the venous plexus changes with the segmental localization of the anastomoses.[12] Large-diameter anastomoses exist at the C6–7, superior thoracic, and entire lumbar regions. These vessels are often located at sites of common interventional pain procedures. In addition, venous plexus distention can occur with anatomical changes in the spinal canal including adjacent level spinal stenosis. The size of venous plexi is also dependent on intrathoracic and intra-abdominal pressure (eg, ascites and pregnancy).

Radiological imaging should be reviewed prior to performing interventional spine and pain procedures in order to assess for central and foraminal stenosis, disk herniations that compromise canal diameter, ligamentum flavum hypertrophy, epidural fibrosis, and previous surgical scarring, which can alter the level of procedural difficulty.[20] Furthermore, previous surgical and epidural interventions (eg, epidural blood patch) at the targeted level may also alter the epidural space and surrounding tissue. Previous epidural entry may result in inflammatory changes that cause connective tissue proliferation and adhesions between the dura mater and the ligamentum flavum and granulation changes in the ligamentum flavum.[21] In addition, it has been suggested that previous surgical intervention, resulting in scarring at the targeted site, may be an independent risk factor for the subsequent development of an epidural hematoma secondary to reduced ability to absorb blood and blood products.[22]

Other locations associated with significant undesirable vascularity include the target ganglia of the middle cervical, stellate, lumbar sympathetic, and celiac plexus. For example, multiple vascular structures surround the location for stellate ganglion blockade including the vertebral, ascending cervical, and inferior thyroid arteries.[23–25] The vertebral artery, which arises from the subclavian artery, passes anteriorly at the C7 level and enters the C6 transverse foramen in 93% of patients. In the remaining cases, the vertebral artery enters the transverse foramen at C3 (0.2%), C4 (1.0%), C5 (5%), and C7 (0.8%).The inferior thyroid artery originates from the thyrocervical trunk. The ascending cervical artery arises from the inferior thyroid artery and passes in front of the anterior tubercles of the cervical vertebral bodies. Inadvertent needle damage to these structures has resulted in retropharyngeal hematomas (Table 1).[25,26]

Chronic Pain and Stress as a Hypercoagulable State

Population and observational studies clearly demonstrate the coexistence of chronic back pain, stress, and other psychosocial comorbidities.[27,28] The stress model for chronic pain is well established in humans and animals as evidenced by the high level of stress hormones compared with control subjects. The sustained endocrine stress response in pain patients may contribute to persistent pain states.[29,30] In clinical studies, altered hypothalamic-pituitary-adrenal axis function has been associated with chronic widespread body pain. These results may be explained by the associated high rates of psychological stress.[31]

Chronic psychosocial stress causes a hypercoagulable state, as reflected by increased procoagulant molecules (fibrinogen or coagulation factor VII), reduced fibrinolytic capacity, and increased platelet activity.[32–34] Stress may also affect coagulation activity via an influence on the regulation of genes coding for coagulation and fibrinolysis molecules.[35] Chronic stress increases many stress hormone levels.[36–38] Catecholamine and cortisol surges may underlie the hypercoagulability observed with chronic psychological distress.[39,40] The situation stimulates the sympathetic nervous system and inhibits fibrinolysis through a β1-mediated effect. Stimulation of vascular endothelial β1 adrenoreceptors leads to reduced intracellular prostacyclin synthesis, which eventually impairs the release of tissue-type plasminogen activator.[41]

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As chronic pain frequently coexists with mental stress, characterized by a hypercoagulable state, chronic pain patients may be at an increased risk of coronary or cerebrovascular events after discontinuation of protective antiplatelet and anticoagulant medications. This underscores the importance of coordinating the perioperative handling of these medications with the prescribing cardiologist or neurologist.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs inhibit prostaglandin production by inhibiting cyclooxygenase (COX). The 2 main forms of COX are COX-1 and COX-2. Cyclooxygenase 1 is involved in constitutive mechanisms, and COX-2 is inducible and part of the inflammatory process. Specifically, platelet function is altered by NSAIDs via inhibition of COX-1–induced acetylation of the serine 529 residue of COX-1, which prevents the formation of prostaglandin H_2. Prostaglandin H_2 is required for the synthesis of thromboxane A_2 (TXA_2). Thromboxane A_2 is produced by platelets and has prothrombotic effects including vasoconstriction.[42] There are multiple classes of NSAIDs including salicylates, acetic acid derivatives, enolic acid derivatives, and selective COX-2 inhibitors.

Aspirin's Effects on Hemostasis

Aspirin is rapidly absorbed from the gastrointestinal (GI) tract, with peak levels occurring approximately 30 minutes following ingestion, resulting in significant platelet inhibition at 1 hour.[43,44] The peak plasma levels for enteric-coated ASA may be delayed until 3 to 4 hours after ingestion.[45,46] Aspirin has 170-fold greater affinity for COX-1 over COX-2 and irreversibly inactivates COX-1 through the acetylation of the amino acid serine.[47,48] By irreversibly inactivating COX-1 and blocking thromboxane production for the life span of a platelet, ASA is effective at inhibiting platelet activation, platelet aggregation, and thrombosis. Aspirin, within 1 hour after ingestion, results in greater than 90% reduction in thromboxane levels.[49] In addition to affecting platelets for their life span, ASA also inactivates COX-1 in mature megakaryocytes (the bone marrow cell type responsible for platelet production). After a single dose of ASA (100–400 mg), it has been demonstrated that COX activity does not return for approximately 48 hours. This delay in return of the activity of COX has been interpreted as the influence of ASA on megakaryocytes.[42,49,50] The average life span of a platelet is 7 to 10 days.[51,52] Each day, approximately 10% of the circulating platelet pool is replaced. At 5 to 6 days, approximately 50% of platelets function normally. In addition, platelet turnover and ASA's antiplatelet effects display significant interindividual variability that is influenced by age, body mass, and specific medical conditions, including diabetes.[53]

Aspirin's effects on platelet function, COX activity, and thromboxane production are time and dose dependent.[42,49,54] A single 20-mg dose of ASA reduces COX activity by 82% as early as 5 minutes after dosing.[42] Furthermore, a single dose of 100 mg of ASA suppresses COX activity by 95% ± 4%.[54] Repeated dosing results in a significant reduction in the required ASA platelet inhibitory dose. The 50% inhibitory dose decreased from 26 mg (single dose) to 3.2 mg after repeated dosing.[42] After daily dosing with 20 to 40 mg of ASA, 92% to 95% of COX activity is inhibited over 6 to 12 days.[42]

Antiplatelet effects have also been studied in healthy volunteers through platelet aggregation tests including optical aggregometry and ASA reaction units (ARUs).[46,55] Aspirin reaction units is a whole blood assay test to aid in the detection of platelet inhibition, and ARU is calculated as a function of the rate and extent of platelet aggregation. In individuals not taking ASA, ARUs are 550 or greater.[46] When examining ARU changes following administration of 4 ASA dosing regimens (enteric-coated 81 mg, uncoated 81 mg, enteric-coated 325 mg, and uncoated 325 mg in normal volunteers), the maximal reductions in ARUs ranged from 37% to 41% from baseline values.[6] When examining the induced inhibition of platelet aggregation in healthy volunteers taking an 81-mg dose, ASA demonstrated a 66.0% ± 18.6% inhibition measured with optical aggregometry with the agonist arachidonic acid.[55]

Aspirin also influences coagulation through non–TXA_2-mediated effects, including dose-dependent inhibition of platelet function, suppression of plasma coagulation, and enhancement of fibrinolysis.[45,56–67] Secondary hemostasis and thrombus stability are also impaired, because of ASA's acetylation of fibrinogen and its enhancement of fibrinolysis.[45] Aspirin, unlike non-ASA NSAIDs, decreases thrombin formation in clotting blood.[66] Aspirin at higher doses prevents endothelial cell prostacyclin production by inhibiting COX-2.[45] Prostacyclin inhibits platelet coagulation and stimulates vasodilation.

Phosphodiesterase Inhibitors

Phosphodiesterase (PDE) inhibitors are also used as antiplatelet therapies. Platelets express 3 PDE isoenzymes: PDE-2, PDE-3, and PDE-5.[68] Two commonly encountered PDE inhibitors are dipyridamole, which is often combined with ASA, and cilostazol. Phosphodiesterase inhibitors influence cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels, which are inhibitory intracellular secondary second messengers that influence fundamental platelet processes. Phosphodiesterase 3 inhibitors (cilostazol) increase cAMP levels, whereas PDE-5 inhibitors increase cGMP levels.

Dipyridamole Combined With ASA

Aspirin may be combined with other drugs to synergistically effect coagulation. One of these drugs is dipyridamole, which acts in vivo to modify several biochemical pathways involved in platelet aggregation and thrombus formation.[56,68–71] The extended release (ER) forms of dipyridamole (200 mg ER) and ASA (25 mg) are often used in combination for the management of cerebral vascular disease including secondary prevention of stroke and transient ischemic attacks (TIAs).[72] Dipyridamole inhibits PDE-3 and PDE-5. By inhibiting cAMP and cGMP PDEs, cAMP and cGMP levels increase, which results in a reduction in platelet aggregation and an increase in vasodilation. Also, extracellular adenosine levels are increased by blocking adenosine reuptake by vascular and blood cells. An increase in adenosine levels leads to further vasodilation.[69,70] Thromboxane synthase and the thromboxane receptor are also blocked with the use of dipyridamole.[73] The final pathway by which dipyridamole affects coagulation is through its negative effects on the formation and accumulation of fibrin.[74] The plasma concentration decline of dipyridamole follows a 2-compartment model with an α half-life of 40 minutes and a β half-life of approximately 10 hours. The β half-life of 10 hours more closely reflects the terminal half-life of the drug. The ER component of dipyridamole used in combination with ASA has an apparent half-life of 13.6 hours.[69] In conclusion, when ASA is combined with dipyridamole, there is an increased risk of bleeding.[44,75]

Cilostazol

Another PDE-3 inhibitor that also has antiplatelet aggregation and arterial vasodilator properties is cilostazol.[42,68] Cilostazol's antiplatelet properties include the inhibition of both primary and secondary platelet aggregation. Cilostazol also has other effects including decreasing the expression of P-selectin, which is a cell adhesion molecule found on activated endothelial cells and platelets.[76] It reduces thromboxane production and platelet factor 4 and

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platelet-derived growth factor release.[77] Some ex vivo tests indicated that cilostazol may inhibit platelet aggregation to a greater degree than ASA.[78] Cilostazol is used to treat lower-extremity claudication.[44,68] It has also been used to prevent stent thrombosis and stroke.[79] In the field of cardiology, cilostazol is used to augment the inhibition of platelet aggregation in clopidogrel low responders.[80–82] After oral administration, cilostazol reaches peak plasma concentrations at approximately 2 hours, with maximum platelet aggregation occurring at 6 hours.[44,68,83] A single dose of 100 mg or greater is required to reduce platelet aggregation. Cilostazol's antiaggregatory effects increase with successive and continuous dosing. After 4 weeks of continuous administration with 100- and 200-mg daily dosing, platelet adenosine diphosphate (ADP)–induced platelet aggregation rates were decreased by 21% to 38%, respectively.[84] The drug is hepatically metabolized, and metabolites are renally excreted. The drug has an elimination half-life of 10 hours. Cilostazol does not increase bleeding time when used alone or in combination with ASA.[85,86] One case report described a spinal epidural hematoma after epidural catheter removal in an individual with a low platelet count who had been taking cilostazol following vascular surgery.[87] Limited data exist evaluating the risk of perioperative surgical bleeding with cilostazol, and no standard perioperative guidelines are available.[88] If the medication is discontinued, even after continuous dosing, at 50 hours (approximately 5 half-lives) less than 5% of the drug remains in the plasma, and improvements in platelet aggregation have been demonstrated.[84,87]

Cardiac and Cerebrovascular Risks Associated With the Discontinuation of ASA

In the United States, a significant number of individuals (>50 million) take ASA for prevention of cardiovascular events.[89] When individuals are taking ASA, it is important to understand whether utilization is for primary or secondary prophylaxis. Primary prophylaxis is used to prevent the first occurrence of a cardiovascular event and is defined by ASA's employment in the absence of established cardiovascular disease as defined by history, examination, and clinical testing. Secondary prophylaxis is used to prevent recurrence of disease and is defined as when ASA is used in the presence of overt cardiovascular disease or conditions conferring particular risk (eg, diabetes mellitus).

Significant evidence exists supporting the use of ASA for secondary prophylaxis for cardiovascular disease, and guidelines recommend initiation and indefinite continuation unless contraindicated in this patient population.[47,90,91] Low-dose ASA, when used for secondary prophylaxis, has been shown to reduce the risk of stroke and myocardial infarction in the range of 25% to 30%.[92–94] Furthermore, the discontinuation of ASA for secondary prophylaxis is associated with significant risk.[95–97] The lowest effective ASA daily dose for the prevention of TIA and ischemic stroke is 50 mg. For men at high risk of cardiovascular disease, the recommended dose increases to 75 mg.[35,43,89,98] The routine long-term use of doses greater than 75 to 81 mg per day has not been shown to have improved efficacy for cardiovascular prevention.[89] Approximately 10% of acute cardiovascular syndromes are preceded by the withdrawal of ASA. The time interval between ASA discontinuation and acute cardiovascular events is typically in the time frame recommended for ASA discontinuation for invasive procedures, 8.5 ± 3.6 days for acute coronary syndromes and 14.3 ± 11.3 days for acute cerebral events.[94,99–102] When ASA is discontinued, a platelet rebound phenomenon may occur, which results in a prothrombotic state characterized by increased thromboxane production, enhancement of thrombus stability, improvement in fibrin cross-link networks, and decreased fibrinolysis.[47,103–105]

When ASA is used for primary prophylaxis, its value in preventing cardiovascular events is unclear, with evidence suggesting no definitive benefit for overall mortality rates.[90,106,107] The Antithrombotic Trialists' Collaboration, after conducting a meta-analysis of individual participant data for randomized trials, concluded that when ASA is used for primary prophylaxis in individuals without previous cardiovascular disease decision making should involve balancing the unclear value of utilization with the increased risk of major bleeds.[90] Future studies are required to determine ASA's role in primary prevention and prophylaxis for cardiovascular events.[108]

Discontinuation of ASA and Restoration of Platelet Function

The return of platelet function after discontinuation is affected by multiple factors including prior ASA dosing, rate of platelet turnover, time interval of discontinuation, and patient-specific response to ASA therapy. As stated previously, approximately 10% of the platelet pool is replaced daily. Because ASA irreversibly inhibits COX, it would take 10 days to completely restore a fully functioning platelet pool. Burch et al[50] confirmed that the return of enzyme activity followed platelet turnover with an average platelet life span of 8.2 ± 2 days, although platelet function may occur earlier.[109–111] Burch et al[50] also confirmed that new unacetylated enzyme did not appear in circulation for 2 days, suggesting that ASA also acetylates COX in the megakaryocytes. As considerable individual-specific variation exists, partial recovery of platelet function has been shown to occur when approximately one-third of the circulating platelet pool has been replaced by uninhibited platelets.[110] A study that examined healthy men demonstrated that complete recovery of platelet aggregation occurred in 50% of the subjects by the third day after discontinuation of taking 325 mg of ASA every other day for 14 days.[111] Eighty percent of subjects demonstrated normal platelet aggregation by the fourth day. Another study examining platelet functional recovery after cessation of ASA in volunteers and surgical patients demonstrated that the majority of volunteers and patients experienced recovery of platelet function at day 3 and within 4 to 6 days, respectively.[112] By day 6, all of the subjects had restored platelet aggregation to at least 85% of baseline level. Also, studies examining the effect of ASA on platelet aggregation in cardiac surgery patients demonstrate earlier platelet recovery and as early as 3 days after discontinuation.[113,114] Gibbs et al[113] examined the effects of recent ASA ingestion on platelet function in cardiac surgical patients. A significant difference existed in platelet function between patients who ingested ASA for 2 days or fewer preoperatively in comparison to the groups who took ASA for 3 to 7 days and more than 7 days. No difference was found in platelet aggregation between the group who took ASA for 3 to 7 days and the group who took for more than 7 days. Coleman and Alberts[46] demonstrated early recovery of platelet aggregation following the discontinuation of ASA with a significant amount of platelet recovery occurring between 48 and 72 hours after discontinuation and with complete recovery occurring 5 days after discontinuation.

Non-ASA NSAIDs' Effects on Hemostasis

Non-ASA NSAIDs bind reversibly and competitively inhibit the active site of the COX enzyme. The non-ASA NSAIDs compete with arachidonic acid's binding to COX-1.[42] The degrees of reversible inhibition of COX-1, after single doses of frequently used NSAIDs (diclofenac, ibuprofen, indomethacin, naproxen, and piroxicam), are dependent on the selected NSAID and measured time frame in the first 24 hours. Besides indomethacin,

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non-ASA NSAIDs do not achieve greater than 90% reversible inhibition of platelet enzyme activity.[42] During the 24-hour period after ingestion of a single dose, the commonly used NSAIDs diclofenac, ibuprofen, and piroxicam reversibly maximally inhibit platelet COX activity in the mean range of 73% to 89%.[42] The degree of inhibition of COX-1 by specific NSAIDs influences the associated procedural bleeding risk. Traditional NSAIDs are nonselective and inhibit both COX-1 and COX-2, although some of the non-ASA NSAIDs, including etodolac, nabumetone, and meloxicam, are associated with more selective inhibition of COX-2.[115] The ratio of COX-2/COX-1 inhibition for meloxicam is approximately 80:25.[116] This group of NSAIDs that is more selective for COX-2 inhibition may be associated with a lower procedural bleeding risk.

Unlike ASA, the platelet effects of these drugs are directly related to systemic plasma drug concentrations and influenced by the pharmacokinetic clearance of these medications. Once steady-state concentrations have been achieved, terminal half-life is a predictive time parameter to guide decision making.[117] For NSAIDs, terminal half-lives and half-lives are interchangeable and equivalent. Because NSAIDs are well absorbed, and absorption is not the limiting factor, half-life is more dependent on the plasma clearance and the extent of drug distribution. Nonsteroidal anti-inflammatory drugs are highly bound to plasma proteins; therefore, their volume of distribution is minimal, and the terminal half-lives and half-lives are similar.[118] It takes approximately 5 half-lives for systemic elimination (Table 2).[129,130] Nonsteroidal anti-inflammatory drugs are excreted either by glomerular filtration or tubular secretion. After 5 half-lives, approximately 3% of the drug remains in the body. Although repeat dosing with ASA has been shown to have cumulative inhibition of platelet COX-1 activity, this has not been demonstrated with NSAIDs such as ibuprofen.[131]

The effect of platelet aggregation with the administration of 1 dose of 10 different NSAIDs has been studied in healthy volunteers.[132] Some conventional NSAIDs that were studied included ASA, diclofenac, ibuprofen, indomethacin, naproxen, acetaminophen, and piroxicam. The non-ASA NSAIDs were found to abolish the second wave of platelet aggregation for variable time periods based on the pharmacokinetics associated with each drug. At 24 hours, more than 50% of tested subjects had return of the second wave of platelet aggregation, except for piroxicam, which took until day 3. Acetaminophen did not have any effect on the second wave of platelet aggregation, and ASA's effects lasted between days 5 and 8 after the administration of the single dose.

TABLE 2. Half-lives of Commonly Administered Non-ASA NSAIDs

Agent	Half-life, h	Discontinuation Time 5 Half-lives, h	Recommended Discontinuation Time, d
Diclofenac[119]	1–2	5–10	1
Etodolac[120]	6–8	30–40	2
Ibuprofen[121]	2–4	10–20	1
Indomethacin[122]	5–10	25–50	2
Ketorolac[123]	5–6	25–30	1
Meloxicam[124]	15–20	75–100	4
Nabumetone[125]	22–30	110–150	6
Naproxen[126]	12–17	60–85	4
Oxaprozin[127]	40–60	200–240	10
Piroxicam[128]	45–50	225–250	10

Another study examined the effect of taking ibuprofen 600 mg every 8 hours for 7 days on platelet function in 11 patients. All 11 patients had return of normal platelet function 24 hours after the last dose of ibuprofen.[133]

Non-ASA NSAIDs' Influence on the Cardiovascular Protective Effects of ASA

Nonselective COX inhibitors, such as ibuprofen, may limit ASA's cardioprotective effects by impeding access of ASA to the serine 529 target.[134] A clinical dose (400 mg) of ibuprofen given 2 hours before ASA ingestion has been shown to block ASA's inhibition of serum thromboxane formation and platelet aggregation. Delayed-release diclofenac was not found to limit the cardioprotective effects of ASA. In addition, meloxicam, which is more selective for COX-2 in lower doses (<15 mg), has not been shown to negatively affect ASA's ability to reduce thromboxane levels and prevent platelet aggregation.[116]

COX-2 Inhibitors' Effects on Hemostasis

Unlike drugs that inhibit the enzyme COX-1, NSAIDs that inhibit only the enzyme COX-2 do not alter platelet function.[135] The expression of COX-2 increases with inflammation.[136] Celecoxib is a COX-2 inhibitor. Multiple studies have demonstrated that celecoxib does not interfere with the normal mechanisms of platelet aggregation and hemostasis.[135,137] Leese et al[135] in a randomized controlled trial demonstrated that supratherapeutic doses (600 mg twice a day [BID]) of celecoxib given for 10 days did not alter platelet aggregation, thromboxane B_2 levels (thromboxane B_2 is an inactive metabolite of TXA_2 that is excreted in the urine and a surrogate marker of TXA_2), or bleeding time. A limited number of studies suggest that COX-2 inhibitors are not associated with increased surgical blood loss.[138,139]

Extra caution should be exercised when individuals are taking both celecoxib and warfarin. Although some studies have suggested that celecoxib does not potentiate the anticoagulant effect of warfarin,[140,141] individuals with genetic differences in the activity of cytochrome P4502C9 enzyme may be at increased risk of international normalized ratio (INR) elevations and bleeding complications when both drugs are coadministered.[142] Both celecoxib and warfarin are metabolized by the CYP2C9 enzyme.

Procedural Recommendations: Overview

The ASRA[143] and European[144] regional guidelines recommend that central neuraxial blocks may be performed in individuals utilizing ASA or NSAIDs. The Scandinavian[145] guidelines for the performance of central neuraxial blocks in individuals utilizing ASA based their recommendations on the indication for ASA utilization and the daily dose. In individuals taking ASA for secondary prevention, a shorter discontinuation time of 12 hours was recommended. For individuals not using ASA for secondary prevention, the discontinuation time is 3 days unless the dose is greater than 1 g/d, for which the discontinuation time is extended to 1 week. For NSAIDs, the Scandinavian guidelines recommendations are guided by the specific half-life for each drug.

Data specifically defining the risk of bleeding with interventional pain medicine procedures with NSAID continuation remain limited since the first publication.[1,146] Recently, small retrospective reviews evaluating bleeding complications in patients undergoing specific interventional pain procedures including joint injections, facet procedures, ESIs, percutaneous spinal cord stimulator trials and implantations, celiac plexus blocks, and intrathecal drug delivery systems have been published.[6–9] Unfortunately, based on the inherent limitations of retrospective

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analyses and the small number of patients receiving NSAIDs, the ability to draw clinical conclusions and imply the safe performance of these interventional pain procedures while continuing NSAIDs and ASA is limited. Bleeding complications in individuals undergoing percutaneous spinal cord stimulator trial implantations were examined in 101 patients who had continued NSAIDs.[9] In this retrospective review, only 48 patients were taking ASA, and 53 patients were taking NSAIDs. Patients were documented as taking ASA and NSAIDs if a dose was taken within 7 days of the procedure. A 7-day discontinuation time frame is an extended period for ASA and NSAIDs discontinuation based on the pharmacokinetics of the drugs. Many of these drugs can be stopped within 1 to 2 days, and the patient would not be expected to have any coagulation deficits or platelet deficiencies. Endres et al[8] examined bleeding complications in 4766 interventional pain procedures for which anticoagulants were continued. A majority of the procedures for which the anticoagulants were continued were for medial branch blocks (2074 patients), transforaminal ESIs (1633 patients), and trigger point injections (456 patients). In this analysis of 4766 interventional pain procedures for which anticoagulants were continued, only 60 patients continued ASA, for which more than 50% of the patients included those who underwent MBNBs. In addition, no interlaminar ESIs were performed with ASA. Therefore, significant limitations exist with the ability to declare safety when performing ESIs via the interlaminar approach while continuing ASA and NSAIDs. In this retrospective analysis, the sample sizes were small, and therefore, meaningful confidence intervals (CIs) around the observed prevalence for bleeding complications could not be provided. In addition because of the small sample size, procedures were not stratified according to cervical, thoracic, and lumbar segment levels. Therefore, it is unknown how many individuals had lumbar versus cervical procedures. For the MBNB patients, a large percentage of patients continued warfarin (1090/2074) and clopidogrel (890/2074). In order to fully determine the risk of continuing NSAIDs and ASA for specific pain procedures, larger numbers are required.

Aspirin has been identified as an important risk factor for postoperative bleeding and the development of hematomas including epidural hematomas in other surgical fields.[147–152] Furthermore, the use of low-dose ASA before spine surgery, even when discontinued for at least 7 days, has been suggested to lead to further blood drainage after surgery.[153] In an extensive review, low-dose ASA has also been shown to increase the rate of bleeding complications by a factor of 1.5 (median; interquartile range, 1.0–2.5).[94] The baseline risk of bleeding varied based on surgical type (cataract surgery vs transurethral prostatectomy).

Bleeding complications also occur after the performance of interventional pain procedures. Spinal hematoma is a rare complication that has been associated with spinal cord stimulator trials, implants with percutaneously placed cylindrical leads and laminotomy-placed paddle leads, lead migration, revisions, and lead removal.[1–4,36,154–156] Aspirin and NSAIDs have been suggested as a risk factor in some of the cases.[2–4] Case reports of subdural hematomas following spinal anesthesia have also questioned ASA's continuation prior to a spinal anesthetic.[157,158] In addition, spinal hematomas have occurred after cervical ESIs in individuals taking non-ASA NSAIDs.[5,159] Other studies examining the performance of lumbar epidurals for pregnancy have not demonstrated an increased risk of bleeding complications with ASA.[160] The CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) did not show an increase in bleeding complications when performing epidurals for pregnancy in individuals taking 60 mg of enteric-coated ASA daily.

Moreover, patients' comorbidities should be evaluated, as this may have a great impact on bleeding tendency. Specifically, renal dysfunction, including nephrotic syndrome, reduces NSAIDs' binding to plasma proteins, which can result in a larger volume of distribution and increased drug concentrations within tissues.[118] Renal dysfunction can also prolong elimination half-life. Hepatic dysfunction may result in hypoalbuminemia and altered NSAID metabolism. Furthermore, alcohol and other pharmacological agents may potentiate the effects of both ASA and non-ASA NSAIDs.[161–170]

Summary Recommendations for Non-ASA NSAIDs

- Non-ASA NSAIDs are used for pain control and, unlike ASA, are not required for cardiac and cerebral protection. Therefore, these drugs may be discontinued without negatively affecting cardiac and cerebral function.
- For interventional pain procedures where the bleeding risks and the consequences of hematoma development may be higher (eg, high-risk procedures; Table 1) consideration should be given to discontinue these medications. Besides ibuprofen, limited NSAIDs-specific trials exist to definitively guide the time of discontinuation for each NSAID; therefore, recommendations will be based on the pharmacokinetics of each specific drug and associated half-life (Table 2). In addition, consideration should be given to the discontinuation of NSAIDs for certain intermediate-risk procedures including interlaminar cervical ESIs and stellate ganglion blocks where specific anatomical configurations may increase the risk and consequences of procedural bleeding.
- Rather than discontinue all NSAIDs for a global period, each NSAID can be discontinued based on its specific half-life. Five half-lives should be sufficient to render the non-ASA NSAIDs' effects on the platelet inactive. For example, in a healthy individual, 24 hours should be adequate for the recommended discontinuation time for ibuprofen and diclofenac. Etodolac should be discontinued for 2 days. Four days of discontinuation is adequate for naproxen and meloxicam.
- Exceptions to the 5 half-life recommendation should occur in individuals with hypoalbuminemia, hepatic dysfunction, and renal dysfunction including nephrotic syndrome.
- Because of the lack of effect on platelet function with COX-2–selective inhibitors and perioperative bleeding risks, these medications do not need to be stopped.

Summary Recommendations for ASA

- A patient- and procedural-specific strategy is recommended when deciding whether to continue or discontinue ASA in the perioperative period for interventional pain procedures. Decision making should include an understanding of the reason for ASA utilization, the vascular anatomy surrounding the target area, the degree of invasiveness of the procedure, and the potential sequelae associated with perioperative bleeding (Table 1).
- In addition, a complete review of the patient's medical record should occur to identify additional medications that may heighten ASA's anticoagulant effect (eg, selective serotonin norepinephrine reuptake inhibitors [SNRIs] and dipyridamole).
- If ASA is being taken for primary prophylaxis, ASA discontinuation is recommended for high-risk procedures in which there is a heightened risk of perioperative bleeding and sequelae. In addition, consideration should be given to the discontinuation of ASA for certain intermediate-risk procedures, including interlaminar cervical ESIs and stellate ganglion blocks, where specific anatomical configurations may increase the risk and consequences of procedural bleeding.

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- When ASA is being utilized for primary prophylaxis, ASA may be discontinued for a longer period, 6 days, to ensure complete platelet functional recovery.[112]
- In individuals utilizing ASA for secondary prophylaxis undergoing high-risk procedures, a shared assessment, risk stratification and management decision should involve the interventional pain physician, patient, and physician prescribing ASA. The risk of bleeding while continuing ASA needs to be weighed against the cardiovascular risks of stopping ASA. Documentation of decision making should occur. If a decision is made to discontinue chronic ASA therapy, the time of discontinuation should be determined individually.
- When performing elective pain procedures where there is either a high risk (Table 1) of potential bleeding and/or the possibility of significant sequelae in an individual taking ASA for secondary prophylaxis, ASA should be discontinued for a minimum of 6 days.[112] In individuals taking ASA for secondary prophylaxis who are undergoing low- or medium-risk procedures for which a decision has been made to discontinue, the length of discontinuation can be shortened to 4 days in an effort to balance the risks of procedural bleeding and cardiovascular events.[46,112] Zisman et al[112] demonstrated that in most ASA-treated patients platelet function recovers 4 days after drug discontinuation.

Summary Recommendations for PDE Inhibitors

The decision to discontinue cilostazol or dipyridamole without ASA or combined with ASA should involve shared decision making between the interventional pain physician, patient, and prescribing physician.

- For high-risk procedures, cilostazol and dipyridamole without ASA should be discontinued 48 hours prior to performing the intervention.[84,87]
- For intermediate- and low-risk procedures, cilostazol and dipyridamole without ASA do not need to be discontinued.
- The discontinuation length for dipyridamole combined with ASA should follow the ASA recommendations described previously for high-, intermediate-, and low-risk procedures. It has been suggested when dipyridamole is combined with ASA the risk of bleeding is increased.[44,75]

Procedural Recommendations Regarding Duration of Spinal Cord Stimulator Trials

- Currently, no consensus exists regarding the required duration for a spinal cord stimulator trial.
- The length of the trial should be sufficient to demonstrate improvement in pain control and allow prospective patients the ability to determine if they desire to progress forward to the implantation stage. Chincholkar et al,[171] in a prospective trial examining 40 patients who underwent a spinal cord stimulator trial, demonstrated that a majority of patients are able to make a decision at a mean duration of 5.27 days. Furthermore, most individuals who had a successful trial arrived at a decision earlier than did those with an unsuccessful trial. In addition, Weinand et al[172] did not demonstrate improvement in outcomes with a prolonged trial. In this study, individuals either had an acute (15 minute intraoperative) or prolonged (5-day) SCS screening trial. Both the acute and prolonged SCS screening had equivalent predictive values for successful long-term SCS pain control.
- Because a platelet rebound phenomenon may occur with the discontinuation of ASA, and the time interval between ASA discontinuation and the occurrence of an acute cardiovascular event is in the range of 8 to 14 days, in individuals taking ASA for secondary prevention it is recommended that the length of the trial be minimized with a risk-benefit ratio considered for adequate trialing versus the possibility of cardiovascular sequelae.
- The Neurostimulation Appropriateness Consensus Committee recommendations formed by the International Neuromodulation Society also published specific measures to reduce the risk of bleeding and neurological injury secondary to impairment of coagulation in the setting of implantable neurostimulation devices in the spine, brain, and periphery. These recommendations are aligned with the recommendations published here.[11]

Timing of Therapy Restoration

- Because NSAIDs are not essential for cardiovascular protection, for high-risk procedures we recommend withholding these drugs for 24 hours after the procedure.
- For elective pain procedures associated with a high risk of bleeding complications, ASA can be resumed 24 hours after the procedure if required for secondary prevention.
- For primary prevention, ASA should not be restarted for at least 24 hours following high-risk procedures and specific intermediate-risk procedures, including interlaminar cervical ESIs and stellate ganglion blocks, where specific anatomical configurations may increase the risk and consequences of procedural bleeding. We recommend a delay because ASA rapidly and significantly affects platelet function after ingestion. Aspirin also influences thrombus stability and fibrinolysis. Clot stabilization probably typically occurs at 8 hours.

P2Y12 Inhibitors: Ticlopidine, Clopidogrel, Prasugrel, Ticagrelor, Cangrelor

The thienopyridines, such as ticlopidine and clopidogrel, block the ADP receptor, P2Y12 subtypes. In the presence of vessel injury, TXA_2 and adenine nucleotides (which contain P2 receptors) are released. P2Y12 receptors are 1 of 3 P2 receptors for adenine nucleotides: P2Y1, P2Y12, and P2X1. Of the P2Y12 receptors, P2Y1 initiates whereas P2Y12 completes the process of platelet aggregation. P2X1 receptor helps accentuate the effects of other platelet agonists[173] Adenosine diphosphate is an agonist for the P2Y1 and P2Y12 receptors, whereas ATP is the agonist for P2X1. P2Y12 receptor inhibitors have become widely used in the treatment of coronary syndromes, cerebrovascular ischemic events, and even peripheral vascular disease. P2Y12 receptor inhibitors are used in combination with ASA, so-called dual antiplatelet therapy, to reduce thrombotic events in the setting of acute coronary syndromes and in patients who undergo percutaneous coronary intervention (PCI).[174,175] Ticlopidine is rarely used, as its antiplatelet effect is delayed[176] and may cause hypercholesterolemia, thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura. Clopidogrel is more commonly used, but has several limitations including a lack of response in 4% to 30% of patients and its susceptibility to drug-drug interactions and to genetic polymorphisms.[177–179] Clopidogrel is a prodrug, requiring 2 metabolic steps to form the active drug.[180] The time to peak effect of clopidogrel takes as long as 24 hours. However, a loading dose of 300 to 600 mg clopidogrel shortens the time to 4 to 6 hours.[181] The maximum percentage of platelet inhibition by clopidogrel is 50% to 60%, which normalizes 7 days after it is discontinued.[182] The most recent ASRA guidelines on regional anesthesia recommended a 5- to 7-day cessation of clopidogrel,[143] whereas the American College of Cardiology

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recommended 7 to 10 days in most patients and 5 days for patients who are at high risk of angina.[183,184] The CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial specifically showed less perioperative bleeding when clopidogrel was stopped 5 days before surgery.[184] The 5-day recommendation is probably acceptable for neuraxial injections as there have been case reports of uneventful neuraxial anesthesia 5 days after discontinuing clopidogrel.[185,186] There is also a retrospective study of 306 patients that showed the absence of spinal hematoma in patients on clopidogrel who had continuous epidural catheters.[187] In a study on the decay of the antiplatelet effect of clopidogrel, Benzon et al[188] noted no difference in the percent platelet inhibition and in the platelet reaction units between 5 and 7 days after discontinuation of clopidogrel. Unfortunately, the 2 studies involved only a small number of patients.[187,188] Most pain procedures are elective, and clopidogrel should preferably be stopped for 7 days. In cases of SCS trial in patients at high risk of thromboembolic events, we recommend consultation with the treating physician and stopping clopidogrel for 5 days before the trial of SCS, keeping the trial to the minimum duration possible during which time the patient remains off clopidogrel. In these circumstances, where clopidogrel will be stopped only 5 days prior to the procedure, a platelet function test such as the VerifyNow P2Y12 assay or platelet mapping portion of the thromboelastograph should be considered whenever available.[188–190] This is to ensure adequate recovery of the platelets.

Prasugrel is a prodrug similar to clopidogrel and also causes irreversible inhibition of the P2Y12 receptor.[191] Unlike clopidogrel, it requires only 1 metabolic step to form its active drug.[180] It is reliably converted to its active metabolite, is not involved in drug-drug interactions, and is not susceptible to genetic polymorphisms.[192,193] Prasugrel has a rapid onset of effect, the median time to peak effect being 1 hour.[182] Peak plasma concentration occurs in 30 minutes, with a median half-life of 3.7 hours.[193,194] Prasugrel causes 90% inhibition of platelet function compared with 60% to 70% for clopidogrel.[182] The superior antiplatelet effect of prasugrel is secondary to its improved metabolism, resulting in more active metabolites being delivered to the platelet.[195,196] Patients older than 75 years, those with history of TIA or stroke, or those with small body mass index are at risk of increased bleeding.[197,198] Platelet activity does not normalize until 7 days after it is stopped.[199] A 7- to 10-day interval before a neuraxial injection has been recommended by the ASRA regional anticoagulation guidelines[143] and European guidelines for regional anesthesia,[144] whereas the Scandinavian guidelines stated that 5-day stoppage may be sufficient.[145] In view of its reliable conversion to its active metabolite, potency, reports of increased bleeding, and studies showing platelet activity normalizing at 7 days, a 7-day interval before medium- and high-risk interventional pain procedures is recommended.

Unlike clopidogrel and prasugrel, ticagrelor is a direct-acting P2Y12 receptor inhibitor.[200] Although both the parent compound and the active metabolite have antiplatelet activities, the parent drug is responsible for the majority of the in vivo platelet inhibition.[201,202] The major metabolism of ticagrelor is via the liver with minor clearance via the kidneys. In the presence of hepatic impairment, the concentrations of ticagrelor and its metabolite are higher, but the percent platelet inhibition and pharmacodynamics are not different from control subjects without liver problems.[203] There are no known drug interactions with ticagrelor, and its pharmacokinetics are predictable and not affected by genetic polymorphisms.[204]

The antiplatelet effect of ticagrelor is rapid, with peak platelet inhibition occurring 2 to 4 hours after intake, compared with 24 hours with clopidogrel.[205] The mean platelet inhibition by ticagrelor is 90%, compared with 50% to 60% for clopidogrel.[206] Similar to clopidogrel, a loading dose hastens the antiplatelet effect of ticagrelor. A study showed that an initial dose of 180 mg of ticagrelor followed by 90 mg BID resulted in a platelet inhibition of 41% at 30 minutes.[206] Platelet recovery is more rapid with ticagrelor, as platelet inhibition is similar to placebo 5 days after discontinuation.[206] The recent ASRA regional guidelines recommended a 5-day interval between the last dose of the drug and neuraxial injection.

Cangrelor (Kengreal) is a new intravenous (IV), direct, and reversible P2Y12 inhibitor. It was approved as an adjunct to PCI to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in the patients who have not been treated with another P2Y12 inhibitor and are not being given a glycoprotein IIb/IIIa (GP IIb/IIa) inhibitor. The drug is given intravenously as a 30-μg/kg bolus followed by an infusion at 4 μg/kg per minute and has a quick onset and offset of effect. Its antiplatelet effect is seen within 2 minutes of administration, causing 95% to 100% inhibition of platelet aggregation.[173] It has a plasma half-life of 3.6 minutes and a clinical half-life of 5 minutes.[207] Recovery of platelet aggregation is quick, within 60 minutes in 80% of patients and within 90 minutes in 90% of patients (Table 3).[208] The adverse effects of cangrelor include bleeding, dyspnea, and decreased renal function.

The approval for cangrelor use was based on the CHAMPION PHOENIX trial wherein the drug showed superiority over clopidogrel in terms of reduction of periprocedural myocardial infarction.[209] The occurrence of severe bleeding was not different between cangrelor and clopidogrel. Most patients given cangrelor for PCI will probably be continued on one of the oral P2Y12 inhibitors. Timing of the loading dose of the oral P2Y12 inhibitors is important because clopidogrel and prasugrel will not work while the cangrelor is being infused—their metabolite cannot bind to the receptor while it is being occupied by cangrelor. Ticagrelor, which has a separate binding site, can be given anytime during cangrelor infusion. It has therefore been recommended that clopidogrel and prasugrel be given immediately after discontinuation of cangrelor, whereas ticagrelor can be given during or immediately after the infusion.[173] The recommended

TABLE 3. Comparison of P2Y12 Inhibitors

P2Y12 Inhibitor	Characteristics	Maximum Inhibition of Platelets	Onset (Loading Dose)	Offset
Clopidogrel	Oral, irreversible inhibition	50%–60%	4–8 h	5–7 d
Prasugrel	Oral, irreversible inhibition	80%	2–4 h	5–9 d
Ticagrelor	Oral, direct, reversible inhibition	85%–90%	2 h	4–5 d
Cangrelor	IV, direct, reversible	95%–100%	2 min	90 min*

For cangrelor, platelet recovery occurs in 90 minutes in 90% of patients. A minimum interval of 3 hours is recommended between drug discontinuation and a neuraxial injection, longer for the high-risk procedures.

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loading doses are 600 mg for clopidogrel, 60 mg for prasugrel, and 180 mg for ticagrelor.

Cangrelor may be used as a bridge therapy, in patients on oral P2Y12, before surgery. This is to protect the patients while their clopidogrel, prasugrel, or ticagrelor are being discontinued. A study evaluated the use of cangrelor for bridging patients on thienopyridines prior to their CABG.[210] This study showed efficacy of cangrelor; the incidence of platelet inhibition greater than 60% was more than 80% of the patients on cangrelor versus 19% for placebo with no significance difference in major bleeding.

Pain medicine physicians typically will not see patients who had cangrelor infusion for their PCI because these patients will be continued on an oral P2Y12 inhibitor. They may see pain clinic patients on cangrelor bridge therapy. In such cases, if a neuraxial injection has to be done, a minimum of 3-hour interval, preferably longer, should observed. This is similar to the recent ASRA guidelines. An interval longer than 3 hours is ideal in high-risk procedures such as SCS placement, vertebroplasty/kyphoplasty, or intrathecal pump placement. As pain procedures are not emergency interventions, every modality should be tried first to manage the patient's pain.

Procedural Recommendations

The ASRA and the European guidelines on regional anesthesia recommended a 7-day interval for clopidogrel, whereas the Scandinavian guidelines noted that 5 days is probably adequate. The Scandinavian guidelines are based on the 10% to 15% formation of new platelets every day,[211] resulting in 50% to 75% of the circulating platelet pool being unaffected by platelets 5 days after stoppage of the antiplatelet drug.[186] We recommend 7-day cessation of clopidogrel prior to spine or pain intervention. If 5 days is recommended by the managing cardiologist or vascular medicine physician, specifically prior to an extended SCS trial, then a test of platelet function should be performed to ensure adequate recovery of platelet function.[186,189,190] For prasugrel, 7 to 10 days is advisable, whereas 5 days is adequate, for ticagrelor.[198] A minimum of 3 hours should be observed in patients who had cangrelor infusion.

For resumption of the antiplatelet drug after a neuraxial procedure or catheter removal, the Scandinavian guidelines recommended that the drug be started after catheter removal,[145] whereas the European guidelines recommended 6 hours after catheter removal before prasugrel and ticagrelor can be started.[144] Baron et al[212] cautioned in restarting prasugrel and ticagrelor early because of their rapid effect and potent antiplatelet inhibition.

Clopidogrel can be restarted 12 to 24 hours after a spine procedure, in view of its slow onset. However, loading doses of clopidogrel, prasugrel, and ticagrelor take effect within 30 minutes to 6 hours. In these cases, a 24-hour interval is more appropriate. For prasugrel and ticagrelor, a 24-hour interval is recommended in view of their rapid antiplatelet effects.

Summary Recommendations for P2Y12 Inhibitors

- For low-risk procedures, the risks and benefits of stopping clopidogrel should be carefully assessed in conjunction with the treating physician(s). We believe that many, if not most, low-risk procedures (Table 1) can be safely done without discontinuing P2Y12 inhibitors.
- We strongly recommend a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) for those patients with higher bleeding risk profiles, especially when (1) taking concomitant antiplatelet medications, (2) advanced patient age, (3) advanced liver or renal disease, or (4) a prior history of abnormal bleeding exists. These factors should be assessed, against the risk of a thromboembolic event, should clopidogrel be stopped.
- For medium- and high-risk procedures, clopidogrel should be routinely stopped for 7 days. In patients with high risk of thromboembolic events, we recommend a 5-day discontinuation interval, and if available, platelet function tests show adequate platelet function.
- For trial of SCS, clopidogrel may be stopped for 5 days upon consultation with the prescribing physician to assess the risk-to-benefit ratio, but available tests of platelet function (such as the VerifyNow P2Y12 assay or the platelet mapping portion of the thromboelastograph) may be considered.
- For medium- and high-risk procedures, prasugrel should be stopped for 7 to 10 days.
- For medium- and high-risk procedures, ticagrelor should be stopped for 5 days.
- For medium- and high-risk procedures, cangrelor should be stopped for a minimum of 3 hours.
- When clopidogrel, prasugrel, or ticagrelor is stopped, a "bridge" therapy with a low-molecular-weight heparin (LMWH) may be instituted in patients with high risk of thromboembolic events (in consultation with the patient's managing physician). The LMWH will then be discontinued 24 hours before the interventional procedure.
- After an intervention, the usual daily dose (75 mg) of clopidogrel can be started 12 hours later. If a loading dose of clopidogrel is used, there should be an interval of 24 hours.
- Prasugrel and ticagrelor can be started 24 hours after a procedure, whether a usual clinical dose or a loading dose is given.

Older Anticoagulants

Warfarin and Acenocoumarol

The oral anticoagulants exercise their pharmacological action by inhibiting the γ-carboxylation of the vitamin K–dependent coagulation factors (II, VII, IX, and X) and proteins C and S. Monitoring of anticoagulation is performed with the INR. In Europe, acenocoumarol is the most commonly used drug in this group, whereas in the United States warfarin is used. The usual time to normalization of coagulation after the drugs are stopped is 3 days for acenocoumarol and 5 days for warfarin. Warfarin inhibits the vitamin K–dependent clotting factors VII, IX, X, and II. The half-life of factor VII (6–8 hours) is shorter than the half-life of factor IX (20–24 hours), factor X (20–42 hours), or factor II (48–120 hours),[213,214] so the initial anticoagulation from warfarin is secondary to a decrease in clotting factor VII. However, this is antagonized by a decrease in anticoagulant protein C,[214] making the INR unreliable during the early phase of warfarin therapy.[214,215] The full anticoagulant effect of warfarin does not occur until 4 days, when the levels of factor II are significantly decreased. Concentrations of clotting factors of 40% or greater are considered adequate for hemostasis[216]; levels less than 20% are associated with bleeding.[217]

Warfarin is difficult to dose, because it has a narrow therapeutic index and wide interpatient dosing variability, with genetic factors accounting for a large proportion of the variations in dose requirements.[218] Although patients with variations in their *CYP2C9* and/or *VKORC1* require lower doses of warfarin, the American College of Cardiology recommended against pharmacokinetic-based dosing, pending clinical studies.[215] Recent studies on genetic-based dosing did not settle this issue because the results were not uniform.[219–221] Patients who have an exaggerated response to warfarin include the elderly, those

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with low weight, female, and those with preexisting liver and renal comorbidities.[222–226]

The ASRA guidelines on regional anesthesia noted that performance of neuraxial anesthesia or removal of epidural catheters within 24 hours of initial warfarin intake is probably safe. The safety of this practice was supported by showing that the levels of clotting factor VII are greater than 40% (levels considered safe for hemostasis) during the first 12 to 16 hours after initial warfarin intake.[214] If warfarin was given more than 24 hours before a neuraxial injection, the ASRA guidelines on regional anesthesia recommended that the INR be checked beforehand.

Another issue is timing of removal of epidural catheters in patients in whom warfarin was started. As noted, epidural catheters can be removed within 24 hours after warfarin initiation.[214] Two reports showed the absence of spinal hematoma when the epidural catheter was removed 2 to 3 days after warfarin was started.[227,228] In these studies, concentrations of the clotting factors were not determined, and the number of patients in whom the epidural catheter was removed on day 3 was only 140. Removal of the epidural catheter within 48 hours is probably safe, because the levels of factors X and II are probably adequate for hemostasis.[214] Beyond 2 days, clotting factors VII, IX, and X are substantially affected, and the status of factor II is not ensured unless its concentration is determined.

In patients who are not on warfarin, the ASRA regional guidelines recommend an INR of 1.4 or less before a neuraxial injection. However, in patients in whom the warfarin is stopped 5 to 6 days, the INR should be normalized (≤1.2). This recommendation is supported by a recent study wherein the authors showed the vitamin K–dependent clotting factors (VII, IX, X, and II) to be acceptable when the INR was 1.2 or less. This was not the case in the 2 patients whose INRs were 1.3 and 1.4.[229]

In patients who are prone to venous thromboembolism (VTE), a bridge therapy with LMWH has been advised. The efficacy and safety of this practice have been questioned by a study that showed that the incidence of thromboembolism was not reduced and that the incidence of major bleeding was higher in the patients who were "bridged."[230] It should be emphasized that the study was done in patients with atrial fibrillation, and it did not include patients with artificial heart valves.

The ASRA regional guidelines recommended vitamin K for elevated INRs, without bleeding, after warfarin. When there is life-threatening bleeding, recombinant factor VIIa, 3-factor prothrombin complex concentrate (PCC), or, preferably, 4-factor PCC (clotting factor VII in addition to factors, II, IX, and X) can be given.

Summary Recommendations for Warfarin and Acenocoumarol

- For low-risk procedures, the decision as to whether warfarin should be stopped should be considered in conjunction with the treating physician(s). We believe that many of these procedures may be safe in the presence of a therapeutic INR (INR <3.0).[231,232]
- We strongly recommend, however, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) for those patients with higher bleeding risk, similar to the antiplatelet agents.
- Warfarin should be stopped for 5 days and the INR normalized (≤1.2) before high- and intermediate-risk pain procedures.
- Acenocoumarol should be stopped for 3 days and the INR normalized before high- and intermediate-risk pain procedures.
- After the procedure, warfarin can be restarted the next day.
- Alternatively, a bridge therapy with LMWH can be instituted in patients who are at high risk of thrombosis after consultation with the treating physicians.

Heparin

Unfractionated heparin inactivates thrombin (factor IIa), factor Xa, and factor IXa. The anticoagulant effect of IV heparin is immediate, whereas subcutaneous heparin takes 1 hour.[233] Heparin has a half-life of 1.5 to 2 hours, and its therapeutic effect ceases 4 to 6 hours after its administration. The effect of heparin is not linear, but its half-life increases with increased dose. Monitoring is via the activated partial thromboplastin time (aPTT); therapeutic anticoagulation is achieved when the aPTT is 1.5 to 2.5 times the initial value. Reversal is achieved with protamine, with the dose being 1 mg of protamine per 100 units of heparin.

The risk factors for the development of spinal hematoma in patients who had a neuraxial procedure and subsequent anticoagulation include heparinization within 1 hour of dural puncture, concomitant ASA therapy, and traumatic spinal punctures.[234] In the study by Ruff and Dougherty,[234] 7 of 342 patients who were subsequently heparinized within 1 hour developed spinal hematoma, whereas none in their control group of another 342 patients did.

The most recent ASRA regional anesthesia guidelines recommended that IV heparin be stopped for 4 to 6 hours and verification of normal coagulation status before a neuraxial procedure should be performed.[143] For pain interventional procedures, the longer 6 hours with normalization of coagulation status interval is recommended, especially for SCS placements, intrathecal drug delivery catheter placements, or vertebral augmentation, for example, kyphoplasty. The clinical setting when IV heparin is given and the elective nature of pain procedures make this scenario unlikely. Analgesics may be given during the heparin administration, and the pain procedure performed after the patient has discontinued IV heparin.

The American Society of Regional Anesthesia and Pain Medicine recommended an interval of at least 1 hour after a spinal or epidural (or catheter removal) before IV heparin is administered.[235] If the neuraxial procedure is bloody, cancellation of surgery has been recommended.[236,237] After high-risk pain interventional procedures such as SCS placement, intrathecal pump, and vertebroplasty/kyphoplasty, wherein it can be bloody, we recommend a 24-hour interval before resumption of IV heparin, similar to the one recommended by Chaney.[237] This interval is similar to recent recommendations on resumption of the new oral anticoagulants (NOACs) after a surgical procedure.[238,239] This scenario should rarely be encountered because moderate- and high-risk pain procedures should not be done in patients who are on IV heparin.

Summary Recommendations for IV Heparin

- Intravenous heparin should be stopped for at least 6 hours before a low-, medium-, or high-risk procedure is performed (Table 2).
- The IV heparin can be started a minimum of 2 hours after a pain procedure. If a moderate- or high-risk procedure was performed, especially if it was bloody, then a 24-hour interval should be observed.
- Situations where pain procedures are performed in patients on IV heparin should rarely exist because alternative analgesics can help manage the pain until the intervention is performed when the patient is off the heparin.

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Subcutaneous Heparin

The anticoagulant effect of low-dose, BID subcutaneous heparin (5000 units every 8–12 hours) is via heparin-mediated inhibition of activated factor Xa. After subcutaneous injection of heparin, maximum anticoagulation is observed in 40 to 50 minutes, which dissipates within 4 to 6 hours. The aPTT of most patients remain within the reference range[240] during subcutaneous minidose heparin; only a small percentage of patients had activated partial thromboplastin time exceeding 1.5 times the normal. The safety of neuraxial anesthesia in the presence of anticoagulation with BID subcutaneous doses of unfractionated heparin has been documented by several publications.[235] The ASRA guidelines on regional anesthesia considered minidose BID subcutaneous heparin not a contraindication to neuraxial injections. Although rare, cases of spinal hematoma have been reported in this setting.[241–243] The occurrence of spinal hematomas, although rare, made us recommend an interval of at least 6 hours before a planned neuraxial procedure including ESIs. It should be noted that we recommended 8 hours in our initial ASRA pain guidelines, a recommendation that has caused some debate.[244–247] We now recommend a 6-hour interval to be more in line with the pharmacokinetics of IV heparin, when its plasma concentrations are the lowest.

Thrice-daily (TID) subcutaneous heparin regimens have become popular in reducing the incidence of postoperative thromboembolism (VTE).[248] This practice has been associated with spontaneous hematomas.[249] In a meta-analysis, King et al[249] noted that while TID subcutaneous heparin is superior to BID regimen in preventing VTE, it is also associated with more bleeding. Most of the major bleeds involved the GI tract, retroperitoneal space, or intracranial locations.

More recent studies showed the safety of neuraxial injections in patients on TID heparin.[250,251] These studies prompted the Writing Committee of the ASRA regional guidelines to allow neuraxial injections in patients on TID heparin. However, it recommends that neuraxial injection or removal of an epidural catheter be done 4 to 6 hours after the subcutaneous heparin. We recommend a 6-hour interval before neuraxial pain injections (ESIs) but a 24-hour interval in the high-risk pain surgical interventions. Again, this scenario should be very rare, and pharmacological and other treatments should be attempted in these patients first.

Summary Recommendations for Subcutaneous Low-Dose Heparin

- For patients on BID or TID dosing, intermediate-risk procedures (eg, ESIs) can be done 6 hours after the subcutaneous heparin.
- For high-risk procedures (eg, SCS, intrathecal pump placements, vertebroplasty/kyphoplasty), we recommend an interval of 24 hours from the last dose of SC heparin and normalization of the aPTT (Table 2).
- The SC heparin can be restarted a minimum of 2 hours after the low-risk procedures but 6 to 8 hours after the intermediate- and high-risk procedures, when the clot has theoretically stabilized.
- These scenarios should be avoided if possible. The patient's pain can be managed with alternative pharmacological therapies (opioids, anticonvulsants, antidepressants) until the procedure can be performed after the patient has discontinued SC heparin.

Low-Molecular-Weight Heparin

The plasma half-life of the LMWHs ranges from 2 to 4 hours after an IV injection and 3 to 6 hours after a subcutaneous injection. Low-molecular-weight heparin has a higher and more predictable bioavailability than standard heparin, and dose adjustment for weight is not necessary. Low-molecular-weight heparin exhibits a dose-dependent antithrombotic effect that is assessed by the anti–factor Xa activity level. The recovery of anti–factor Xa activity after a subcutaneous injection of LMWH approaches 100%,[252] and laboratory monitoring is unnecessary except in patients with renal insufficiency or those with body weight less than 50 kg or more than 80 kg.[253]

Although the LMWHs constitute a relatively homogeneous pharmacological group, the most studied and referenced drug is enoxaparin; there are different commercial preparations on the market that share common characteristics but that also possess different clinical and pharmacological properties and must be regarded as similar but not equal drugs.

The commercially available LMWHs in the United States are enoxaparin (Lovenox) and dalteparin (Fragmin). Tinzaparin has been discontinued for low usage. Enoxaparin is given either once daily or every 12 hours when used as thromboembolic prophylaxis, whereas dalteparin is given once daily. The drugs seem to have comparable efficacy in the treatment and prevention of VTE.[254] The recommended thromboprophylactic dose in the United States is 30 mg enoxaparin BID, although some clinicians increase the dose in patients who are obese (1.5 mg/kg daily or 1 mg/kg every 12 hours).

The European dosing schedule for prophylaxis is enoxaparin 20 to 40 mg once daily and 1 mg/kg per 12 hours for therapeutic purposes. Generally speaking, 3 regimens of LMWH administration as thromboprophylaxis are used daily and are summarized below[255,256]: (1) preoperative protocol, administration of the first dose of LMWH approximately 12 hours before surgery, followed 24 hours after the first administration, and so on; (2) postoperative protocol, in which administration of the first dose of LMWH is performed from 12 hours after surgery; subsequent dosing varies depending on when thromboprophylaxis begins, with the following dose given 12 hours after the first (if the latter was given 12 hours after surgery) or 24 hours (if begun after 24 hours); and (3) perioperative protocol, with thromboprophylaxis starting between 12 hours before and 12 hours after surgery.

The ASRA guidelines for regional anesthesia recommend a 12-hour interval after prophylactic enoxaparin dose before a neuraxial procedure but recommend a 24-hour interval when higher doses of enoxaparin are used and also for dalteparin. If there is blood during catheter placement, ASRA guidelines recommend that postoperative administration of LMWH therapy be delayed for 24 hours. The same guidelines are recommended for low-, intermediate-, and high-risk interventional pain procedures.

The most recent ASRA regional guidelines recommended a minimum of 4 hours after epidural catheter removal before LMWH is restarted.[143] This was partly based on a US Food and Drug Administration (FDA) Drug Safety Communication on November 6, 2013, that recommended a 4-hour interval.[257] A review of its data showed the following as risk factors: female sex, elderly (≥65 years), abnormalities of spinal cord or vertebral column, patients at increased risk of hemorrhage, renal insufficiency, traumatic needle/catheter placement, indwelling epidural catheter during enoxaparin administration, early postoperative administration (<12 hours), BID administration (vs once-daily administration), and concomitant medications affecting hemostasis (antiplatelet, anticoagulant, NSAIDs, etc). Another rationale for the 4-hour interval is the difference between the time for a solid clot to form (8 hours) and the peak effect of LMWH (4 hours).

Similar to the regional guidelines, we recommend a minimum interval of 4 hours before LMWH heparin is started after a neuraxial injection (ESI, facet injections). However, the committee recommends at least 12 hours' interval after a high-risk

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surgical pain procedure for extra safety. This is for additional safety as the administration of enoxaparin within 24 to 48 hours after a cerebral embolic clot was shown not to enlarge the hematoma.[258]

Summary Recommendations for LMWHs

- We recommend a 12-hour interval between discontinuation of a prophylactic dose of enoxaparin (except when the dose is 1 mg/kg) and low-, medium-, and high-risk pain procedures.
- When a therapeutic dose of enoxaparin (1 mg/kg) is used and likewise for dalteparin, we recommend a 24-hour interval between discontinuation of the drug and low-, medium-, and high-risk pain procedure.
- The LMWH can be resumed 4 hours after low-risk pain procedures but at least 12 hours after intermediate- and high-risk pain procedures.
- Concomitant drugs that affect hemostasis (antiplatelet, NSAIDs, SSRIs, other anticoagulants) should be used with extreme caution in patients on LMWH.

Fibrinolytic Agents

Thrombolytic agents convert plasminogen and thrombi to plasmin, the enzyme that causes fibrinolysis. Recombinant tissue-type plasminogen activator, an endogenous agent, is more fibrin selective than streptokinase or urokinase and has less effect on circulating plasminogen levels. Although the half-life of thrombolytic drugs is a few hours, the inhibition of plasminogen and fibrinogen may last for up to 27 hours.[143]

Cases of spontaneous spinal hematoma have been reported in patients on thrombolytic therapy.[259–265] There are also cases of spinal hematoma in patients who had neuraxial procedures and had subsequent thrombolytic therapy.[266–269] In some case reports, the patients were also given heparin. The risk of spinal hematoma in patients who receive thrombolytic therapy is not well defined because of the understandable lack of prospective studies.

The Scandinavian guidelines recommend a 24-hour interval between discontinuation of the drug and neuraxial procedure,[145] based on the short half-lives of the different thrombolytic drugs. The new ASRA regional guidelines recommended that neuraxial injections not be performed except in highly unusual situations. If it has to be done, then a minimum of 48 hours and confirmation of normal clotting studies have been suggested.[143] Similar to the regional guidelines, we recommend a minimum of 48 hours and normalization of coagulation studies before neuraxial injections are done. Longer intervals should be considered for high-risk surgical pain procedures.

There are rare instances when a patient needs an emergency thrombolytic therapy soon after a neuraxial procedure, for example, myocardial infarction, pulmonary, or cerebral embolism. If notified, the pain physician should remove in situ epidural or intrathecal catheters before initiation of thrombolytic therapy. The dilemma occurs when a thrombolytic agent is given before catheter removal. Thrombolytics are effective if given within 6 hours of an embolic clot—this is the reason for the initiation of thrombolytic therapy once the diagnosis was made.[270,271] In this situation and in patients with an indwelling intrathecal catheter, the ASRA guidelines on regional anesthesia suggested measuring the fibrinogen level to assess the state of thrombolysis and in guiding the timing of removal of an epidural catheter.[143] The European guidelines recommend leaving the epidural catheter during thrombolysis and removing the catheter when the effect of the drug is gone.[144] In patients who just had a percutaneous SCS lead trial or in whom an epidural/intrathecal catheter was placed, the catheter/leads can be left in place if the thrombolytic agent has already been given, a practice recommended by the European guidelines. Fibrinogen levels can be intermittently determined. Frequent neurologic monitoring, for example, every 2 hours, is recommended for an appropriate length of time in patients who have recently received neuraxial blocks after fibrinolytic or thrombolytic therapy. Removal of epidural leads/catheters should be made after shared discussion and decision making with other physicians caring for the patient, preferably at least 48 hours from the last dose of the thrombolytic agent.

Summary Recommendations for Thrombolytic Agents

- Interventional pain procedures should be avoided in patients who just had fibrinolytic agents. Other measures, including analgesic medications, should be attempted to manage the patient's pain. If an intervention has to be performed, a minimum of 48 hours between discontinuation of a thrombolytic agent and a neuraxial injection is probably safe (Table 4). Longer intervals, ie, 72 hours, should be considered for high risk surgical pain procedures.
- In emergency situations wherein a thrombolytic needs to be administered after a spine pain intervention, the pain service should preferably be informed. Shared assessment, risk stratification, and management decisions regarding the timing of administration of the fibrinolytic agent should be observed. If the patient has a neuraxial catheter or SCS lead, the device can be left in place. Fibrinogen levels can be determined and the device removed after 48 hours or after a minimum of 2 half-lives of the drug has elapsed.

Fondaparinux

Fondaparinux is a synthetic anticoagulant that selectively inhibits factor Xa. The drug is 100% bioavailable, attains maximum concentration within 1.7 hours of administration, and has a half-life of 17 to 21 hours.[272] Its extended half-life allows once-daily dosing. It is usually administered 6 hours after surgery.[273]

TABLE 4. Recommended Intervals of Discontinuation and Resumption of Anticoagulants and Pain Procedures

Anticoagulant	Discontinuation → Procedure	Procedure → Resumption*
Coumadin	5 d, INR normalized (≤1.2)	6 h
IV heparin	6 h	2–24 h†
Subcutaneous heparin, BID or TID	6–24 h†	2–6 h†
LMWH	12–24 h‡	4–24 h†
Fibrinolytic agents	48 h	§
Fondaparinux	4 d	6–24 h†

*Resumption of drugs: coumadin: 6-hour time is empirical; it can be started sooner because clot stabilizes after 8 hours, and the initial effect of warfarin on the INR is due to inhibition of clotting factor VII, which has a half-life of 6 to 8 hours, so theoretically the clot will have stabilized by the time warfarin takes effect; fondaparinux: the 6-hour time is based on the 8-hour time it takes for a clot to be stable and the 2-hour peak effect of the drug.

†The shorter time interval is for low-risk procedures; the longer time interval is for intermediate- and high-risk procedures.

‡Twelve hours for prophylactic enoxaparin, 24 hours for therapeutic enoxaparin and dalteparin.

§Thrombolytic agents are given to patients in emergency cases (see text).

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Fondaparinux is recommended as an antithrombotic agent after major orthopedic surgery[274] and as initial treatment of pulmonary embolism.[275]

The actual risk of spinal hematoma with fondaparinux is unknown. A study showed no complications in 1603 patients who had neuraxial catheters or deep peripheral nerve catheters.[276] Fondaparinux 2.5 mg was given 6 to 12 hours after surgery, the catheters were removed 36 hours after the last dose of fondaparinux, and redosing was 12 hours after catheter removal. Patients were excluded from the study if difficulties were encountered in performing the neuraxial procedure (>3 attempts), the procedure was complicated by bleeding, if they were taking antiplatelet drugs, or the plan was to withdraw the epidural catheter the day after surgery. Because of these unrealistic requirements in clinical practice, the ASRA regional guidelines on regional anesthesia recommended against the use of fondaparinux in the presence of an indwelling epidural catheter. Their recommendations were based on the sustained and irreversible antithrombotic effect of fondaparinux, early postoperative dosing, and spinal hematoma being reported during the initial clinical trials of the drug.[143] The guidelines further recommended that performance of neuraxial techniques should occur under conditions used in clinical trials (single needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters).

In the study of Singelyn et al,[276] the authors observed a 2-half-life interval between discontinuation of the drug and removal of the catheter. With 2 half-lives, only 75% of the drug is eliminated,[130] a situation that may not be safe in elderly pain patients who have spinal stenosis. An interval of 5 half-lives is more acceptable.

Summary Recommendations for Fondaparinux

- We recommend a 5-half-life, or 4-day, interval discontinuation of fondaparinux before medium- and high-risk pain procedures (Table 4).
- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with treating physician(s) should guide whether fondaparinux should be discontinued. If a more conservative approach is needed, then 2-half-life, or 2-day, interval is probably adequate.
- For low-risk procedures, we recommend an interval of 6 hours before fondaparinux is resumed. For intermediate- and high-risk surgical pain procedures, then a 24-hour delay is suggested. This is in view of the short onset of the effect of fondaparinux.

New Anticoagulants: Dabigatran, Rivaroxaban, Apixaban, Edoxaban

Unlike warfarin, NOACs do not require serial coagulation monitoring and are safer, partly because of their short half-lives. They are more expensive than warfarin and are shorting acting, and missed doses may increase the risk of VTE. Only recently have specific antidotes to reverse their anticoagulant effect been approved or were undergoing clinical trials.

The most recent ASRA regional guidelines recommended a 2- to 5-half-life interval between stoppage of the drug and neuraxial injection: 2 half-lives for the patient with minimal medical problems and 5 half-lives for the higher doses of NOACs and for patients with medical comorbidities especially kidney insufficiency.[143] The 2-half-life interval is based on a recommendation of 2 half-lives as an adequate compromise between prevention of VTE and spinal hematoma.[277] But there is no consensus on the "exact" time for this management. Several experts recommended intervals of 1 to 5 days between discontinuation of the drug and invasive procedures or surgery.[278–280]

The reasons for allowing residual anticoagulation include the occurrence of pulmonary embolism during the initial phase of warfarin therapy[214] and subclinical deep vein thrombosis soon after surgery[277] and to facilitate full anticoagulation.[281] However, the pharmacokinetics of the new anticoagulants were studied in young healthy individuals, not the elderly patients with spinal stenosis. Concomitant antiplatelet therapy was an exclusion criterion in some of the total joint surgery trials,[282] and antiplatelet therapy has been implicated in case reports of spinal hematoma.[3,4] Also, the postmarketing surveillance on dabigatran showed an increased incidence of GI tract bleeding.[283]

Twenty-five percent of the drug still remains in the plasma after 2 half-lives, but only 3% remains after 5 half-lives.[130] Because patients with back pain may have spinal stenosis and because some interventional procedures are actually surgical in nature (permanent SCS or intrathecal pump placements), we recommend a 5-half-life interval between discontinuation of the drug and neuraxial pain procedures. There is minimal difference between 5 and 6 half-lives (3.125% and 1.5625% of the drug remains in the blood), so there is little justification to go beyond 5 half-lives. If the risk of VTE is high, then a bridge therapy with LMWH may be instituted.

For resumption of new anticoagulants after removal of an epidural catheter or neuraxial injection, the Scandinavian guidelines recommended 8 hours minus the time it takes for the anticoagulant to reach peak effect.[145] This was based on the article by Rosencher et al,[277] wherein they stated that it takes approximately 8 hours for a platelet plug to become a stable clot. The basis for this statement is not well documented, but the recommendation may be acceptable in regional anesthesia. Serial magnetic resonance imaging after epidural blood patches showed the clot to be stable by 7 hours.[284] A study showed that enoxaparin given 24 to 48 hours after intracerebral hemorrhage did not enlarge the size of the hematoma.[258] Although thrombolytics are still effective when given within 6 hours of a cerebral embolic clot,[270] thrombolytics are more effective when given within 3 hours after the onset of stroke.[271] These studies[270,271] imply that anticoagulants (not thrombolytics) may have a hard time lysing a clot if given after 6 hours and most probably will not lyse a clot if given 24 to 48 hours after a neuraxial injection. Other authors noted that the reinstitution of antithrombotic therapy within 24 hours after a major procedure might increase the risk of bleeding after the procedure.[212] Liew and Douketis[285] recommended a minimum of 24 hours in patients with low bleeding risk and 48 hours in those with a high bleeding risk, before resuming dabigatran, rivaroxaban, or apixaban. Baron et al[212] recommended 48 hours, while Connolly and Spyropoulos[286] recommended 24 hours but at half the usual dose. The risks posed by the elderly with spine abnormalities, our typical pain clinic patients, make us recommend a 24-hour interval after intermediate- and high-risk procedures before resumption of the new anticoagulants. This 24-hour recommendation is similar to recommendations on starting NOACs after surgery. If the risk of VTE is very high, a 12-hour interval, at half the baseline dose, may be considered. Such decisions should be made on an individual basis and in consultation with the treating physician(s). Dabigatran, rivaroxaban, and apixaban have short onsets of action and should hopefully make up for the delay in reinstitution of these drugs.

Summary Recommendations for the NOACs

- We recommend a 5-half-life interval between discontinuation of any one of the new anticoagulants and medium- and high-risk pain procedures (see Table 5 for the days specific to each new anticoagulant).

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TABLE 5. Recommended Intervals of Discontinuation and Resumption of the NOACs and Pain Procedures

Drug	Half-life	Recommended Interval Between Stoppage of Drug and Pain Procedure (5 Half-lives)*	Recommended Interval Between Procedure and Resumption of Drug†
Dabigatran	12–17 h 28 h (renal disease)	4 d 5–6 d (patients with renal disease)	24 h
Rivaroxaban	9–13 h	65 h (3 d)	24 h
Apixaban	15.2 ± 8.5 h	75 h (3 d)	24 h
Edoxaban	9–14 h	70 h (3 d)	24 h

*In view of the added risks involved in chronic pain patients (elderly, spinal stenosis) and the surgical nature of some of our interventional procedures, we recommend an interval of 5 half-lives between the last dose of the drug and moderate and high-risk procedures.

†The procedures include medium- and high-risk interventional pain procedures. For low-risk procedures, a shared decision making should be followed; 2-half-life interval may be considered.

- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide whether these new anticoagulants should be stopped. A 2-half-life interval may be considered.
- If the risk of VTE is high, then an LMWH bridge therapy can be instituted during stoppage of the anticoagulant, and the LMWH can be discontinued 24 hours before the pain procedure.
- We recommend a 24-hour interval after interventional pain procedures before resumption of the new anticoagulants.
- If the risk of VTE is very high, half the usual dose may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's other physician(s) (Table 5).

Case Reports of Spinal Hematoma in Patients Who Were on NOACs

There have been case reports of spinal hematoma in patients on NOACs: 2 from dabigatran,[290,291] (Table 6) 7 from rivaroxaban,[287–289,292–295] and 1 from apixaban.[296] The spinal hematomas after dabigatran and apixaban and 5 of the 7 spinal hematomas in patients on rivaroxaban were spontaneous. In 2 patients, the timing of the rivaroxaban intake and the interval between stoppage of the drug and removal of the epidural catheter then resumption of the drug can be questioned. In 1 one patient, the hematoma was probably due to the rivaroxaban being given to the patient approximately 24 hours after 40 mg enoxaparin and 7 mg warfarin were stopped.[287] The patient was on warfarin for 3 days, which was stopped 24 hours before the rivaroxaban, a situation in which the drug was still very active when the rivaroxaban was given. In the other patient, the interval between stoppage of rivaroxaban and removal of the catheter was 18 hours, or 2 half-lives of the drug.[288] The interval between removal of the epidural catheter and resumption of the drug was 6 hours. As the maximum effect of rivaroxaban is reached within 2 to 3 hours, the clot was barely stable when the rivaroxaban reached maximum inhibition of clotting factor Xa (Table 6).

TABLE 6. Case Reports of Spinal Hematoma Related to NOACs*

Drug	History	Outcome	Comments
Rivaroxaban (Radcliff et al[287])	53 y old, female; TKR (spinal); 5–7 mg warfarin on hospital day 1 and POD2–3, and 40 mg enoxaparin on POD1–3. Switched to rivaroxaban on POD4 (dose not stated); leg pain on POD6 and numbness on POD7; L4–5 SEH on MRI	Emergency laminectomy inferior vena cava filter; residual peroneal anesthesia and neurogenic bladder at 2-y follow-up	Patient had spinal stenosis; SEH may have been initiated or aggravated by the multiple anticoagulants and the intake of rivaroxaban while warfarin was still fully active
Rivaroxaban (Madhisetti et al[288])	59 y old, female; TKR (CSE), postop epidural infusion; 10 mg rivaroxaban started the night of surgery, epidural catheter removed 18 h after rivaroxaban; rivaroxaban repeated 6 h after removal; bladder incontinence and back pain 12 h after last dose of rivaroxaban; L2–L4 SEH on CT	Emergency laminectomy; complete recovery after 5 d	Short interval between rivaroxaban dose and removal of epidural catheter (18 h); 6-h interval between catheter removal and resumption of rivaroxaban (6 h) may be just a little short
Rivaroxaban (Zaarour et al[289])	58 y old, male; 20 mg rivaroxaban daily for AF; interscapular pain after 30 d on rivaroxaban; bilateral LE weakness; C7–T2 intradural hematoma on MRI	IV dexamethasone, sensory/motor improvement after 1 d; C7 corpectomy done on the fourth day; almost complete recovery	Spontaneous hematoma? Patient had THR (spinal) 3 wk before episode; rivaroxaban stopped 3 d before surgery and restarted a few days later

*Case reports of other spontaneous spinal hematomas, although noted in the text, are not included.

AF indicates atrial fibrillation; CT, computed tomography; CSE, combined spinal epidural; LE, lower extremity; MRI, magnetic resonance imaging; POD, postoperative day; SEH, spinal epidural hematoma; THR, total hip replacement; TKR, total knee replacement.

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Dabigatran

Dabigatran etexilate is a prodrug that is hydrolyzed by esterases in the stomach to the active drug dabigatran. The drug is a direct thrombin inhibitor that blocks the interaction of thrombin with different substrates[297–299]; it acts independently of antithrombin. Thrombin converts fibrinogen to fibrin; activates factors V, VIII, and XI; and stimulates platelets. The bioavailability of dabigatran after oral dabigatran etexilate is 7.2%,[300] and peak plasma concentrations are attained 1.5 to 3 hours after intake of the prodrug.[300–302] Dabigatran has a half-life of 14 to 17 hours.[303,304] The pharmacokinetic profile of dabigatran is predictable and not affected by sex, body weight or obesity, ethnic origin, or mild to moderate hepatic impairment.[302] Renal clearance accounts for 80% of the clearance of dabigatan,[305] elimination half-life of the drug is doubled from 14 hours to 28 hours in patients with end-stage renal disease.[305,306] The drug is contraindicated in patients with creatinine clearance (CrCl) of less than 30 mL/min.[307]

Dabigatran is effective in the prevention of stroke in patients with nonvalvular atrial fibrillation[308] and has been approved for such use in the United States, Canada, and Europe. It has also been approved for use in Europe and Canada for the prevention of VTE after total hip or knee replacement but not in the United States. This is probably because dabigatran was noted to be superior to enoxaparin in a European study[309] but not in a North American study.[310] A meta-analysis of the trials noted no differences between dabigatran and enoxaparin in any of the end points that were analyzed.[311]

In the studies on dabigatran's use as VTE prophylaxis after total joint surgery, the drug was started after surgery.[309–315] Approximately 4785 patients had neuraxial anesthesia (many had spinal anesthesia), but the exact interval between the neuraxial procedure and catheter removal and institution of the drug was not stated.[316] Although there was no instance of spinal hematoma, the small number in relation to the incidence of spinal hematoma makes it difficult for one to make a definitive conclusion on the interval between a neuraxial procedure and resumption of the drug. It should be noted that the manufacturer states that epidural catheters should not be placed in patients receiving dabigatran.[144]

The aPTT is prolonged after dabigatran, but the relationship is curvilinear; there is a greater than linear increase at lower concentrations (at or <200 ng/mL) and a linear relationship at higher concentrations (>200 ng/mL).[317,318] The thrombin time (TT), also known as thrombin clotting time, is highly sensitive to the effects of dabigatran[318–320] and is more appropriate to detect the presence of, but not to quantify, the anticoagulant effect of dabigatran.[320] A dilute TT (hemoclot thrombin inhibitory assay) has become available and has linearity across pharmacologically relevant plasma dabigatran concentrations.[317,319] The ecarin clotting time (ECT), which directly measures thrombin generation, is prolonged by dabigatran[320] and is linearly related to dabigatran concentrations.[317] The ECT is the most sensitive assay for dabigatran, but very few institutions have availability. The prothrombin time (PT) is the least sensitive test. The dilute TT and the ECT are the tests of choice for dabigatran.[317]

It is unlikely that fresh frozen plasma is effective in the reversal of dabigatran. Activated charcoal prevents absorption of the dabigatran but needs to be given within 2 hours of ingestion of the drug. Dialysis might speed elimination of the drug. Recombinant factor VIIa (NovoSeven, Princeton, New Jersey) has been recommended to control hemorrhage. Prothrombin complex concentrates or concentrated pooled plasma products contain either 3 (factors II, IX, and X) or 4 (factors II, VII, IX, and X) clotting factors. Nonspecific hemostatic agents such as recombinant factor VII, factor VIII inhibitor bypassing activity, or PCCs have been suggested based on clinical need.[321–323] A dabigatran-directed neutralizing antibody, idarucizumab, has been approved for use. A prospective study showed that idarucizumab normalized the elevated ECT in 88% to 98% of patients, an effect that was seen within minutes.[324] The dose of idarucizumab was 5 g intravenously, administered as 2 50-mL bolus infusions, 2.5 mg per dose, given no more than 15 minutes apart.

The new ASRA regional guidelines recommended a 34-hour interval (2 half-lives) between the last dose of dabigatran and neuraxial procedure (or catheter placement/removal).[143] This interval should be increased to 48 to 85 hours (4–5 half-lives) in higher doses (eg, 220 mg/d) and to 72 to 90 hours in patients with CrCl of 30 to 49 mL/min. In contrast, we recommend 5 half-lives, or 4 days, between stoppage of the drug and moderate- and high-risk interventional procedures. As noted earlier, this is due to the higher risks inherent in our patient population and the surgical nature of some of our pain interventions. The interval should be extended to 5 to 6 days in patients with renal insufficiency.

Summary recommendations with dabigatran

- We recommend a 5-half-life interval, or 4 days, between discontinuation of dabigatran and medium- or high-risk pain procedure (Table 5).
- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide whether dabigatran should be stopped. If a more conservative approach is desired, then 2 half-lives (2 days) may be considered.
- For patients with end-stage renal disease, we recommend a 5- to 6-day interval because the half-life of dabigatran increases to 28 hours in this condition.
- We recommend a 24-hour interval after interventional pain procedures before resumption of dabigatran. This recommendation is similar to recommendations after surgical procedures.
- If the risk of VTE is very high, dabigatran may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's treating physician(s).

Rivaroxaban

Rivaroxaban, a direct factor Xa inhibitor, has a rapid onset of action. Peak plasma concentrations are observed within 2.5 to 4 hours,[325,326] and maximum inhibition of factor Xa (up to 68%) occurs 3 hours after dosing. Factor Xa inhibition occurs for 12 hours[326] or 24 to 48 hours when higher doses are given in the elderly.[327] The half-life of rivaroxaban is 5.7 to 9.2 hours[325,326] and can be as long as 13 hours in elderly patients secondary to the age-related decline in renal function.[328,329] A third of the drug is eliminated each by the kidneys and the fecal/biliary route, with the remaining one-third being metabolized to inactive metabolites.[325,330] The renal clearance of rivaroxaban decreases with increasing renal impairment.[331] Rivaroxaban is partly metabolized by the liver, and its use is to be avoided in patients with severe liver disease.[329,332] The concomitant use of ASA and rivaroxaban is an independent risk factor for bleeding. When added to ASA and clopidogrel, rivaroxaban enhanced the inhibition of ADP-induced platelet aggregation.[333] Risks for increased bleeding include the advanced age, patients with low body weight, and those with renal insufficiency.

Rivaroxaban is as effective as enoxaparin in the treatment of symptomatic VTE[334] and noninferior to warfarin for the

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prevention of embolic stroke during atrial fibrillation.[335] Because of the efficacy of rivaroxaban in these conditions, it has been approved in the United States, Canada, and Europe for the treatment of VTE. It has been approved for the prevention of stroke in nonvalvular atrial fibrillation because factor Xa inhibitors have been associated with fewer strokes and embolic events, fewer intracranial hemorrhages, and lower all-cause mortality compared with warfarin.[336] Rivaroxaban is also approved for prevention of VTE after orthopedic surgery in the United States, Canada, and Europe as the drug was noted to be as effective or superior to enoxaparin in preventing VTE after total joint surgery.[337–341] In all 4 RECORD studies, 10 mg rivaroxaban was given 6 to 8 hours after surgery. Although the number of patients who had neuraxial anesthesia or epidural catheters was not stated in the RECORD studies, there was no spinal hematoma in the 4622 patients who received rivaroxaban and had "regional anesthesia." According to Rosencher et al,[342] the epidural catheters were not removed until at least 2 half-lives after the last dose of rivaroxaban, and the next rivaroxaban dose was given 4 to 6 hours after catheter removal. None of the 1141 patients who were given rivaroxaban and had neuraxial anesthesia developed spinal hematoma.[342] This small number of patients does not provide assurance as to the safety of the 2-half-life interval observed in the RECORD studies. There is a black-box warning about the risk of spinal/epidural hematoma in patients receiving rivaroxaban. Factors that increase the risk of spinal hematoma are indwelling epidural catheters, concomitant use of drugs that inhibit platelet function, traumatic or repeated epidural or spinal punctures, and a history of spinal deformity or surgery.[332]

A minimum of 18 hours between the last dose of rivaroxaban and removal of an indwelling catheter and a minimum of 6 hours before resumption of the drug have been recommended by the Scandinavian Society guidelines.[145] The European Society guidelines recommended an interval of 22 to 26 hours between the last dose of rivaroxaban and removal of an indwelling catheter and an interval of 4 to 6 hours between epidural catheter removal and the next dose of rivaroxaban.[144] These 2 recommendations represent a 2-half-life interval between rivaroxaban discontinuation and epidural catheter placement or removal. The 4- to 6-hour interval before resumption of the next dose is also in agreement with the recommendation of Rosencher et al[277] of 8 hours minus the peak effect of the drug, as rivaroxaban takes 2.5 to 4 hours to reach peak effect. As noted earlier, a 5-half-life interval is more appropriate for pain interventions. This corresponds to 3 days.

A linear correlation was observed between the effects of rivaroxaban and the PT, especially.[318,320] Overall, the PT and the anti–factor Xa are the tests best suited for monitoring the effects of rivaroxaban.[317] It should be noted that each NOAC requires an analyte-specific test; for example, the test for rivaroxaban will not give correctly calibrated results for apixaban.[343] Activated charcoal may be effective in removing rivaroxaban if given within 8 hours of rivaroxaban ingestion.[320] Rivaroxaban may not be dialyzable because of high protein binding.[344] Nonspecific hemostatic agents, including recombinant factor VII and PCCs, may be used to reverse the NOACs.[321–323]

Andexanet is a recombinant modified human factor Xa decoy protein that binds and sequesters factor Xa inhibitors within the vascular space, restoring the factor Xa activity. A 2-part randomized, placebo-controlled study was recently conducted in older healthy volunteers.[345] Among the rivaroxaban-treated patients, anti–factor Xa activity was reduced by 92% after andexanet compared with 18% in the patients who received placebo. In the study, andexanet was administered as a 400-mg IV bolus (30 mg/min) or as a 400-mg IV bolus followed by a continuous infusion of 4 mg/min for 120 minutes (total of 480 mg). Andexanet is undergoing phase II/III clinical trials in the United States.

The most recent ASRA regional guidelines stratified their recommendation based on the dose of rivaroxaban and the presence of kidney impairment.[143] When the dose is less than 10 mg/d, the Writing Committee recommended a 22- to 26-hour interval (2 half-lives) between the last dose and neuraxial injection and 44 to 65 hours (3 days) when the dose is greater than 10 mg/d or when the CrCl is less than 50 mL/min. Six hours is recommended after neuraxial injection or removal of catheter before the drug is resumed. In contrast, we recommend that 5 half-lives, or 3 days, elapse before pain interventional procedures are performed and 24 hours before the drug is resumed. The case report of a spinal hematoma in a patient wherein an 18-hour interval was observed between the last dose of rivaroxaban and epidural catheter removal and resumption of the drug 6 hours later[288] reinforces our recommendation of intervals of 5 half-lives and resumption 24 hours after a pain procedure.

Summary recommendations with rivaroxaban

- We recommend a 5-half-life interval, or 3 days, between discontinuation of rivaroxaban and medium- or high-risk pain procedures (Table 5).
- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide whether rivaroxaban should be stopped. In these procedures with lower risk of bleeding, 2-half-life interval may be considered.
- We recommend a 24-hour interval after interventional pain procedures before resumption of rivaroxaban.
- If the risk of VTE is very high, half the usual dose may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's treating physician(s).

Apixaban

Similar to rivaroxaban, apixaban is a specific factor Xa inhibitor. It is also rapidly absorbed, attaining peak concentrations in 1 to 2 hours. Studies showed the half-life of apixaban to be 13.5 ± 9.9 hours after a single 20-mg dose,[346] 15.2 ± 8.5 hours after a single 5-mg dose, and 11.7 ± 3.3 after multiple 5-mg doses.[347,348] Fifteen hours is probably the higher end of apixaban's half-life and 17.5 hours in patients with renal insufficiency. When given BID, steady-state concentrations of apixaban are reached on day 3.[347] Apixaban has an oral bioavailability of more than 45%. It is eliminated via multiple elimination pathways and direct renal and intestinal excretion[349]; 24% to 29% of the dose is excreted via the kidneys, and 56% of the dose is recovered in the feces.[346]

For the treatment of acute VTE, apixaban was found to be noninferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) and was associated with significantly less bleeding.[350] Apixaban was also noted to reduce the risk of recurrent VTE without increasing the rate of major bleeding.[351] In patients with atrial fibrillation, apixaban is superior to ASA or warfarin in preventing stroke or systemic embolism.[352,353] The drug has been approved in the United States, Canada, and Europe for stroke prevention in patients with atrial fibrillation.

Apixaban has been noted to be an effective thromboprophylactic agent in total knee and total hip arthroplasties, comparable or superior to enoxaparin or warfarin.[354–357] In these studies, apixaban was given 12 to 24 hours after surgery. In 1 trial, "devices

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in connection with intrathecal or epidural anesthesia were removed at least 5 hours before the first dose" of apixaban.[357]

As apixaban was started after surgery in the published studies, one depends on the half-life of apixaban in determining the interval between discontinuation of the drug and neuraxial procedures. Whereas the Scandinavian guidelines did not make recommendation on the interval between cessation of apixaban and neuraxial injection because of lack of available data,[145] the European guidelines recommended a 26- to 30-hour interval.[144] The Scandinavian guidelines recommended 6 hours after a neuraxial injection or catheter removal before resumption of the drug, whereas the European guidelines recommended a 4- to 6-hour interval. Other recommendations ranged from 2- to 3-day stoppage of the drug and 24 (one-half the usual dose on the first 24 hours) to 48 hours before resumption of the drug.[284,285,297] In the absence of adequate data, we recommend a 5-half-life interval, or 3 days, between discontinuation of the drug and pain interventional procedures. The drug can be resumed the next day or 24 hours after the procedure.

The aPTT is not an appropriate test for monitoring factor Xa inhibitors, and apixaban has little effect on the PT.[318] The dilute PT assay, wherein the thromboplastin reagent is diluted 16 times, has improved sensitivity over the conventional PT.[318] Apixaban can be evaluated with the anti–factor Xa assay.[358,359] The anti–factor Xa assay is more sensitive than the PT and as sensitive as the dilute PT assay[359] and seems to be the best choice for clinical monitoring of the anticoagulant effect of apixaban.[317] Activated charcoal, given within 3 hours of ingestion, reduces the absorption of apixaban. As noted with the other NOACs, nonspecific hemostatic agents such as recombinant factor VII and PCCs can be used. In the aforementioned andexanet study of Siegal et al[345] for apixaban-treated patients, anti–factor Xa activity was reduced by 94% after andexanet administration compared with 21% in the placebo group.

In the recently published ASRA regional guidelines, a 26- to 30-hour (2-half-life) interval between the last dose of 2.5 mg apixaban and neuraxial injection was recommended.[143] An interval of 40 to 75 hours (3–5 half-lives) was recommended in patients older than 80 years, body weight less than 60 kg, serum creatinine greater than 1.5 mg/dL, or on doses of 5 mg/d. As our pain clinic patients are older, with spinal stenosis, and in view of the surgical nature of our interventional procedures, we recommended an interval of 5 half-lives (75 hours or 3 days). The drug should be resumed 24 hours later.

Summary recommendations with apixaban

- We recommend a 5-half-life interval, or 3 days, between discontinuation of apixaban and medium- or high-risk pain procedures (Table 5).
- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide whether apixaban should be stopped. In these situations, 2 half-lives interval may be considered.
- We recommend a 24-hour interval after interventional pain procedures before resumption of apixaban.
- If the risk of VTE is very high, half the usual dose may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's other physician(s).

Edoxaban

Edoxaban is a factor Xa inhibitor recently approved by the FDA. The drug is indicated for the prevention of stroke in patients with atrial fibrillation and for treatment of deep venous thrombosis and pulmonary embolism. Maximum concentration is attained in 1 to 2 hours; it is 60% bioavailable, and 50% of the drug is excreted by the kidneys. Its half-life is 8.75 to 14 hours.[360–362] In the presence of kidney impairment, the half-life of the drug is proportionately prolonged in relation to the degree of renal insufficiency, that is, 8 hours for mild and 17 hours for severe insufficiency.[363,364] A specific reagent factor Xa assay is recommended in assessing the effect of edoxaban.

The recent ASRA regional guidelines recommended a 2-half-life interval (20–28 hours) before a neuraxial injection in patients taking 30 mg/d or less.[143] For patients at higher risk (weight of ≤60 kg, CrCL 15–49 mL/min) or those taking more than 30 mg/d, a 4- to 5-half-life (40- to 70-hour) interval is recommended. As pain clinic patients likely represent higher risk and because of the surgical nature of many procedures, we recommend a 5-half-life interval, or 3 days. A longer delay may be considered in patients with severe renal disease.

Summary recommendations with edoxaban

- We recommend a 5-half-life interval, or 3 days, between discontinuation of edoxaban and medium- or high-risk pain procedures (Table 5).
- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide whether edoxaban should be stopped. In these situations, 2-half-life interval may be considered.
- We recommend a 24-hour interval after interventional pain procedures before resumption of edoxaban.
- If the risk of VTE is very high, half the usual dose may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's other physician(s).

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors are frequently used during PCIs by cardiologists because they are very potent platelet inhibitors. These drugs include abciximab (ReoPro), eptifibatide (Integrillin), and tirofiban (Aggrastat).

Mechanism of Action

Glycoprotein IIb/IIIa prevents platelet aggregation and thrombus formation. Platelets contribute to hemostasis by adhering to and spreading over subendothelial surfaces, aggregating together, and supplying a substrate for blood plasma coagulation reactions, leading to fibrin formation. Platelet-fibrin plug formation is crucial to normal hemostasis and prevention of bleeding. This process can become pathological and lead to thrombosis when proaggregatory and prothrombotic processes are excessive or inappropriate.

Platelet aggregation is initiated by extrinsic agonists such as subendothelial collagen exposure, thrombin, and also by intrinsic agonists such as ADP. Such agonists incite intracytoplasmic reactions leading to rearrangement of 2 closely associated platelet membrane GP IIb and IIIa. This rearranged GP IIb/IIIa complex becomes a receptor site for fibrinogen. Fibrinogen attaches to the GP IIb/IIIa complexes of adjacent platelets to form a platelet-to-platelet bridge. This platelet-fibrinogen interaction via the GP IIb/IIIa complex is the final common platelet aggregation pathway.[365–371] As such, drugs that inhibit GP IIb/IIIa prevent platelet aggregation.

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Pharmacology and Pharmacokinetics

The drugs are usually administered intravenously. Abciximab causes a noncompetitive but irreversible inhibition of the GP IIb-IIIa. It does not need dose adjustment in patients with renal failure, unlike the small molecule eptifibatide.[365] Its onset is rapid as it binds to platelets in minutes, and platelet aggregation is almost completely inhibited after 2 hours. Although its half-life is short (10–30 minutes), its dissociation from GP is measured in hours, resulting in slow recovery of platelet function (24–48 hours).[365,366] Platelet recovery is noted by 48 hours after stoppage, although platelet-bound abciximab can be detected up to 10 days.[367] Similar to abciximab, eptifibatide and tirofiban have rapid onsets of action. Unlike abciximab, which takes several hours to dissociate, dissociation of these 2 drugs occurs in 10 to 15 seconds. The half-lives are 2.5 hours for eptifibatide and 2 hours for tirofiban. Recovery of platelet function occurs in 4 hours with eptifibatide and 4 to 8 hours with tirofiban. Following IV eptifibatide, the bleeding time normalizes 15 to 30 minutes after drug discontinuation, and in vitro platelet function begins to recover 4 hours after drug discontinuation.[372] After tirofiban administration, both bleeding time and platelet aggregation normalize by 3 to 8 hours after stopping treatment.[367]

Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving GP IIb/IIIa antagonists has been noted.[373] In general, the cardiac surgical and interventional radiology literature recommends that elective surgery be delayed 24 to 48 hrs after abciximab and 4 to 8 hours after eptifibatide or tirofiban. For semiurgent surgery, if possible, delay until the antiplatelet effects have significantly dissipated (approximately 12 to 24 hours for abciximab and 4 to 6 hours for peptidomimetic agents such as eptifibatide or tirofiban) is advocated.[371] Surgery performed within 12 hours of abciximab administration will most likely necessitate a platelet transfusion as has been shown in patients having coronary artery bypass grafting.[373]

Although rare, abciximab, eptifibatide, and tirofiban can produce thrombocytopenia immediately after drug administration in a small proportion of patients. Reactions usually occur within hours but may occasionally be delayed.[374] In randomized controlled trials, mild thrombocytopenia (platelet count <100,000/μL) developed in approximately 5% of treated patients compared with approximately 2% of control subjects. Severe thrombocytopenia (platelet count <20,000/μL) occurred in approximately 0.7% of patients receiving abciximab for the first time, more often than with either eptifibatide or tirofiban (0.2%).[375] A pooled analysis of 8 placebo-controlled studies concluded that abciximab, but not eptifibatide or tirofiban, increased the incidence of thrombocytopenia in patients also treated with heparin.[375]

Interventional Pain Procedures in Patients Receiving GP IIb/IIIa Inhibitors

The pharmacological differences make it impossible to extrapolate between these drugs regarding the coagulation profile for patients undergoing interventional pain procedures. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial.[143] No series involving the performance of epidural injections in the presence of GP IIb/IIIa receptor antagonists have been performed.

Generally, surgery or interventional procedures would require adequate platelet function, and therefore, high- or intermediate-risk interventional pain procedures (outlined above) should be delayed until platelet function has returned to normal, which is at least 48 hours for abciximab.[369] The European Society guidelines noted that a minimum of 48 hours for abciximab and 8 to 10 hours for eptifibatide or tirofiban may be adequate.[144,368]

Procedural Recommendations

All chronic interventional pain procedures are elective, and as such, extreme caution needs to be exercised in terms of timing of procedures in the patients receiving GP IIb/IIIa inhibitors. The actual risk of spinal hematoma or bleeding with GP IIb/IIIa antagonists is unknown. Management is based on labeling precautions and the known surgical and interventional cardiology experience. Caution needs to be observed if surgery is performed within 7 to 10 days of abciximab administration as this drug exerts a profound and irreversible effect on platelet aggregation. It is critical to determine the absolute platelet count before interventional pain procedures if patients have been on GP IIb/IIIa inhibitors to determine that there is no drug-induced thrombocytopenia. Although GP IIb/IIIa inhibitors are contraindicated immediately after surgery[376] because of increased risk of bleeding, should one be administered in the postoperative period (after high- or intermediate-risk interventional pain procedure), we recommend that the patient have careful neurological monitoring for 24 hours.

Summary Recommendations for GP IIb/IIIa Inhibitors

- Instances where an interventional pain procedure needs to be performed in a patient who is on or who just had GP IIb/IIa inhibitor are rare because these drugs are usually used in conjunction with percutaneous coronary procedures.
- There are no studies on interventional procedures in patients on GP IIb/IIIa inhibitors. Shared decision making should therefore be observed in these instances.
- For abciximab, recovery of platelet function occurs at 24 to 48 hours. However, platelet-bound abciximab is noted up to 10 days, and it causes irreversible binding, making recommendations on the interval between discontinuation of the drug and interventional procedure difficult to state. A minimum interval of 48 hours is recommended even for low-risk procedures. As there has been no study of platelet function after discontinuation of the drug, 5 days is probably adequate, based on daily formation of new platelets, for intermediate- and high-risk procedures.
- For eptifibatide and tirofiban, an 8-hour stoppage before a low-risk interventional procedure is probably adequate. For intermediate- and high-risk procedures, a 24-hour interval is ideal.
- The GP IIb/IIa inhibitors have rapid onsets of actions, so an adequate time should be observed for the clot to stabilize. An 8- to 12-hour interval is probably adequate.

Antidepressants and SRIs

Chronic pain patients frequently have concomitant depressive illnesses and are often prescribed antidepressants to block reuptake of serotonin and norepinephrine for their adjuvant analgesic actions, as well as activation of descending inhibitory pain pathways, among numerous beneficial effects. Both SSRIs and SNRIs, however, have been associated with increased bleeding risk. The tricyclic antidepressants (TCAs) and other nonserotonergic antidepressants seem not to be associated with bleeding.[164,377–381]

Mechanisms of Increased Bleeding Risk

Serotonin reuptake inhibitors decrease platelet serotonin uptake from the blood. As platelets do not synthesize serotonin and

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are dependent on its reuptake, platelet serotonin content is depleted, resulting in inhibition of serotonin-mediated platelet aggregation and increased bleeding.[380,382] The bleeding risk is dependent on the potency of serotonin reuptake inhibition rather than selectivity.[380] Other mechanisms have also been proposed including decreased platelet binding affinity, inhibition of calcium mobilization, and reduced platelet secretion in response to collagen.[383]

Fluoxetine, paroxetine, and fluvoxamine have a potent cytochrome P450 enzyme inhibitory effect, which, in turn, may inhibit the metabolism and increase blood levels of NSAIDs and other antiplatelets concomitantly metabolized by these enzymes. This may contribute to the increased bleeding risk associated with the concurrent use of SRIs and NSAIDs.[384] The added risk of increased GI tract bleeding can be attributed to the SRI-induced increase in gastric acid secretion.[377,378]

Evidence of Increased Bleeding Risk

There have been several reports of bleeding in patients on SRIs. Although the absolute bleeding risk of SRIs is modest, approximately equivalent to low-dose ibuprofen, the risk increases in elderly patients, patients with liver cirrhosis, and those using anticoagulants and other antiplatelet medications.[164,377,378,381]

The risk of reoperation due to surgical bleeding after breast cancer surgery was increased to 7.0% among current SSRI users (adjusted relative risk, 2.3; 95% CI, 1.4–3.9). Comparatively, the risk of reoperation was 2.6% and 2.7% in naive and former users, respectively.[385] Similar findings were observed in another study of elective breast surgery. Patients using SSRIs had a 4-fold greater risk of breast hematoma formation requiring intervention compared with nonusers.[167]

Serotonin reuptake inhibitor use was also associated with increased perioperative bleeding in orthopedic surgery.[170,386] In a retrospective follow-up study of 520 patients undergoing orthopedic surgery, the risk of intraoperative blood transfusion almost quadrupled in the SRI group compared with nonusers. (Adjusted odds ratio [OR] was 3.7, and 95% CI was 1.4–10.2.) In contrast, patients using nonserotonergic antidepressants had no increased risk compared with nonusers (OR, 0.7; CI, 0.1–6.0).[170] Similar findings have been reported in elective spine surgery as well. In extensive lumbar fusion surgery, the mean blood loss was increased by 2.5-fold compared with nonusers.[168]

A recent meta-analysis also suggested that SSRI exposure was associated with increased risks of intracerebral and intracranial hemorrhage, although the absolute risk was very low.[387] Conversely, few studies have reported a significant relationship between SRIs and perioperative bleeding risk in coronary artery bypass graft surgery.[388–390]

SRIs and Antiplatelet Agents

The risk of GI tract bleeding associated with SRIs increases with concurrent use of ASA or antiplatelet medications.[164,377,378] Similarly, patients taking SSRIs together with antiplatelet medications following acute myocardial infarction were at increased risk of bleeding.[169]

A large epidemiologic study showed that combined use of an SSRI and NSAIDs or low-dose ASA increased the risk of upper GI tract bleeding to 12.2 (95% CI, 7.1–19.5) and 5.2 (95% CI, 3.2–8.0), respectively. Nonselective SRIs also increased the risk of upper GI tract bleeding to 2.3 (95% CI, 1.5–3.4), whereas antidepressants without action on the serotonin receptor had no significant effect on the risk of upper GI tract bleeding. The risk with SSRI use returned to unity after termination of SSRI use.[378] Another population-based case-control study confirmed the increased bleeding risk with SSRIs and concurrent ASA or NSAID use.[391] The adjusted OR of upper GI tract bleeding among current users of SSRIs was 1.67 (95% CI, 1.46–1.92). The adjusted OR increased to 8.0 (95% CI, 4.8–13) with concurrent use of SSRI and NSAIDs and 28 (95% CI, 7.6–103) with concurrent use of SSRI, NSAID, and ASA.[391]

The increased risk of bleeding with SSRIs and NSAID combinations was greater than the additive risk of the individual drugs.[392] A recent review article indicated that SSRI use is associated with approximately doubled odds of upper GI tract bleeding. The risk of bleeding increased with the concurrent use of NSAIDs, anticoagulants, and antiplatelet agents and in patients with liver cirrhosis/failure.[164]

SRIs and Anticoagulants

The risk of GI tract bleeding associated with SRIs increases with concurrent use of anticoagulants.[393,394] In a large population-based study of approximately 2 million patients on warfarin, SSRI users were at significantly increased risk of hospitalization because of non–GI tract bleeding (adjusted OR, 1.7; 95% CI, 1.1–2.5). Nonsteroidal anti-inflammatory drug users had a similar increased risk of non–GI tract bleeding (adjusted OR, 1.7; 95% CI, 1.3–2.2).[394]

Procedural Recommendations

The management plan should be individualized according to the type of pain procedure, type and dosage of antidepressants, severity of depression and suicide risk, other risk factors for bleeding, and concomitant use of antiplatelets and anticoagulants. Moreover, a shared assessment, risk stratification, and management approach should be coordinated with the treating psychiatrist/physician to assist with bridging to other nonserotonergic antidepressants, manage drug discontinuation syndromes, or treat worsening depression.

Because the absolute risk of abnormal bleeding with SSRIs is low, and uncontrolled depression is associated with poorer surgical outcome,[395] routine discontinuation of SRIs before pain procedures is not recommended.[381,396] Serotonin reuptake inhibitor discontinuation is probably necessary only in high-risk patients with stable depression. High-risk factors are elderly patients; those patients concomitantly using ASA, NSAIDs, other antiplatelets, or anticoagulants; and in those with liver cirrhosis or failure.[164,378,381]

However; in high-risk patients with severe depression, suicidal risk, or history of uncontrolled discontinuation syndrome, switching from SRIs to nonserotonergic antidepressants (bupropion, mirtazapine, some TCAs) should be considered.[168,381] This should involve shared decision making with other treating physicians.

Few TCAs and most SSRIs and SNRIs, such as fluoxetine, sertraline, paroxetine, escitalopram, duloxetine, and venlafaxine, have intermediate to high degrees of serotonin reuptake inhibition (Table 7).[165] In contrast, nonserotonergic antidepressants such as bupropion, mirtazapine, and some TCAs do not inhibit serotonin reuptake.[381,415] In fact, intraoperative bleeding risk was not higher in the nonserotonergic antidepressant users than in nonusers.[168,170,386] It has previously been shown that GI tract bleeding induced by high-dose fluoxetine resolved after switching to mirtazapine.[416]

When to Stop SRIs

Antidepressant discontinuation can be associated with a significant risk of suicide attempts during the early period after discontinuation.[417] Moreover; rapid tapering or abrupt discontinuation of SRIs can result in the development of discontinuation syndrome. This syndrome is characterized by a constellation of

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TABLE 7. Serotonergic Effects of Commonly Used Antidepressants in Ranking Order

		Receptor Occupancy,[397] %							
Antidepressants†	**Class**	**5-HT Transporter**	**Norepinephrine Transporter**	**5-HT_{2c} Receptor**	**$t_{½}$, h**	**5-$t_{½}$ (Approx)**	**Active Metabolite[377]**	**$t_{½}$, h**	**5-$t_{½}$ (Approx)**
Clomipramine[398]	TCA	96.44	11.05	11.62	24	5 d	*N*-desmethylclomipramine	69	2 wk
Paroxetine[399]	SSRI	95.7	4.7	0.06	21	5 d			
Escitalopram[400]	SSRI	93.66	0.37	1.04	27–32	5–6 d			
Citalopram[401]	SSRI	93.45	1.08	11.1	35	7 d			
Fluvoxamine[402]	SSRI	92.74	3.33	1.35	16–26	5 d			
Fluoxetine[403]	SSRI	88.96	7.37	19.74	24–72*	5–15 d	Norfluoxetine	7–15 d	5–10 wk
Sertraline[404]	SSRI	88.25	1.14	0.062	24	5 d	*N*-desmethylsertraline	64–104	2–3 wk
Imipramine[405]	TCA	86.17	38.59	35.69	24	5 d	Desipramine	21	4–5 d
Venlafaxine[406]	SNRI	84.52	12.47	14.83	5	1 d	*O*-desmethylvenlafaxine	11	2 d
Doxepin[407]	TCA	67.08	82.44	94.03	15	3 d			
Amitriptyline[408]	TCA	66.49	49.24	91.29	13–36	3–7 d	Nortriptyline	22–88	1–3 wk
Duloxetine[409]	SNRI	56.25	15.35	0.17	12	2–3 d			
Nortriptyline[410]	TCA	18.83	80.25	42.27	30	7 d			
Nefazodone[411]	SSRI/antag	4.22	3.05	40.6	4	1 d			
Maprotiline[412]	Tetra	1.3	87.34	38.57	51	10 d			
Bupropion[413]	Misc	0.74	0.71	0.71	15–22	5 d	Hydroxybupropion	20	4–5 d
Mirtazapine[414]	α-2	0.34	0.73	46.51	20–40	5–7 d			

Data from References [379–396].

*$t_{½}$ in chronic use is 96 to 144 hours.

†The bottom ones have fewer tendencies to cause increased risk of abnormal bleeding.

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various physical and psychological symptoms, including flulike symptoms, nausea, GI upset, dizziness, irritability, agitation, anxiety, and sleep disturbances. Antidepressant discontinuation symptoms usually develop within 1 week and may last up to 3 weeks. In particular, discontinuation syndrome can emerge strongly in patients treated with paroxetine and venlafaxine.[418] However, these symptoms can be minimized or avoided by gradually tapering off the antidepressant dose, and they improve or resolve after restarting the antidepressants.[419,420]

As platelets do not synthesize serotonin and are dependent on its reuptake from the blood, the duration of bleeding risk will be dependent on the duration of the serotonin reuptake inhibition rather than the platelet's life span. The risk of bleeding will end when the degree of serotonin reuptake inhibition is not clinically significant with SRI discontinuation and the drug is washed out of the body.[164]

Serotonin reuptake inhibitors in general have relatively long half-lives (Table 7). Animal studies have indicated that most SRIs required 5 half-lives of washout period to normalize serum levels. In general, a discontinuation period of approximately 1 to 2 weeks is required for most SRIs other than fluoxetine.[421,422] In contrast, the half-life of fluoxetine and its active metabolite norfluoxetine is 2 to 4 days and 7 to 15 days, respectively, requiring a washout period of approximately 5 weeks,[422,423] although 1 case report showed that discontinuation of fluoxetine for 2 weeks was enough to eliminate abnormal bleeding and normalize bleeding time.[424]

Summary Recommendations With Antidepressants

- Routine discontinuation of SRIs before pain procedures is not recommended.
- Patients with stable depression who are at a high risk of bleeding associated with SRI use (old age, advanced liver disease, and concomitant ASA, NSAID, antiplatelet, or anticoagulant use) should undergo gradual tapering of the SRI dose and discontinue usage 1 to 2 weeks before the procedure (see Table 7 for the individual recommended times).
- Gradual tapering of the dose is especially important in SRIs with known serious discontinuation symptoms (paroxetine or venlafaxine).
- Fluoxetine is an exception because it has an active metabolite with a long half-life. The dose should be gradually tapered off and discontinued 5 weeks before planned procedure.
- Patients with unstable depression or with suicidal risk, who are at a high risk of bleeding associated with SRI use, should be switched to nonserotonergic antidepressants that do not or less potently inhibit serotonin reuptake (eg, bupropion, mirtazapine, TCAs).
- Serotonin reuptake inhibitors should be restarted as soon as possible after the disappearance of the bleeding risk from the procedure, usually the next day.
- Perioperative management of SRIs should be coordinated with the treating psychiatrist.

Herbal/Alternative and Dietary Supplements

The use of various herbal therapies and dietary supplements is ubiquitous throughout the world, with a recent review suggesting that nearly one-fourth of surgical patients may use these substances for health reasons.[425] Several of these substances have pharmacological effects that vary from effects on platelet aggregation to either inhibition or augmentation of warfarin effects. Some of these effects are increased with coadministration of herbal/dietary agents and mainstream anticoagulants. Although some guidelines have suggested that these products need not necessarily be stopped prior to neuraxial procedures,[143] other reviews have suggested that use of the herbal therapies should be ceased prior to surgery.[426] As these adjunctive agents are usually not of critical importance to patient health, as a general rule they should be stopped for pain surgical procedures and may need to be stopped for other pain procedures. The herbal agents that seem to be most likely to cause significant bleeding or interact with other anticoagulants are garlic (*Allium sativum*), *Ginkgo biloba*, ginseng (*Panax quinquefolius* L., Araliaceae), Asian ginseng (*Panax ginseng* C. A. Meyer), Danshen (radix *Salvia miltiorrhiza*), and Dong quai (radix *Angelica sinensis*). Dietary supplements including fish oil and vitamin E all may have effects on coagulation. Multiple other agents including glucosamine/chondroitin, ginger, green tea, kava, and many others may have effects on coagulation but require further study; extremely large doses may require additional testing.

As noted in earlier sections of this guideline, the authors feel that interventional pain procedures are not necessarily equivalent to perioperative perineural and neuraxial techniques and may be quite different. Pain procedures are nearly always elective, though, and thus more caution should be exercised if possible. Certainly, higher-risk interventional pain procedures, as previously defined in this guideline, may involve larger needles, multiple instrumentations, and altogether different target end points. Studies are necessary to further clarify the risks of any of these agents in these settings. Problematically, many herbal agents may not be reported to the pain physician, even in the context of a thorough history and physical examination unless specifically asked. Furthermore, these compounds have no oversight by regulatory agencies such as the FDA and can be available in various combination products and dosages. All pain physicians should take a thorough substance use history from their patients and err on the side of safety if effects are unknown.

Garlic

Garlic (*A. sativum*) has its primary effects on platelet aggregation. Previous studies have shown that garlic effects on bleeding are dose dependent.[427] Allicin, the odiferous sulfinyl compound that provides garlic's flavor, is formed from the crushing of garlic cloves. Ajoene, derived from allicin via extravasation in edible oils or solvents, effects platelet aggregation by inhibition of granule release and fibrinogen binding[428] and also potentiates the inhibition of aggregation by prostacyclin, forskolin, indomethacin, and dipyridamole.[429] There are no good studies that have examined the impact of high-dose garlic or its extracts on procedural-induced bleeding. One case report describes an elderly man who developed a spontaneous spinal epidural hematoma requiring surgical decompression due to paralysis at presentation. No risk factors other than consumption of approximately 2000 mg/d of garlic were noted. His bleeding time was prolonged despite a normal platelet count, but later normalized after garlic cessation.[430] Daily doses of 25 mg/d have been shown to result in significant inhibition of platelet aggregation.[431]

As the antiplatelet effect of garlic is dose dependent, we recommend inquiry as to the daily dose of garlic intake. Platelet function test (whichever available) should be considered when patients with several comorbidities take doses greater than 1000 mg/d or when there is concomitant intake with ASA, NSAIDs, or SRIs.

Dong Quai

Dong quai is from radix *A. sinensis*, a dried root from a family of plants that include celery, carrots, parsley, and poison hemlock. It has been very popular in Chinese medicine for over 2000 years and is marketed for painful menstrual cramps,

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premenstrual syndrome, anemia during menstruation, recovery from childbirth, and other conditions in women, spawning the nickname "female ginseng." Although the agent has been purported to have estrogen-like activity, this is not substantiated, and its main anticoagulant effects from phytochemical analysis are likely due to natural coumarin compounds.[432,433] Typical case reports included a 46-year-old African American woman on stable dosing of warfarin, who after starting dong quai, had prolongation of her INR and PT. These later normalized after discontinuation of the herb for 1 month. Other derivatives from the root including osthole and ferulic acid have effects on platelet aggregation and release through antagonism of COX and thromboxane synthetase in arachidonic acid and TXA_2 metabolism.[433] Dong quai is used in a number of agents marketed under various names, and thus physicians should be prepared to investigate the actual constituents of these products.

In patients taking warfarin and also dong quai, the INR should be checked before medium- and high-risk procedures. The herb should be discontinued when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations for interventional procedures.

Danshen

Danshen (radix *S. miltiorrhiza)* is a popular traditional Chinese agent that is widely used for various cardiac ailments. Its pharmacological effects seem to include positive inotropic and negative chronotropic effects, coronary vasodilatation, and inhibition of platelet aggregation. Danshen through unknown effects on coagulation mechanisms can decrease the elimination of warfarin and result in overanticoagulation.[434]

Case reports of interactions between danshen and warfarin are described. A 62-year-old man required mitral valve replacement and postoperatively was stabilized on warfarin with an INR of 3.0. Six weeks after discharge, the patient was readmitted with anemia, lethargy, and shortness of breath and was found to have pleural and pericardial effusions with an INR of 8.4. Rigorous history taking revealed the recent addition of danshen by a Chinese herbalist to help "mend" his heart. Upon cessation of the herbal preparation, his INR was reestablished in the therapeutic range. The temporal relationships and lack of other causative factors suggested an interaction between danshen and warfarin.[435]

In patients taking warfarin and also danshen, the INR should be checked before medium- and high-risk procedures. The herb should be stopped when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations for interventional procedures. As there can be inhibition of platelet aggregation, interaction between danshen and other antiplatelet drugs (ASA, NSAIDs, SSRIs) should be kept in mind especially in patients with several comorbidities.

Ginkgo Biloba

The *G. biloba* extracts (GBEs) have been used for thousands of years by practitioners of Chinese medicine. In the United States, ginkgo supplements are marketed mostly as treatments for memory dysfunction, (including dementia) and claudication/cardiovascular disease; however, other uses have been identified; none of which have strong evidence for its use.

The clinically significant components of GBEs producing the greatest physiologic effects are unknown; however, the 2 considered most pharmacologically active are flavonol glycosides and terpene lactones. Other constituents are quercetin, ginkgolic acids, proanthocyanidins, carboxylic acids, and nonflavone glycosides.[436] The chemical constituents can vary depending on the strain of ginkgo, as well growing conditions.[437]

Standardized extracts on the market contain 22% to 26% flavone glycosides (primarily quercetin, kaempferol and isorhamnetin) and 5% to 7% terpene lactones (ginkgolides A, B, and C and bilobalide).[438,439] The most frequently included GBE formulations in clinical trials to date are EGb 761 and LI 1370.[439] Inhibition of platelet activation factor is considered to be the main mechanism of action resulting in ginkgo-related biologic activity.[440–443]

Spontaneous bleeding, including postsurgical bleeding, spontaneous subdural hematomas and hyphemas, subarachnoid hemorrhage, and retrobulbar hemorrhage have been reported in multiple case reports in patients taking GBE. The hypothesized mechanism of toxicity is that antagonism of platelet activation factor and collagen leads to inhibition of platelet aggregation.[444] Many reported cases of spontaneous bleeding involved concurrent use of antiplatelet or anticoagulant therapies.[445] Diamond et al[446] concluded that adverse events, as described in case reports, occurred in patients who were taking additional medicines or had comorbid conditions.

In patients taking *G. biloba* and other antiplatelets (ASA, NSAIDs, SSRIs), platelet function test (whichever is available) should be considered before high-risk procedures. Refer to the section on antiplatelets regarding guidelines on their discontinued or continued use.

Panax Ginseng

Panax ginseng (C. A. Meyer), *Panax quinquefolius* (American ginseng), and *Panax notoginseng* ([Burk] F. H. Chen [Araliaceae]) are but 3 of several ginseng compounds that are commercially used. Ginseng herbal products are the second most used herbal preparation and are often combined with other herbal products in a single formula. The word *Panax* derives from the Greek "roots pan" (all) and "akos" (healing), whereas *ginseng* literally means "man-root."[447]

Ginseng effects are thought to include increased well-being; cognitive, physical, and sexual performance; and increased immunity. Unfortunately, few studies have substantiated these claims. A randomized controlled trial in volunteers suggested that American ginseng reduces the effect of warfarin in healthy patients. Twenty volunteers receiving warfarin during weeks 1 and 4 in combination with either ginseng or placebo noted significant declines in peak INR levels as compared with the placebo group.[448] Studies using raw and steamed roots of *P. notoginseng* with *P. ginseng* and *P. quinquefolius* noted differences in effects, with *P. notoginseng* in the steamed form having more potent effects on platelet aggregation and plasma anticoagulation. The steaming duration was correlated with increasing potency of effect. Rat bleeding times were prolonged by the use of either raw or steamed forms.[449] Other trials have shown little effect on warfarin resistance, with 1 randomized trial of ischemic stroke patients showing no effect of coadministered *P. ginseng* on warfarin-induced INR.[450] Although isolated reports of increased vaginal bleeding after use of ginseng facial cream have been reported, the paucity of major adverse outcomes in large systematic reviews by Coon and Ernst[447] and others suggest that the adverse effects of this agent are less severe than many other agents.

Panax ginseng does not appear to have significant anticoagulant effect. Diminution of the anticoagulant effect of warfarin is a possibility.

Summary Recommendations for Herbal Medications and Dietary Supplements

- Physicians should inquire about the use of herbal/alternative therapies and make this part of the reconciled medication list,

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with actual dosages of the agent, if possible. Practitioners should be aware that these agents are not regulated like FDA-approved drugs are, thus the potential for widely disparate amounts.
- High-risk procedures are most likely to have a significant bleeding risk. Although there are no published cases, these completely elective procedures requiring extensive forethought and screening should be performed in idealized settings, that is, with discontinuation of several known herbal agents and dietary supplements with known coagulation risks.
- Lower- and medium-risk procedures are probably safe as long as other anticoagulants have been stopped according to the guidelines for those particular agents. However, patients who have other risk factors, such as advanced age, renal and/or hepatic disease, history of major bleeding episodes from procedures, and so on, should likewise have these preparations stopped, even if the procedures are low to medium risk.
- Timing of cessation is likely variable, but a 1-week period seems appropriate, given that many of the involved agents pose risks due to effects on platelet aggregation and/or potentiation of warfarin effect.
- As the antiplatelet effect of garlic is dose dependent, we recommend inquiry as to the daily dose of garlic intake. Test of platelet function should be ordered when patients with several comorbidities take doses greater than 1000 mg/d or when there is concomitant intake with ASA, NSAIDs, or SSRIs.
- In patients taking warfarin and also dong quai, the INR should be checked before medium- and high-risk procedures. The herb should be discontinued when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations for interventional procedures.
- In patients taking warfarin and also danshen, the INR should be checked before medium- and high-risk procedures. The herb should be stopped when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations for interventional procedures. As there can be inhibition of platelet aggregation, interaction between danshen and other antiplatelet drugs (ASA, NSAIDs, SSRIs) should be kept in mind, especially in patients with several comorbidities.
- In patients taking *G. biloba* and other antiplatelets (ASA, NSAIDs, SSRIs), a test of platelet function should probably be ordered before high-risk procedures. Refer to the section on antiplatelets regarding guidelines on their discontinued or continued use.

Dietary Supplements

Vitamin E

Vitamin E may have significant effects on platelet aggregation and adhesion.[451] In vitro studies have demonstrated a concentration-dependent effect, with higher concentrations producing more robust effects.[452] In noncoagulated patients, platelet uptake of α-tocopherol led to markedly decreased platelet aggregation via a protein kinase C–dependent mechanism at doses between 400 and 1200 IU daily via oral administration.[453] As vitamin E may have dose-ranging effects on platelet function, patients taking higher doses and those with concomitant platelet inhibiting actions may require caution.

Fish Oil

Fish oil supplements contain the omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid. Omega-3 fatty acids are found in saltwater fish, which are a large part of the diet of Greenland Eskimos. Researchers originally noted a decreased risk of cardiovascular deaths in that population despite their high-fat diets. A comparative study of 21 Eskimos to age- and sex-matched Danish patients noted longer bleeding times and reduced platelet aggregation.[454] Subsequent studies have been conflicting, but most recent reviews suggest little effect on coagulation parameters or prolonged bleeding.[455]

Summary Recommendations for Dietary Supplements

- Vitamin E at doses greater than 400 IU daily may require caution when performing high-risk procedures. Cessation timing should be similar to other drugs whose effects on platelet activity, such as ASA, are considered.
- Although fish oil effects remain unlikely to be major sources of bleeding, caution also suggests they be treated similar to other antiplatelet agents with 6-day stoppage prior to high-risk procedures, such as spinal cord or dorsal root ganglion stimulation.
- Unless history suggests other sources of bleeding, low- and intermediate-risk procedures likely require no change in fish oil consumption at normal daily doses (~1000 mg/d).

Miscellaneous Medications

Pentosan Polysulfate Sodium

Pentosan polysulfate sodium (Elmiron), a plant-derived semisynthetic mucopolysaccharide used to treat the pain and discomfort associated with interstitial cystitis, possesses anticoagulant activity as an LMWH-like compound. Pentosan polysulfate sodium inhibits thrombin-induced platelet aggregation and generation of factor Xa and possesses a fibrinolytic effect. Although the drug has approximately only 1/15 activity of heparin, both bleeding times and clotting times have been shown to increase. In addition, rectal hemorrhage and bleeding have been reported in 6.3% of patients receiving this drug. The mean half-life of the drug is 20 to 27 hours.[456,457]

For patients undergoing high- or intermediate-risk spinal procedures, it is recommended that pentosan polysulfate sodium is discontinued for 5 days prior to the procedure, and the medication can be resumed 24 hours after the procedure.

Summary Recommendations for Pentosan Polysulfate Sodium

- We recommended 5-day discontinuation of pentosan polysulfate sodium prior to intermediate- and high-risk procedures.
- Pentosan polysulfate sodium can be resumed 24 hours after the conclusion of the procedure.

SUMMARY

These guidelines were produced with the goal of facilitating clinical decision making by interventional spine and pain physicians. Differences between these guidelines and the ASRA regional anesthesia guidelines were pointed out throughout the text and summarized in Table 8. For the pain guidelines, the authors felt that stratification into procedural risk would help simplify clinical decision making. However, one should not construe that a high-risk procedure is necessarily "risky," as the rating system reflects relative, not absolute, risk. Evidence, where available, was considered, but many recommendations are primarily based on pharmacological principles and/or consensus. It was also thought important that a shared decision-making process with other medical providers was important. A procedural anticoagulation management checklist is strongly recommended for clinicians, taking these factors into consideration (Table 9). It is intended that the outcomes associated

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TABLE 8. Summary of Periprocedural Management of Anticoagulants and Antiplatelet Medications

Drug	When to Stop			When to Restart
	High-Risk Procedures	Intermediate-Risk Procedures	Low-Risk Procedures	
ASA and ASA combinations	Primary prophylaxis: 6 d Secondary prophylaxis: shared assessment and risk stratification	Shared assessment and risk stratification*†	No	24 h
NSAIDs	5 Half-lives	No‡	No	24 h
Diclofenac	1 d			
Ketorolac	1 d			
Ibuprofen	1 d			
Etodolac	2 d			
Indomethacin	2 d			
Naproxen	4 d			
Meloxicam	4 d			
Nabumetone	6 d			
Oxaprozin	10 d			
Piroxicam	10 d			
Phosphodiesterase inhibitors				
Cilostazol	2 d	No	No	24 h
Dipyridamole	2 d	No	No	
ASA combinations	Follow ASA recommendations	Shared assessment and risk stratification*		
Anticoagulants				
Coumadin	5 d, Normal INR	5 d, Normal INR	No Shared assessment and risk stratification*	6 h
Acenocoumarol	3 d, Normal INR	3 d, Normal INR	No Shared assessment and risk stratification*	24 h
IV heparin	6 h	6 h	6 h	2 h§
Subcutaneous heparin, BID & TID	24 h	6 h	6 h	2 h (Low-risk procedures) 6–8 h (Intermediate- and high-risk procedures)
LMWH				
Enoxaparin (prophylactic)	12 h	12 h	12 h	4 h (Low risk) 12–24 h (Intermediate-/high-risk procedures)
Enoxaparin (therapeutic)	24 h	24 h	24 h	4 h (Low-risk procedures) 12–24 h (Intermediate-/high-risk procedures)
Dalteparin	24 h	24 h	24 h	4 h (Low-risk procedures) 12–24 h (Intermediate-/high-risk procedures)
Fibrinolytic agents	48 h	48 h	48 h	NA‖

Continued next page

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TABLE 8. *(Continued)*

Drug	When to Stop			When to Restart
	High-Risk Procedures	Intermediate-Risk Procedures	Low-Risk Procedures	
Fondaparinux	4 d	4 d	Shared assessment and risk stratification	6 h (Low-risk procedures) 24 h (Intermediate- and high-risk procedures)
P2Y12 inhibitors				
Clopidogrel	7 d	7 d	No Shared assessment and risk stratification	12–24 h*
Prasugrel	7–10 d	7–10 d	No Shared assessment and risk stratification	24 h
Ticagrelor	5 d	5 d	No Shared assessment and risk stratification	24 h
Cangrelor	3 h	3 h	Shared assessment and risk stratification	24 h
NOACs				
Dabigatran	4 d 5–6 d (Impaired renal function)	4 d 5–6 d (Impaired renal function)	Shared assessment and risk stratification*	24 h
Rivaroxaban	3 d	3 d	Shared assessment and risk stratification*	24 h
Apixaban	3 d	3 d	Shared assessment and risk stratification*	24 h
Edoxaban	3 d	3 d	Shared assessment and risk stratification*	24 h
GP IIb/IIIa inhibitors				
Abciximab	2–5 d	2–5 d	2–5 d	8–12 h
Eptifibatide	8–24 h	8–24 h	8–24 h	8–12 h
Tirofiban	8–24 h	8–24 h	8–24 h	8–12 h
Antidepressants and SRIs	See text and Table 7	No	No	See text and Table 7

Major areas of differences from the ASRA guidelines for regional anesthesia are in yellow boxes.

*See detailed text in the corresponding section.

†Consideration should be given to the discontinuation of ASA for certain intermediate-risk procedures including interlaminar cervical ESIs and stellate ganglion blocks where specific anatomical configurations may increase the risk and consequences of procedural bleeding.

‡Consideration should be given to the discontinuation of NSAIDs for certain intermediate-risk procedures including interlaminar cervical ESIs and stellate ganglion blocks where specific anatomical configurations may increase the risk and consequences of procedural bleeding (refer to the section entitled Anatomical Considerations for Hematoma Development in Spinal and Nonspinal Areas).

§If a moderate- or high-risk procedure was bloody, then a 24-hour interval should be observed.

||After an intervention, the usual daily dose (75 mg) of clopidogrel can be started 12 hours later. If a loading dose of clopidogrel is given, then the interval should be 24 hours.

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TABLE 9. Procedural Anticoagulation Patient-Specific Management Checklist

Procedural Anticoagulation Management Checklist
• Evaluate baseline patient-specific risk factors from history, physical examination, and chart review
• Family history of bleeding disorders
• Physical examination → signs of easy bruising including petechiae, mucosal bleeding, and ecchymoses
• Renal and hepatic disease → order laboratory tests to evaluate coagulation status
• Evaluate coagulation tests if required (complete blood count, PT, aPTT)
• Screening for antiplatelet, antithrombotic, or thrombolytic therapy
• Identify non-ASA NSAID use
Categorize individual reason for ASA utilization
• Primary prophylaxis → absence of established cardiovascular disease or risk factor
• Secondary prophylaxis → presence of cardiovascular disease
Informed decision making involving procedural physician, prescribing medical physician, and patient
Identify and manage pharmacologic coagulopathies
• Understand drug elimination and appropriate discontinuation time
• Recognize other drugs that may alter coagulation (eg, SSRIs, SNRIs)
Process the anatomical location of procedural intervention into decision making
• Cervical/thoracic vs lumbar/sacral neuraxial area
• High-, intermediate-, or low-risk procedures
Review appropriate radiographic imaging to identify/understand anatomical challenges
• Cervical, thoracic, lumbar spinal stenoses that alter spinal canal anatomy
• Epidural fibrosis and significant scar tissue from previous surgical intervention
Appropriate timing for reinitiation of anticoagulation
Appropriate postprocedure surveillance and monitoring

with these guidelines be studied for future incremental improvements and updates. Finally, it is expected that many practitioners might choose to post some of the tables and use these as their daily "cookbook" for patients taking anticoagulant agents. While this is understood, we emphasize that these guidelines are not meant to be a standard of care; rather, we implore the reader to strive to understand the reasoning behind the guideline recommendations, for example, "5 half-lives," and the impact of possible patient and situational confounders to optimal outcomes.

ADDENDUM

Betrixaban is a new oral anti-factor Xa inhibitor recently approved by the FDA for VTE prophylaxis. Peak plasma levels are reached 3 to 4 hours after intake, half-life of the drug is 19 to 37 hours. For a low-risk procedure, a 3-day (2 half-lives) discontinuation of the drug is recommended, 5 to 6 days (5 half-lives) for intermediate and high-risk procedures.[458]

We recommend a 24-hour interval after interventional pain procedures before resumption of betrixaban. If the risk of VTE is very high, half the usual dose may be given 12 hours after the pain intervention. The decision regarding timing of drug resumption should be shared with the patient's treating physician(s). If the risk of VTE is high, then an LMWH bridge therapy can be instituted during stoppage of the anticoagulant, and the LMWH can be discontinued 24 hours before the pain procedure.

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