

Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications

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: Interventional spine and pain procedures cover a far broader spectrum than those for regional anesthesia, reflecting diverse targets and goals. When surveyed, interventional pain and spine physicians attending the American Society of Regional Anesthesia and Pain Medicine (ASRA) 11th Annual Pain Medicine Meeting exhorted that existing ASRA guidelines for regional anesthesia in patients on antiplatelet and anticoagulant medications were insufficient for their needs. Those surveyed agreed that procedure-specific and patient-specific factors necessitated separate guidelines for pain and spine procedures.

In response, ASRA formed a guidelines committee. After preliminary review of published complication reports and studies, committee members stratified interventional spine and pain procedures according to potential bleeding risk as low-, intermediate-, and high-risk procedures. The ASRA guidelines were deemed largely appropriate for the low- and intermediate-risk categories, but it was agreed that the high-risk targets required an intensive look at issues specific to patient safety and optimal outcomes in pain medicine.

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 as 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.

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A survey was conducted among participants at the Anticoagulation/Antiplatelets and Pain Procedures open forum held at the 11th Annual Pain Medicine Meeting of the American Society of Regional Anesthesia and Pain Medicine (ASRA), November 15 to

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18, 2012, in Miami, Florida. 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 used. Additionally, the survey queried the frequency of adherence to specific elements of the current ASRA practice guidelines for regional anesthesia in patients on antiplatelet and anticoagulant medications and/or if respondents incorporated different protocols for different pain procedures.

One hundred twenty-four active participants attended the 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.

Most of the respondents (98%) followed ASRA 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 the effects of selective serotonin reuptake inhibitors (SSRIs) on platelets. Only 36% knew that SSRIs may lead to a bleeding disorder.

Most expressed the need for pain physicians to communicate with other physicians, as 88% stated that they get approval from primary care physicians, cardiologists, or neurologists before holding anticoagulants or antiplatelet agents.

On the basis of these results, the need for separate ASRA guidelines, specifically for interventional spine and pain procedures in patients on antiplatelets/anticoagulants, was evident. Hence, the ASRA Board of Directors recommended that the society’s journal, *Regional Anesthesia and Pain Medicine*, appoint a committee to develop separate guidelines for pain interventions.¹ The committee has an international representation and was endorsed by the European Society of Regional Anesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. The latest evidence was sought through extensive database search strategies. Although the guidelines are not always 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.

These recommendations are 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).²⁻⁴ 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.¹

DISCUSSION

Spine and pain procedures for chronic cancer and noncancer pain patients should be treated differently from regional anesthesia blocks for several reasons. These can be divided into procedure-specific 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 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 stylet leads to enhance directional control. In many cases, the technique is simple with little tissue stress produced to the region; but in some clinical settings, the procedure itself may expose the epidural space to multiple traumatic processes, as there may be multiple needle and lead insertions as well as multiple attempts to steer and redirect the leads.^{1,3}

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 compact the epidural venous plexus within tight epidural spaces.^{4,5} 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 SSRIs.¹

Anatomic Considerations for Hematoma Development in Spinal and Nonspinal Areas

Although most cases of a spinal hematoma have a multifactorial etiology, certain anatomic features may pose higher risks secondary to the anatomy and vascular supply of that specific spinal location.⁶ 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 after previous surgical intervention). The amount of epidural fat in the posterior epidural space is directly related to age and body weight.^{7,8} Epidural fat decreases with age. The amount of epidural fat according to spinal location increases with caudal progression, being absent in the cervical spine and highest in the lumbosacral spinal region.⁹ 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 to T1, 7.5 mm in the upper thoracic spine, 4.1 mm at the T11 to T12, and 4 to 7 mm in the lumbar regions.¹⁰

The epidural space has extensive thin-walled valveless venous plexi (plexus venosus vertebralis inferior, anterior, and posterior), which are vulnerable to damage during needle puncture 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.¹¹⁻¹³ Furthermore, the fragility of these vessels increases with age. Igarashi et al⁸ demonstrated blood vessel trauma in 28% of patients who underwent an epidural puncture at L2 to L3. The size of the venous plexus changes with the segmental localization of the anastomoses.⁶ Large diameter anastomoses exist at the C6 to C7, 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).

Radiographic imaging should be reviewed before performing interventional spine and pain procedures to assess for central and foraminal stenosis, disc herniations that compromise canal

TABLE 1. Pain Procedure Classification According to the Potential Risk for Serious Bleed

High-Risk Procedures	Intermediate-Risk Procedures*	Low-Risk Procedures*
SCS trial and implant	Interlaminar ESIs (C, T, L, S)	Peripheral nerve blocks
Intrathecal catheter and pump implant	Transforaminal ESIs (C, T, L, S)	Peripheral joints and musculoskeletal injections
Vertebral augmentation (vertebroplasty and kyphoplasty)	Facet MBNB and RFA (C, T, L)	Trigger point injections including piriformis injection
Epiduroscopy and epidural decompression	Paravertebral block (C, T, L)	Sacroiliac joint injection and sacral lateral branch blocks
	Intradiscal procedures (C, T, L)	
	Sympathetic blocks (stellate, thoracic, splanchnic, celiac, lumbar, hypogastric)	
	Peripheral nerve stimulation trial and implant	
	Pocket revision and IPG/ITP replacement	

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

C indicates cervical; L, lumbar; MBNB, medial branch nerve block; RFA, radiofrequency ablation; S, sacral; T, thoracic.

diameter, ligamentum flavum hypertrophy, epidural fibrosis, and previous surgical scarring which can alter the level of procedural difficulty.¹⁴ 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.¹⁵ 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.¹⁶

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.^{17–19} The vertebral artery, which arises from the subclavian artery, passes anteriorly at the C7 level, and enters the transverse foramen in 93% of cases at the C6 level. 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.^{19,20}

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.^{21,22} 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.^{23,24} 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.²⁵

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.^{26–28} Stress may also affect coagulation activity via an influence on the regulation of genes coding for coagulation and fibrinolysis molecules.²⁹ Chronic stress increases many stress hormone levels.^{30–32} Catecholamine and cortisol surges may underlie the hypercoagulability observed with chronic psychological distress.^{33,34} The situation stimulates the sympathetic nervous system and inhibits fibrinolysis through a β 1-mediated effect. Stimulation of vascular endothelial β 1 adrenoreceptors leads to reduced intracellular prostacyclin synthesis, which eventually impairs the release of tissue-type plasminogen activator.³⁵

As chronic pain frequently coexists with mental stress, characterized by a hypercoagulable state, patients with chronic pain may be placed at an increased risk for 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 (NSAIDs) inhibit prostaglandin production by inhibiting cyclooxygenase (COX). The 2 main

forms of COX are cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (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 (TXA₂). Thromboxane A_2 is produced by platelets and has prothrombotic effects including vasoconstriction.³⁶ 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 (ASA) is rapidly absorbed from the gastrointestinal (GI) tract with peak levels occurring approximately 30 minutes after ingestion, resulting in significant platelet inhibition at 1 hour.^{37,38} The peak plasma levels for enteric-coated aspirin may be delayed until 3 to 4 hours after ingestion.^{39,40} 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.^{41,42} By irreversibly inactivating COX-1 and blocking thromboxane production for the lifespan of a platelet, aspirin 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.⁴³ In addition to affecting platelets for their lifespan, aspirin also inactivates COX-1 in mature megakaryocytes (the bone marrow cell type responsible for platelet production). After a single dose of aspirin (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 aspirin on megakaryocytes.^{36,43,44} The average lifespan of a platelet is 7 to 10 days.^{45,46} 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 aspirin's antiplatelet effects display significant interindividual variability that is influenced by age, body mass, and specific medical conditions, including diabetes.⁴⁷

Aspirin's effects on platelet function, COX activity, and thromboxane production is time and dose dependent.^{36,43,48} A single 20-mg dose of aspirin reduces COX activity by 82% as early as 5 minutes after dosing.³⁶ Furthermore, a single dose of 100 mg of aspirin suppresses COX activity by 95% \pm 4%.⁴⁸ Repeated dosing results in a significant reduction in the required aspirin platelet inhibitory dose. The 50% inhibitory dose decreased from 26 mg (single dose) to 3.2 mg after repeated dosing.³⁶ After daily dosing with 20 to 40 mg of aspirin, 92% to 95% of COX activity is inhibited over 6 to 12 days.³⁶

Antiplatelet effects have also been studied in healthy volunteers through platelet aggregation tests including optical aggregometry and aspirin reaction units (ARUs).^{40,49} 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 aspirin, ARUs are 550 or greater.⁴⁰ When examining ARU changes after administration of 4 aspirin 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.⁴⁰ When examining the induced inhibition of platelet aggregation in healthy volunteers taking an 81-mg dose, aspirin demonstrated a 66.0% \pm 18.6% inhibition measured with optical aggregometry with the agonist arachidonic acid.⁴⁹

Aspirin also influences coagulation through non-TXA₂-mediated effects, including dose-dependent inhibition of platelet function, suppression of plasma coagulation, and enhancement of fibrinolysis.^{39,50–61} Secondary hemostasis and thrombus stability

is also impaired, due to aspirin's acetylation of fibrinogen and its enhancement of fibrinolysis.³⁹ Aspirin, unlike non-aspirin NSAIDs, decreases thrombin formation in clotting blood.⁶⁰ Aspirin at higher doses prevents endothelial cell prostacyclin production by inhibiting COX-2.³⁹ Prostacyclin inhibits platelet coagulation and stimulates vasodilation.

Phosphodiesterase Inhibitors

Phosphodiesterase (PDE) inhibitors are also used as antiplatelet therapies. Platelets express 3 PDE isoenzymes as follows: PDE-2, PDE-3, and PDE-5.⁶² Two commonly encountered PDE inhibitors are dipyridamole, which is often combined with aspirin, 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 aspirin

Aspirin may be combined with other drugs to synergistically affect coagulation. One of these drugs is dipyridamole, which acts in vivo to modify several biochemical pathways involved in platelet aggregation and thrombus formation.^{50,62-65} The extended release (ER) forms of dipyridamole (200 mg ER) and aspirin (25 mg) are often used in combination for the management of cerebral vascular disease including secondary prevention of stroke and transient ischemic attacks.⁶⁶ Dipyridamole inhibits PDE-3 and PDE-5. By inhibiting cAMP and cGMP PDEs, cAMP and cGMP levels increase which result 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.^{63,64} Thromboxane synthase and the thromboxane receptor are also blocked with the use of dipyridamole.⁶⁷ The final pathway by which dipyridamole affects coagulation is through its negative effects on the formation and accumulation of fibrin.⁶⁸ 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 aspirin has an apparent half-life of 13.6 hours.⁶³ In conclusion, when aspirin is combined with dipyridamole, there is an increased risk of bleeding.^{38,69}

Cilostazol

Another PDE-3 inhibitor that also has antiplatelet aggregation and arterial vasodilator properties is cilostazol.^{38,62} 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.⁷⁰ It reduces thromboxane production and platelet factor 4 and platelet-derived growth factor release.⁷¹ Some ex-vivo tests indicated that cilostazol may inhibit platelet aggregation to a greater degree than aspirin.⁷² Cilostazol is used to treat lower extremity claudication.^{38,62} It has also been used to prevent stent thrombosis, and for the prevention of stroke.⁷³ In the field of cardiology, cilostazol is used to augment the inhibition of platelet aggregation in clopidogrel low-responders.⁷⁴⁻⁷⁶ After oral administration, cilostazol reaches peak plasma concentrations at approximately 2 hours, with maximum platelet aggregation occurring at 6 hours.^{38,62,77} 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.⁷⁸ 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 aspirin.^{79,80} One case report described a spinal epidural hematoma after epidural catheter removal in an individual with a low platelet count that had been taking cilostazol after vascular surgery.⁸¹ Limited data exist evaluating the risk of perioperative surgical bleeding with cilostazol and no standard perioperative guidelines are available.⁸² 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.^{78,81}

Cardiac and Cerebrovascular Risks Associated With the Discontinuation of Aspirin

In the United States, a significant number of individuals (>50 million) take aspirin for prevention of cardiovascular events.⁸³ When individuals are taking aspirin, it is important to understand whether use is for primary or secondary prophylaxis. Primary prophylaxis is used to prevent the first occurrence of a cardiovascular event and is defined by aspirin's use 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 aspirin is used in the presence of overt cardiovascular disease or conditions conferring particular risk (eg, diabetes mellitus).

Significant evidence exists supporting the use of aspirin for secondary prophylaxis for cardiovascular disease and guidelines recommend initiation and indefinite continuation unless contraindicated in this patient population.^{41,84,85} Low-dose aspirin, when used for secondary prophylaxis, has been shown to reduce the risk of stroke and myocardial infarction in the range of 25% to 30%.⁸⁶⁻⁸⁸ Furthermore, the discontinuation of aspirin for secondary prophylaxis is associated with significant risk.⁸⁹⁻⁹¹ The lowest effective aspirin daily dose for the prevention of TIA and ischemic stroke is 50 mg. For men at high risk for cardiovascular disease, the recommended dose increases to 75 mg.^{28,29,83,92} The routine long-term use of doses greater than 75 to 81 mg/d have not been shown to have improved efficacy for cardiovascular prevention.⁸³ Approximately 10% of acute cardiovascular syndromes are preceded by the withdrawal of aspirin. The time interval between aspirin discontinuation and acute cardiovascular events is typically in the timeframe recommended for aspirin discontinuation for invasive procedures: 8.5 ± 3.6 days for acute coronary syndromes and 14.3 ± 11.3 days for acute cerebral events.^{88,93-96} When aspirin is discontinued, a platelet rebound phenomenon may occur, resulting in a prothrombotic state characterized by increased thromboxane production, enhanced thrombus stability, improved fibrin cross-link networks, and decreased fibrinolysis.^{41,97-99}

When aspirin is used for primary prophylaxis, its value in preventing cardiovascular events is unclear, with evidence suggesting no definitive benefit for overall mortality rates.^{84,100,101} The Antithrombotic Trialists' Collaboration, after conducting a meta-analysis of individual participant data for randomized trials, concluded that when aspirin 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.⁸⁴ Future studies are required to determine aspirin's role in primary prevention and prophylaxis for cardiovascular events.¹⁰²

Discontinuation of Aspirin and Restoration of Platelet Function

The return of platelet function after discontinuation is affected by multiple factors including prior aspirin dosing, rate of platelet turnover, time interval of discontinuation, and patient-specific response to aspirin therapy. As stated previously, approximately 10% of the platelet pool is replaced daily. Because aspirin irreversibly inhibits COX, it would take 10 days to completely restore a fully functioning platelet pool. Burch et al⁴⁴ confirmed that the return of enzyme activity followed platelet turnover with an average platelet lifespan of 8.2 ± 2 days, although platelet function may occur earlier.¹⁰³⁻¹⁰⁵ Burch et al⁴⁴ also confirmed that new unacetylated enzyme did not appear in circulation for 2 days, suggesting that aspirin 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.¹⁰⁴ 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 aspirin every other day for 14 days.¹⁰⁵ Eighty percent of subjects demonstrated normal platelet aggregation by the fourth day. Another study examining platelet functional recovery after cessation of aspirin in volunteers and surgical patients demonstrated that most of the volunteers and patients experienced recovery of platelet function at day 3 and within 4 to 6 days, respectively.¹⁰⁶ By day 6, all of the subjects had restored platelet aggregation to at least 85% of baseline level. Also, studies examining the effect of aspirin on platelet aggregation in cardiac surgery patients demonstrate earlier platelet recovery, as early as 3 days postdiscontinuation.^{107,108} Gibbs et al¹⁰⁷ examined the effects of recent aspirin ingestion on platelet function in cardiac surgical patients. A significant difference existed in platelet function between patients who ingested aspirin 2 days or less preoperatively in comparison to the 3-to-7-days and more-than-7-days groups. No difference was found in platelet aggregation between the 3-to-7-days and more-than-7-days groups. Coleman and Alberts⁴⁰ demonstrated early recovery of platelet aggregation after the discontinuation of aspirin 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-Aspirin NSAIDs' Effects on Hemostasis

Non-aspirin NSAIDs bind reversibly and competitively inhibit the active site of the COX enzyme. The non-aspirin NSAIDs compete with arachidonic acid's binding to COX-1.³⁶ 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 timeframe in the first 24 hours. Besides indomethacin, non-aspirin NSAIDs do not achieve greater than 90% reversible inhibition of platelet enzyme activity.³⁶ 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%.³⁶ The degree of inhibition of COX-1 by specific NSAIDs influences the associated procedural bleeding risk. Traditional NSAIDs are non-selective and inhibit both COX-1 and COX-2, although some of the non-aspirin NSAIDs, including etodolac, nabumetone, and meloxicam, are associated with more selective inhibition of COX-2.¹⁰⁹ The ratio of COX-2/COX-1 inhibition for meloxicam is approximately 80:25.¹¹⁰ This group of NSAIDs that is more selective for COX-2 inhibition may be associated with a lower procedural bleeding risk.

Unlike ASA (aspirin), 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.¹¹¹ 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 plasma clearance and the extent of drug distribution. The NSAIDs are highly bound to plasma proteins; therefore, their volume of distribution is minimal and the terminal half-lives and half-lives are similar.¹¹² It takes approximately 5 half-lives for systemic elimination (Table 3).^{113,114} The NSAIDs 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 aspirin has been shown to have cumulative inhibition of platelet COX-1 activity, this has not been demonstrated with NSAIDs such as ibuprofen.¹¹⁵

The effect of platelet aggregation with the administration of 1 dose of 10 different NSAIDs has been studied in healthy volunteers.¹¹⁶ Some conventional NSAIDs that were studied included aspirin, diclofenac, ibuprofen, indomethacin, naproxen, acetaminophen, and piroxicam. The non-aspirin NSAIDs were found to abolish the second wave of platelet aggregation for variable periods based on the pharmacokinetics associated with each drug. At 24 hours, greater 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 aspirin's effects lasted between days 5 and 8 after the administration of the single dose. 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.¹¹⁷

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

Nonselective COX inhibitors, such as ibuprofen, may limit aspirin's cardioprotective effects by impeding access of aspirin to the serine 529 target.¹¹⁸ A clinical dose (400 mg) of ibuprofen given 2 hours before aspirin ingestion has been shown to block aspirin's inhibition of serum thromboxane formation and platelet aggregation. Delayed-release diclofenac was not found to limit the cardioprotective effects of aspirin. In addition, meloxicam, which is more selective for COX-2, has not been shown to negatively affect aspirin's ability to reduce thromboxane levels and prevent platelet aggregation.¹¹⁰

COX-2 Inhibitors' Effects on Hemostasis

Unlike drugs that inhibit the enzyme COX-1, NSAIDs that selectively inhibit the enzyme COX-2 do not alter platelet function.¹¹⁹ The expression of COX-2 increases with inflammation.¹²⁰ Multiple studies have demonstrated that celecoxib, a COX-2 inhibitor, does not interfere with the normal mechanisms of platelet aggregation and hemostasis.^{119,121} At therapeutic doses, celecoxib does not inhibit COX-1. Leese et al¹¹⁹ in a randomized controlled trial demonstrated that supratherapeutic doses (600 mg twice a day) of celecoxib given for 10 days did not alter platelet aggregation, thromboxane B₂ levels (thromboxane B₂ is an inactive metabolite of TXA₂ which is excreted in the urine and a surrogate marker of TXA₂), or bleeding time. A limited number of studies suggest that COX-2 inhibitors are not associated with increased surgical blood loss.^{122,123}

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,^{124,125} individuals with genetic differences in the activity of cytochrome P450 2C9 enzyme may be at increased risk for international normalized ratio (INR) elevations and bleeding complications when both drugs are coadministered.¹²⁶ Both celecoxib and warfarin are metabolized by the CYP 2C9 enzyme.

Procedural Recommendations

The ASRA¹²⁷ and European¹²⁸ guidelines recommend that central neuraxial blocks may be performed in individuals using aspirin or NSAIDs. The Scandinavian¹²⁹ guidelines for the performance of central neuraxial blocks in individuals using aspirin, based their recommendations on the indication for aspirin use and the daily dose. In individuals taking aspirin for secondary prevention, a shorter discontinuation time of 12 hours was recommended. For individuals not using aspirin 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 guideline 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 are limited¹³⁰; however, aspirin has been identified as an important risk factor for postoperative bleeding and the development of hematomas including epidural hematomas in other surgical fields.¹³¹⁻¹³⁶ Furthermore, low-dose aspirin utilization before spine surgery, even when discontinued for at least 7 days, has been suggested to lead to further blood drainage after surgery.¹³⁷ In an extensive review, low-dose aspirin has also been shown to increase the rate of bleeding complications by a factor of 1.5 (median, interquartile range: 1.0-2.5).⁸⁸ The baseline risk of bleeding varied based on surgical type (cataract surgery vs transurethral prostatectomy).

Bleeding complications may also occur after the performance of interventional pain procedures. Spinal hematoma is a very rare complication that has been associated with spinal cord stimulator trials, implants with percutaneous placed cylindrical leads and laminotomy placed paddle leads, lead migration, revisions, and lead removal.^{1-3,30,138-140} Aspirin has been suggested as a risk factor in some of the cases.¹⁻³ Case reports of subdural hematomas after spinal anesthesia have also questioned aspirin's continuation before a spinal anesthetic.^{141,142} In addition, spinal hematomas have occurred after cervical ESIs in individuals taking non-aspirin NSAIDs.^{4,143} Other studies examining the performance of lumbar epidurals for pregnancy have not demonstrated an increased risk of bleeding complications with aspirin.¹⁴⁴ 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 aspirin 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.¹¹² 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 aspirin and non-aspirin NSAIDs.¹⁴⁵⁻¹⁵⁴

For individuals taking aspirin for secondary prophylaxis who will be discontinuing aspirin while undergoing a spinal cord stimulator trial, it is recommended that the length of the trial be minimized. It is suggested that, for these patients, one considers a risk-benefit ratio for adequate trialing versus the possibility of cardiovascular sequelae. Presently, no consensus exists regarding

the required duration for a spinal cord stimulator trial needed to allow for appropriate patient selection. Chincholkar et al,¹⁵⁵ in a prospective trial examining 40 patients who underwent a spinal cord similar trial, demonstrated that most 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 those with an unsuccessful trial.

Summary recommendation for non-aspirin NSAIDs

- Non-aspirin NSAIDs are used for pain control and, unlike aspirin, 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 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-aspirin NSAIDs effects on the platelet inactive. For example, in a healthy individual, 24 hours should be adequate for the recommended discontinuation time for ibuprofen.
- 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 recommendation for aspirin

- A patient- and procedural-specific strategy is recommended when deciding whether to continue or discontinue aspirin in the perioperative period for interventional pain procedures. Decision making should include an understanding of the reason for aspirin utilization, vascular anatomy surrounding the target area, degree of invasiveness of the procedure, and potential sequelae associated with perioperative bleeding (Table 1).

TABLE 2. Half-Lives of Commonly Administered Non-Aspirin NSAIDs

Agent	Half-life, h	Discontinuation Time, 5 Half-lives, h	Recommended Discontinuation Time, d
Diclofenac ¹⁵⁶	1-2	5-10	1
Etodolac ¹⁵⁷	6-8	30-40	2
Ibuprofen ¹⁵⁸	2-4	10-20	1
Indomethacin ¹⁵⁹	5-10	25-50	2
Ketorolac ¹⁶⁰	5-6	25-30	1
Meloxicam ¹⁶¹	15-20	75-100	4
Nabumetone ¹⁶²	22-30	110-150	6
Naproxen ¹⁶³	12-17	60-85	4
Oxaprozin ¹⁶⁴	40-60	200-240	10
Piroxicam ¹⁶⁵	45-50	225-250	10

- In addition, a complete review of the patient's medical record should occur to identify additional medications that may heighten aspirin's anticoagulant effect [eg, selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and dipyridamole].
- If aspirin is being taken for primary prophylaxis, aspirin discontinuation is recommended for high-risk procedures in which there is a heightened risk for perioperative bleeding and sequelae. In addition, consideration should be given to the discontinuation of aspirin 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.
 - When aspirin is being used for primary prophylaxis, aspirin may be discontinued for a longer period, 6 days, to ensure complete platelet functional recovery.¹⁰⁶
- In individuals using aspirin 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 aspirin. The risk of bleeding while continuing aspirin needs to be weighed against the cardiovascular risks of stopping aspirin. Documentation of decision making is recommended. If a decision is made to discontinue chronic aspirin 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 aspirin for secondary prophylaxis, aspirin should be discontinued for a minimum of 6 days.¹⁰⁶ In individuals taking aspirin 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.^{40,106} Zisman et al¹⁰⁶ demonstrated that in most aspirin-treated patients, platelet function recovers 4 days after drug discontinuation.

Summary recommendations for PDE inhibitors

The decision to discontinue cilostazol or dipyridamole combined with aspirin should involve shared decision making between the interventional pain physician, patient, and prescribing physician.

- For high-risk procedures, cilostazol and dipyridamole should be discontinued 48 hours before performing the intervention.^{78,81}
- The discontinuation length for dipyridamole combined with aspirin should follow the aspirin recommendations described previously. It has been suggested that, when dipyridamole is combined with aspirin, the risk of bleeding is increased.^{38,69}

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.
- Because a platelet rebound phenomenon may occur with the discontinuation of aspirin and the time intervals between aspirin discontinuation and the occurrence of an acute cardiovascular event is in the range of 8 to 14 days, in individuals taking aspirin 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.

Timing of therapy restoration

- Because NSAIDs are not essential for cardiovascular protection, for high-risk procedures, we recommend withholding these drugs for 24 hours postprocedure.
- For elective pain procedures associated with a high risk for bleeding complications, aspirin can be resumed 24 hours postprocedure if required for secondary prevention.
- For primary prevention, aspirin should not be restarted for at least 24 hours after 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 aspirin 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

The thienopyridines, ticlopidine and clopidogrel, block the ADP receptor, P2Y12 subtype. In the presence of vessel injury, TXA₂ and adenosine nucleotides (which contain P2 receptors) are released. Of the P2Y12 receptors, P2Y1 initiates whereas P2Y12 completes the process of platelet aggregation. 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 aspirin; the so-called dual antiplatelet therapy, to reduce thrombotic events in the setting of acute coronary syndromes and in patients who undergo percutaneous coronary intervention.^{166,167}

Ticlopidine is rarely used, as its antiplatelet effect is delayed¹⁶⁸ 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.¹⁶⁹⁻¹⁷¹ Clopidogrel is a prodrug, requiring 2 metabolic steps to form the active drug.¹⁷² 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.¹⁷³ The maximum percentage of platelet inhibition by clopidogrel is 50% to 60%, which normalizes 7 days after it is discontinued.¹⁷⁴

The current ASRA guidelines on regional anesthesia recommend a 7-day cessation of clopidogrel,¹²⁷ whereas the American College of Cardiology recommend 7 to 10 days in most patients and 5 days for patients who are at high risk for angina.^{175,176} The CURE trial specifically showed less perioperative bleeding when clopidogrel was stopped 5 days before surgery.¹⁷⁶ 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.^{177,178} There is also a retrospective study of 306 patients which showed the absence of spinal hematoma in patients on clopidogrel who had continuous epidural catheters.¹⁷⁹ In a study on the decay of the antiplatelet effect of clopidogrel, Benzon and colleagues¹⁸⁰ noted no difference in the percent platelet inhibition and platelet reaction units between 5 and 7 days after discontinuation of clopidogrel. Unfortunately, the 2 studies involved only a small number of patients.^{179,180} Most pain procedures are elective and clopidogrel should preferably be stopped for 7 days. In cases of SCS trial in patients at high risk for 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 is still off clopidogrel. In these circumstances, where clopidogrel will be stopped only 5 days

before the procedure, a platelet function test such as the VerifyNow P2Y12 assay or platelet mapping portion of the thrombelastograph should be considered whenever available.^{180–182}

Prasugrel is a prodrug similar to clopidogrel and also causes irreversible inhibition of the P2Y12 receptor.¹⁸³ Unlike clopidogrel, it requires only 1 metabolic step to form its active drug.¹⁷² It is reliably converted to its active metabolite, not involved in drug-drug interactions and not susceptible to genetic polymorphisms.^{184,185} Prasugrel has a rapid onset of effect, the median time to peak effect being 1 hour.¹⁷⁴ Peak plasma concentration occurs in 30 minutes with a median half-life of 3.7 hours.^{185,186} Prasugrel causes 90% inhibition of platelet function compared with 60% to 70% for clopidogrel.¹⁷⁴ The superior antiplatelet effect of prasugrel is secondary to its improved metabolism, resulting in more active metabolites being delivered to the platelet.^{187,188} Patients older than 75 years, those with history of transient ischemic attack or stroke, or those with small body mass index are at risk for increased bleeding.^{189,190} Platelet activity does not normalize until 7 days after prasugrel discontinuation.¹⁹¹ A 7- to 10-day interval before a neuraxial injection has been recommended by the ASRA¹²⁷ and European guidelines for regional anesthesia,¹²⁸ whereas the Scandinavian guidelines stated that 5-day stoppage may be sufficient.¹²⁹ 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.¹⁹² Although both the parent compound and the active metabolite have antiplatelet activities, the parent drug is responsible for most of the *in vivo* platelet inhibition.^{193,194} 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.¹⁹⁵ There are no known drug interactions with ticagrelor and its pharmacokinetics are predictable and not affected by genetic polymorphisms.¹⁹⁶

The antiplatelet effect of ticagrelor is rapid, with peak platelet inhibition occurring 2 to 4 hours after intake, compared to 24 hours with clopidogrel.¹⁹⁷ The mean platelet inhibition by ticagrelor is 90%, compared to 50% to 60% for clopidogrel.¹⁹⁸ 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 twice daily resulted in a platelet inhibition of 41% at 30 minutes.¹⁹⁸ Platelet recovery is more rapid with ticagrelor, as platelet inhibition is similar to placebo 5 days after discontinuation.¹⁹⁸

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,¹⁹⁹ resulting in 50% to 75% of the circulating platelet pool being unaffected by platelets 5 days after stoppage of the antiplatelet drug.¹⁷⁸ We recommend 7-day cessation of clopidogrel before spine or pain intervention. If 5 days is recommended by the treating cardiologist or vascular medicine physician, specifically before an extended SCS trial, then a test of platelet function should be performed to assure adequate recovery of platelet function.^{178,181,182} For prasugrel, 7 to 10 days is advisable, whereas 5 days is adequate for ticagrelor.¹⁹⁰

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,¹⁹¹ whereas the European guidelines recommended 6 hours after catheter removal before prasugrel and ticagrelor can be started.¹⁹⁰ Baron et al²⁰⁰ 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, a 300- to 600-mg loading dose of clopidogrel takes effect within 4 to 6 hours. If a loading dose of clopidogrel is used, then a 24-hour interval is more appropriate (Figure 2). 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) in the presence of 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-risk and high-risk procedures, clopidogrel should be routinely stopped for 7 days. In patients with high risk for thromboembolic events, we recommend a 5-day discontinuation interval if available platelet function tests show adequate platelet function.
- For medium-risk and high-risk procedures, prasugrel should be stopped for 7 to 10 days.
- For medium-risk and high-risk procedures, ticagrelor should be stopped for 5 days.
- 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.

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 differences between both lie mainly in their duration of action, with the drug-free interval established for the normalization of coagulation usually being 3 days for acenocoumarol and 5 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),^{201,202} 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,²⁰² making the INR unreliable during the early phase of warfarin therapy.^{202,203} 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 more are considered adequate for hemostasis,²⁰⁴ levels below 20% are associated with bleeding.²⁰⁵

Warfarin is difficult to dose, as 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.²⁰⁶ 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.²⁰³ Recent studies on genetic-based dosing did not settle this issue, as the results were not uniform.^{207–209}

In some centers, warfarin is given the night before total joint surgery. The latest 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 a study by Benzon et al,²⁰² who showed 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. 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. The dose of preoperative warfarin and the age of the patient should be noted when warfarin is given the night before surgery, as spinal hematoma has been reported in the elderly. In one case of spinal hematoma, 10-mg warfarin was given to an 85-year old woman the night before surgery.²¹⁰ In the other case, the age or weight of the patient or the dose of warfarin was not mentioned.²¹¹ These reports are not surprising, as Garcia et al²¹² showed that warfarin requirement progressively decreases with age in both men and women. For example, at age 50 years, 5 mg daily is needed to keep the INR therapeutic, whereas at age 70 years, only 3.5 mg is required. At all ages, women require less than men.²¹²

Another controversial issue is timing of removal of epidural catheters in patients in whom warfarin was started. As previously noted, epidural catheters can be removed within 24 hours after warfarin initiation.²⁰² Two papers showed the absence of spinal hematoma when the epidural catheter was removed 2²¹³ to 3 days after warfarin was started.²¹⁴ 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 likely adequate for hemostasis.²⁰² Beyond 2 days, clotting factors VII, IX, and X are substantially affected and the status of factor II is not assured unless its concentration is determined.

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).^{215,216}
- 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 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 low-molecular-weight heparin (LMWH) can be instituted in patients who are at high risk for thrombosis after consultation with the treating physicians.

Heparin

Unfractionated heparin inactivates thrombin (factor IIa), factor Xa, and IXa.¹²⁷ The anticoagulant effect of intravenous (IV) heparin is immediate, whereas subcutaneous heparin takes 1 hour.²¹⁷ 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.²¹⁸ Reversal is achieved with protamine, with the dose being 1 mg of protamine per 100 U 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 aspirin therapy, and traumatic spinal punctures.²¹⁹ In the study by Ruff and Dougherty, 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 ASRA guidelines recommended that IV heparin be stopped for 2 to 4 hours before a neuraxial procedure.¹²⁷ For interventional pain procedures, the longer 4-hour interval is recommended, especially for high-risk procedures. The elective nature of pain procedures makes this scenario unlikely.

The ASRA recommended an interval of at least 1 hour after a spinal or epidural (or catheter removal) before IV heparin is administered.²²⁰ If the neuraxial procedure is bloody, cancellation of surgery has been recommended.^{221,222} This recommendation has been a source of controversy. After elective pain interventional procedures, wherein it can be bloody, we recommend a 24-hour interval before resumption of heparin, similar to the recommendations by Chaney.²²² This scenario should rarely be encountered as 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 4 hours before a low-, medium-, or high-risk procedure is performed (Table 3).

TABLE 3. Recommended Intervals Between Discontinuation of the Anticoagulants and Interventional Pain Procedure and the Procedure and Resumption of the Anticoagulant

Anticoagulant	Recommended Interval Between Discontinuation of Drug and Pain Procedure	Recommended Interval Between Pain Procedures and Resumption of Drug
Coumadin	5 d, normalization of INR	24 h
IV heparin	4 h	2 h†
Subcutaneous heparin, BID and TID	8–10 h	2 h†
LMWH	24 h	24 h
Fibrinolytic agents	At least 48 h*	At least 48 h*
Fondaparinux	4 d	24 h

*Note that blood clots are not completely stable until approximately 10 days after fibrinolytic therapy and that increased bleeding may occur if pain procedure is done within 10 days of thrombolytic therapy.

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

- The IV heparin can be started a minimum of 2 hours after a pain procedure. If a moderate- or high-risk procedure 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 bridge the time until the intervention is performed when the patient is off the heparin.

Subcutaneous Heparin

The anticoagulant effect of low-dose twice-a-day subcutaneous heparin (5000 U 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 remains in the reference range²²³ during subcutaneous minidose heparin; only a small percentage of patients' PTT exceed 1.5 times normal. The safety of neuraxial anesthesia in the presence of anticoagulation with twice-a-day subcutaneous doses of unfractionated heparin has been documented by several publications.²²⁰ The ASRA guidelines on regional anesthesia considered minidose twice-a-day subcutaneous heparin not a contraindication to neuraxial injections. However rare cases of spinal hematoma have been reported in this setting.²²⁴⁻²²⁶ It is for this reason that we recommend discontinuation of subcutaneous heparin for at least 8 hours before a planned neuraxial procedure including ESIs.

Thrice-a-day subcutaneous heparin regimens have become popular in reducing the incidence of postoperative venous thromboembolism (VTE).²²⁷ This practice has been associated with spontaneous hematomas.²²⁸ In a meta-analysis, King et al²²⁸ noted that while TID subcutaneous heparin is superior to 2-a-day 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. The absence of prospective studies prompted the previous iterations of ASRA guidelines on regional anesthesia to prefer the use of twice daily (bid) subcutaneous heparin.¹²⁷ We make the same recommendation as it pertains to pain procedures.

Summary recommendations for subcutaneous heparin

- Interventional pain procedures are preferably performed in patients on bid subcutaneous heparin.
- Subcutaneous heparin should be discontinued a minimum of 8 to 10 hours before pain procedures (Table 3).
- Subcutaneous heparin can be restarted a minimum of 2 hours after the pain procedure.

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. The LMWH has a higher and more predictable bioavailability than standard heparin and dose adjustment for weight is not necessary. The LMWH exhibits a dose-dependent antithrombotic effect that is assessed by the anti-Xa activity level. The recovery of anti-factor Xa activity after a subcutaneous injection of LMWH approaches 100%,²²⁹ 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.²³⁰

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 which 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 either given 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.²³¹ The recommended thromboprophylactic dose in the United States is 30 mg enoxaparin twice daily, 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 hour for therapeutic purposes. Generally, the following 3 regimens of LMWH administration as thromboprophylaxis are used daily^{232,233}: (1) preoperative protocol—administration of the first dose of LMWH about 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 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 ASRA guidelines for regional anesthesia recommend a minimum of 2 hours after epidural catheter removal, before LMWH is restarted. A US Food and Drug Administration (FDA) Safety Communication released on November 6, 2013, recommends a 4-hour interval based on data provided to them by the manufacturer of enoxaparin, Sanofi-Aventis.²³⁴ A review of their 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), twice daily administration (vs once daily administration), and concomitant medications affecting hemostasis (eg, antiplatelet, anticoagulant, NSAIDs). The identification of administration of LMWH within 12 hours after removal of the epidural catheter as a risk factor made us recommend a 12- to 24-hour interval between medium- and high-risk procedures and resumption of LMWH. The administration of enoxaparin within 24 to 48 hours after a cerebral embolic clot did not enlarge the hematoma.²³⁵

The presence of spine abnormalities has been noted to be a risk factor for spinal hematoma in several publications.^{234,236,237} Similar to the ASRA guidelines on regional anesthesia, we recommend a 12-hour interval for prophylactic enoxaparin and 24-hour interval for therapeutic enoxaparin and dalteparin between discontinuation of the LMWH and a spine interventional procedure. We also recommend a 24-hour interval before resumption of the drug. This is similar to the ASRA guidelines for regional anesthesia, which recommend a 24-hour interval when blood is noted in the epidural catheter,¹²⁷ a situation similar to high-risk pain procedures (kyphoplasty, SCS placement, intrathecal catheter placements).

Summary recommendations for LMWHs

- We recommend a 12-hour interval between stoppage of a prophylactic dose of enoxaparin (except when the dose is 1 mg/kg) and the performance of low-, medium-, and high-risk pain procedures (Table 3).

- When a therapeutic dose of enoxaparin (1 mg/kg) is used and also for dalteparin, we recommend a 24-hour interval between discontinuation of the drug and a pain procedure.
- The LMWH can be resumed 4 hours after a low-risk pain procedure but 12 to 24 hours after medium- and high-risk pain procedures.
- Concomitant drugs that affect hemostasis (eg, 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.¹²⁷

Although experience is scant, there is a general agreement that the use of a neuraxial regional anesthetic technique in patients who have received fibrinolytic medication would lead to an increased risk of spinal hematoma due to the profound coagulation alteration involved and that most of the patients in this situation frequently receive concomitant anticoagulant medication.

Cases of spontaneous spinal hematoma have been reported in patients on thrombolytic therapy.^{238–244} There are also cases of spinal hematoma in patients who had neuraxial procedures and had subsequent thrombolytic therapy.^{245–247} 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. Because of sparse data, the ASRA guidelines on regional anesthesia did not specify the duration of discontinuation of thrombolytics before a neuraxial procedure. The Scandinavian guidelines recommend a 24-hour interval between discontinuation of the drug and neuraxial procedure,¹²⁹ based on the short half-lives of the different thrombolytic drugs. Conversely, avoidance of the drug for 10 days has been recommended.²⁴⁸ This interval is probably too long. Because interventional pain procedures are elective, the longest reasonable time interval between discontinuation of the drug and spine interventional pain procedures that is considered safe should be observed. Because the fibrinolytic effect of the drugs can occur up to 27 hours, a minimum of 48 hours before a pain procedure should be observed. Longer intervals should be considered to avoid unnecessary bleeding. Alternative analgesics can be used until the procedure is safer. Note that blood clots are not completely stable until approximately 10 days after fibrinolytic therapy and that increased bleeding may occur if a pain procedure is done within 10 days of thrombolytic therapy.

There are rare instances when a patient needs an emergency thrombolytic therapy soon after a neuraxial procedure (eg, 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. Studies showed that *thrombolytics* are effective if given within 6 hours of an embolic clot.^{249,250} For pain patients with an intrathecal catheter, the ASRA guidelines on regional anesthesia suggest measuring the fibrinogen level to assess the state of thrombolysis and in guiding the timing of removal of an epidural catheter. The European guidelines recommend leaving the epidural catheter during thrombolysis and removing the catheter when the effect of the drug is gone.¹²⁸ In patients who just had a percutaneous SCS lead trial or 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 received fibrinolytic agents. Other measures, including analgesic medications, should be attempted to relieve the patient's pain. If an intervention has to be performed, a minimum of 48 hours between discontinuation of a thrombolytic agent and a pain procedure is probably safe. However, longer intervals should be sought in view of the elective nature of pain interventions (Table 3).
- In emergency situations wherein a thrombolytic needs to be administered after a spine pain intervention, the managing service should be notified of the patient's pain procedure. 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 a minimum of 48 hours.

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.²⁵¹ Its extended half-life allows once-daily dosing. It is usually administered 6 hours after surgery.²⁵² Fondaparinux is recommended as an antithrombotic agent after major orthopedic surgery,²⁵³ and as initial treatment of pulmonary embolism.²⁵⁴

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.²⁵⁵ 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 (more than 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 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.¹²⁷ 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,²⁵⁵ the authors observed a 2 half-life interval between stoppage of drug and removal of catheter. With 2 half-lives, only 75% of the drug is eliminated,¹¹⁴ a situation that is probably not 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 interval discontinuation of fondaparinux, wherein 97% of the drug is already eliminated, before medium- and high-risk pain procedures. This corresponds to 3 to 4 days (Table 3).

- 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, a 2 half-life interval is probably adequate.
- We recommend resuming the drug after 24 hours, as fondaparinux has a very short onset of effect.

New Anticoagulants: Dabigatran, Rivaroxaban, Apixaban

Overview

Unlike warfarin, the new oral anticoagulants do not require regular monitoring and there are no dietary restrictions. They are more expensive than warfarin, are shorter acting, and missed doses may increase the risk of VTE. There are also no specific antidotes to reverse their anticoagulant effect.

There are no published studies on the intervals between discontinuation of the new oral anticoagulants and neuraxial procedures and subsequent resumption of the drug. The ASRA guidelines on regional anesthesia did not make recommendations,¹²⁷ probably because of the lack of studies, whereas the European and the Scandinavian guidelines based their recommendations on the half-life of the drug. The European and Scandinavian guidelines adopted a 2 half-life interval between discontinuation of the drug and neuraxial injection.^{128,129} based on the recommendation of Rosencher et al. Rosencher and her colleagues²⁵⁶ recommended 2 half-lives as an adequate compromise between prevention of VTE and spinal hematoma. But there is no consensus on the “exact” time for this management. Moreover, for selected patients at high thrombotic risk (defined as a CHA₂DS₂-VASc score more than 4²⁵⁷ or as CHADS₂ more than 2²⁵⁸ or, with moderate to severe renal impairment (defined as a creatinine clearance <50 mL/min), a periprocedural bridging strategy for novel oral anticoagulants has been proposed.^{257–259}

The pharmacokinetics of the new anticoagulants was studied in young healthy individuals,²⁶⁰ not the elderly patients (degenerative spine abnormalities and multiple medical comorbidities) common to pain practices. Also, concomitant antiplatelet therapy was an exclusion criterion in some of the total joint surgery trials,²⁶¹ and antiplatelet therapy has been implicated in case reports of spinal hematoma.^{2,3} There has been no postmarketing surveillance on the new anticoagulants except for dabigatran; such surveillance showed an increased incidence of GI bleeding.²⁶² Finally, a specific antidote for the new oral anticoagulants is not yet available.^{200,263,264}

It should be noted that 25% of the drug still remains in the plasma after 2 half-lives, but only 3% remains after 5 half-lives.¹¹⁴ In view of the problems presented by patients with chronic pain

and because some pain procedures involve more than an injection or insertion of a needle or catheter (eg, SCS or kyphoplasty), 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, respectively) 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.¹²⁹ This was based on the paper by Rosencher et al²⁵⁶ 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 resolved by 7 hours.²⁶⁵ A study showed that enoxaparin given 24 to 48 hours after intracerebral hemorrhage did not enlarge the size of the hematoma.²³⁵ Although *thrombolytics* are still effective when given within 6 hours of a cerebral embolic clot,²⁴⁹ *thrombolytics* are more effective when given within 3 hours after the onset of stroke.²⁵⁰ These studies^{249,250} 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.²⁰⁰ Liew and Douketis²⁶⁶ 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 al²⁰⁰ recommended 48 hours, whereas Connolly and Spyropoulos²⁶⁷ recommended 24 hours but at half the usual dose. The risks posed by the elderly with spine abnormalities make us recommend a 24-hour interval after ESIs, SCS, kyphoplasty, or intrathecal catheter/pump placement before resumption of the new anticoagulants. 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 new anticoagulants

- We recommend a 5 half-life interval between discontinuation of one of the new anticoagulants and medium- and high-risk pain procedures (Table 4).
- For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating

TABLE 4. Recommended Intervals Between Discontinuation of the New Anticoagulants and Interventional Pain Procedure and Between the Procedure and Resumption of the New Anticoagulants

Drug	Half-life	Recommended Interval Between Discontinuation of Drug and Interventional Pain Procedure* (5 Half-lives)†‡	Recommended Interval Between Procedure and Resumption of Drug
Dabigatran	12–17 h 28 h (renal disease)	4–5 d 6 d (renal disease)	24 h
Rivaroxaban	9–13 h	3 d	24 h
Apixaban	15.2 ± 8.5 h	3–5 d‡	24 h

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

†Because of the lack of published studies and in view of the added risks involved in patients with spine abnormalities, we took the upper limit of the half-life of each drug in calculating the 5 half-lives.

‡The potency and the wide variability in the pharmacokinetics of these drugs make us recommend a longer interval.

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).

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^{268–270}; 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%,²⁷¹ and peak plasma concentrations are attained 1.5 to 3 hours after intake of the prodrug.^{271–273} Dabigatran has a half-life of 14 to 17 hours.^{274,275} The pharmacokinetic profile of dabigatran is predictable and not affected by sex, body weight or obesity, ethnic origin, or mild-to-moderate hepatic impairment.²⁷³ Renal clearance accounts for 80% of the clearance of dabigatran,²⁷⁶ elimination half-life of the drug is doubled from 14 to 28 hours in patients with end-stage renal disease.^{276,277} The drug is contraindicated in patients with creatinine clearance less than 30.²⁷⁸

Dabigatran is effective in the prevention of stroke in patients with nonvalvular atrial fibrillation²⁷⁹ 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 study²⁸⁰ but not in a North American study.²⁸¹ A meta-analysis of the trials noted no differences between dabigatran and enoxaparin in any of the end points that were analyzed.²⁸²

In the studies on dabigatran's use as VTE prophylaxis after total joint surgery, the drug was started after surgery.^{280–286} 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.²⁶⁸ Although there was no instance of spinal hematoma, the small number in relation to the incidence of spinal hematoma²⁸⁷ makes it hard 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.¹²⁸

The aPTT is prolonged after dabigatran but the relationship is curvilinear: there is a greater than linear increase at lower concentrations (at or below 200 ng/mL) and a linear relationship at higher concentrations (>200 ng/mL).^{288,289} The thrombin time (TT), also known as thrombin clotting time is highly sensitive to the effects of dabigatran;^{289–291} the test is more appropriate to detect the presence of an anticoagulant effect of dabigatran and not to quantify its effect.²⁹¹ A dilute TT (Hemoclott Thrombin Inhibitory assay) has become available and has linearity across pharmacologically relevant plasma dabigatran concentrations.^{288,290} The ecarin clotting time (ECT), which directly measures thrombin generation, is prolonged by dabigatran²⁹¹ and is linearly related to dabigatran concentrations.²⁸⁸ 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.²⁸⁸

It is unlikely that fresh frozen plasma is effective in the reversal of dabigatran.²⁹² 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 (PCCs) or concentrated pooled plasma products contain either 3 (factors II, IX, and X) or 4 (factors II, VII, IX, and X) clotting factors. The use of 4-factor PCCs has been suggested, but may not be able to reverse the anticoagulant effect of dabigatran.^{290,291} A dabigatran-directed neutralizing antibody is under development.²⁹³

Summary recommendations with dabigatran

- We recommend a 5 half-life interval between discontinuation of dabigatran and medium- or high-risk pain procedure. This corresponds to 4 to 5 days.
- 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. A 2 half-life interval may be considered.
- For patients with end-stage renal disease, we recommend a 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.
- 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^{294,295} and maximum inhibition of factor Xa (up to 68%) occurs 3 hours after dosing. Factor Xa inhibition occurs for 12 hours²⁹⁵ or 24 to 48 hours when higher doses are given in the elderly.²⁹⁶ The half-life of rivaroxaban is 5.7 to 9.2 hours,^{294,295} and can be as long as 13 hours in elderly patients^{297,298} secondary to the age-related decline in renal function.^{297,298} A third of the drug is eliminated each by the kidneys and fecal/biliary route, with the remaining one third being metabolized to inactive metabolites.^{294,299} The renal clearance of rivaroxaban decreases with increasing renal impairment.³⁰⁰ Rivaroxaban is partly metabolized by the liver and its use is to be avoided in patients with severe liver disease.^{298,301} The concomitant use of aspirin and rivaroxaban is an independent risk factor for bleeding. When added to aspirin and clopidogrel, rivaroxaban enhanced the inhibition of ADP-induced platelet aggregation.³⁰² 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 VTE³⁰³ and noninferior to warfarin for the prevention of embolic stroke during atrial fibrillation.³⁰⁴ 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.³⁰⁵ 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.^{306–310} In all 4 RECORD studies, 10 mg of 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,³¹¹ 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.³¹¹ 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.³⁰¹

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 has been recommended by the Scandinavian Society guidelines.¹²⁹ The European Society guidelines recommend 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.¹²⁸ 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 al²⁵⁶ 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.^{289,291} The INR, however, is not recommended as a monitor of rivaroxaban activity because the INR is dependent on the thromboplastin reagent, and thromboplastins vary greatly in their sensitivity to rivaroxaban.²⁸⁸ Factor Xa may be used as a surrogate for the plasma concentrations of rivaroxaban.³¹² Overall, the PT and anti-Xa are the tests best suited for monitoring the effects of rivaroxaban.²⁸⁸ Activated charcoal may be effective in removing rivaroxaban if given within 8 hours of rivaroxaban ingestion.²⁹¹ Rivaroxaban may not be dialyzable because of high protein binding.³¹³ A 4-factor PCC has been shown to reverse the *in vitro* anticoagulant activity of rivaroxaban in healthy volunteers.³¹⁴ Recombinant factor VIIa has been shown to be effective in reversing the effect of fondaparinux²⁹¹ but has not demonstrated efficacy for reversing bleeding from the new oral anticoagulants.³¹³

Summary recommendations with rivaroxaban

- We recommend a 5 half-life interval between discontinuation of rivaroxaban and medium- or high-risk pain procedures. This corresponds to 3 days (Table 4).
- 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. A 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,³¹⁵ 15.2 ± 8.5 hours after a single 5-mg dose, and 11.7 ± 3.3 after multiple 5-mg doses.^{316,317} Fifteen hours is probably the higher end of apixaban's half-life. When given twice-a-day, steady-state concentrations of apixaban are reached on day 3.³¹⁶ Apixaban has an oral bioavailability of more than 45%. It is eliminated via multiple elimination pathways and direct renal and intestinal excretion.³¹⁸ A 24% to 29% of the dose is excreted via the kidneys and 56% of the dose is recovered in the feces.³¹⁵

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.³¹⁹ Apixaban was also noted to reduce the risk of recurrent VTE without increasing the rate of major bleeding.³²⁰ In patients with atrial fibrillation, apixaban is superior to aspirin or warfarin in preventing stroke or systemic embolism.^{321,322} 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.^{323–326} In these studies, apixaban was given 12 to 24 hours after surgery. In one trial, “devices in connection with intrathecal or epidural anesthesia were removed at least 5 hours before the first dose” of apixaban.³²⁶

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. Although the Scandinavian guidelines did not make recommendation on the interval between cessation of apixaban and neuraxial injection because of lack of available data,¹²⁹ the European guidelines recommend a 26- to 30-hour interval.¹²⁸ The Scandinavian guidelines recommend 6 hours after a neuraxial injection or catheter removal before resumption of the drug, whereas the European guidelines recommend a 4- to 6-hour interval. Other recommendations range from 2 to 3 days stoppage of the drug and 24 (with half of the usual dose on the first 24 hours) to 48 hours before resumption of the drug.^{200,266,268} 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.²⁸⁹ The dilute PT assay, wherein the thromboplastin reagent is diluted 16 times, has improved sensitivity over the conventional PT.²⁸⁹ Apixaban can be evaluated with the anti-Xa assay.³²⁷ The anti-Xa assay is more sensitive than the PT and as sensitive as the dilute PT assay,^{314,328} and seems to be the best choice for clinical monitoring of the anticoagulant effect of apixaban.²⁸⁸ Activated charcoal, given within 3 hours of ingestion, reduces the absorption of apixaban. Whether PCCs would be effective in controlling bleeding due to apixaban has not been adequately assessed.²⁹¹

Summary recommendations with apixaban

- We recommend a 5 half-life interval between discontinuation of apixaban and medium- or high-risk pain procedures. This corresponds to 3 days (Table 4). However, the wide variability in the pharmacokinetics of the drug makes us recommend 3 to 5 days.
- 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. A 2 half-life 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).

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors are frequently used during percutaneous coronary interventions by cardiologists as they are very potent platelet inhibitors. These drugs include abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat).

Mechanism of Action

GPIIb/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 GPIIb/IIIa complex becomes a receptor site for fibrinogen. Fibrinogen attaches to the GPIIb/IIIa complexes of adjacent platelets to form a platelet-to-platelet bridge. This platelet-fibrinogen interaction via the GPIIb/IIIa complex is the final common platelet aggregation pathway.^{329–335} As such, drugs that inhibit GPIIb/IIIa prevent platelet aggregation.

Pharmacology and Pharmacokinetics

The drugs are usually administered IV. Abciximab causes a noncompetitive but irreversible inhibition of the GPIIb-IIIa. It does not need dose adjustment in patients with renal failure, unlike the small molecule eptifibatide.³²⁹ Its onset is rapid as it binds to platelets in minutes and platelet aggregation is almost completely inhibited after 2 hours. Although the half-life of abciximab is short (10–30 minutes), its dissociation from glycoprotein is measured in hours, resulting in slow recovery of platelet function (24–48 hours).^{329,330} Platelet recovery is noted 48 hours after stoppage, although platelet-bound abciximab can be detected up to 10 days.³³¹

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. After 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.³³⁶ After tirofiban administration, both bleeding time and platelet aggregation normalize by 3 to 8 hours after stopping treatment.³³¹

Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving GPIIb/IIIa antagonists has been noted.³³⁷ In general, the cardiac surgical and interventional radiology literature recommend that elective surgery be delayed 24 to 48 hours 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 12–24 hours for abciximab, and 4–6 hours for peptidomimetic agents like eptifibatide or tirofiban) is advocated.³³⁵ 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.³³⁷

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.³³⁸ In randomized controlled trials, mild thrombocytopenia (platelet count <100,000/ μ L) developed in approximately 5% of treated patients compared with approximately 2% of controls. Severe thrombocytopenia (platelet count <20,000/ μ L) occurred in approximately 0.7% of patients receiving abciximab for the first time, more often than with either eptifibatide or tirofiban (0.2%).³³⁹ 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.³³⁹

Interventional Pain Procedures in Patients Receiving GPIIb/IIIa Inhibitors

The pharmacologic 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.¹²⁷ No series involving the performance of epidural injections in the presence of GPIIb/IIIa receptor antagonists have been performed.

Generally, surgery or interventional procedures would require adequate platelet function and therefore procedures of high- or intermediate-risk category of interventional pain procedures (outlined previously) should be delayed until platelet function has returned to normal, which is at least 48 hours for abciximab.³³³ The European Society guidelines note that a minimum of 48 hours for abciximab, and 8 to 10 hours for eptifibatide or tirofiban may be adequate.^{128,332}

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 GPIIb/IIIa inhibitors. The actual risk of spinal hematoma or bleeding with GPIIb/IIIa antagonists is unknown. Management is based on labeling precautions and the known surgical and interventional cardiology experience. Caution needs to be exerted 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 GPIIb/IIIa inhibitors to determine that there is no drug-induced thrombocytopenia. Although GPIIb/IIIa inhibitors are contraindicated immediately after surgery,³⁴⁰ due to 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 be carefully monitored neurologically for 24 hours.

Summary recommendations for GPIIb/IIIa inhibitors

- Instances where an interventional pain procedure needs to be performed in a patient who is on or who just had GPIIb/IIIa 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 GPIIb/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 causes irreversible binding, making recommendations on the interval between discontinuation of the drug and

interventional procedures difficult. 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 (Table 5).

- For eptifibatid 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 GPIIb/IIIa 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 Serotonin Reuptake Inhibitors

Patients with chronic pain 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.^{148,341-345}

Mechanisms of Increased Bleeding Risk

Serotonin reuptake inhibitors (SRIs) decrease platelet serotonin uptake from the blood. As platelets do not synthesize serotonin and are dependent on its reuptake, platelet serotonin content is depleted, resulting in inhibition of serotonin-mediated platelet aggregation and increased bleeding.^{344,346} The bleeding risk is dependent on the potency of serotonin reuptake inhibition rather than selectivity.³⁴⁴ Other mechanisms have also been proposed including decreased platelet binding affinity, inhibition of calcium mobilization, and reduced platelet secretion in response to collagen.³⁴⁷

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.³⁴⁸ The added risk of increased GI bleeding can be attributed to the SRI-induced increase in gastric acid secretion.^{341,342}

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, about equivalent to low-dose ibuprofen, the risk increases in

elderly patients, patients with liver cirrhosis, and those using anticoagulants and other antiplatelet medications.^{148,341,342,345}

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% confidence interval (CI), 1.4-3.9]. Comparatively, the risk of reoperation was 2.6% and 2.7% in never and former users, respectively.³⁴⁹ 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.¹⁵¹

The SRI use was also associated with increased perioperative bleeding in orthopedic surgery.^{154,350} 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), 3.7; 95% CI, 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).¹⁵⁴ 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.¹⁵²

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.³⁵¹ Conversely, few studies have reported a significant relationship between SRIs and perioperative bleeding risk in coronary artery bypass graft surgery.³⁵²⁻³⁵⁴

SRIs and Antiplatelet Agents

The risk of GI bleeding associated with SRIs increases with concurrent use of aspirin or antiplatelet medications.^{148,341,342} Similarly, patients taking SSRIs together with antiplatelet medications after acute myocardial infarction were at increased risk of bleeding.¹⁵³

A large epidemiologic study showed that combined use of an SSRI and NSAIDs or low-dose aspirin increased the relative risk of upper GI bleeding to 12.2 (95% CI, 7.1-19.5) and 5.2 (95% CI, 3.2-8.0), respectively. Non-SSRIs also increased the relative risk of upper GI 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 bleeding. The risk with SSRI use returned to baseline after termination of SSRI use.³⁴² Another population-based case-control study confirmed the increased bleeding risk with SSRIs and concurrent aspirin or NSAIDs use.³⁵⁵ The adjusted OR of upper GI 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 aspirin.³⁵⁵

TABLE 5. GPIIb/IIIa Inhibitors and Interventional Pain Procedures

Drug	Half-life	Recovery of Platelet Function, h	Interval Between Drug Discontinuation and Intervention*	Resumption of Drug After Intervention, h†
Abciximab	10-30 min	48	48-120 h (2-5 d)	8-12
Eptifibatid	2.5 h	4	8-24 h	8-12
Tirofiban	2 h	4-8	8-24 h	8-12

Data from De Luca³²⁹ and Schenider and Aggarwal.³³⁰

*The shorter interval is for low risk whereas the longer interval is for intermediate- and high-risk procedures. These are minimum intervals as there are no studies on regional anesthesia or pain interventional procedures in patients on GPIIb/IIIa inhibitors. Note that although abciximab has a quick onset of action, it causes an irreversible binding with the GPIIb/IIIa. The platelet count should be checked before a procedure.

†The time to resumption of the drug is based on the minimum 8 hour time it takes for the clot to be stable. Note that all the GPIIb/IIIa inhibitors have rapid onsets of action.

The increased risk of bleeding with SSRI and NSAID combinations was greater than the additive risk of the individual drugs.³⁵⁶ A recent review article indicated that SSRI use is associated with approximately doubled odds of upper GI bleeding. The risk of bleeding increased with the concurrent use of NSAIDs, anticoagulants, and antiplatelet agents and in patients with liver cirrhosis/failure.¹⁴⁸

SRIs and Anticoagulants

The risk of GI bleeding associated with SRIs increases with concurrent use of anticoagulants.^{357,358} 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). The NSAID users had a similar increased risk of non-GI bleeding (adjusted OR, 1.7; 95% CI, 1.3–2.2).³⁵⁸

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, managing drug discontinuation syndromes, or treating worsening depression.

Because the absolute risk of abnormal bleeding with SSRIs is low and uncontrolled depression is associated with poorer surgical outcome,³⁵⁹ routine discontinuation of SRIs before pain procedures is not recommended.^{345,360} The SRI discontinuation is probably necessary only in high-risk patients with stable depression. High-risk factors are use in elderly patients, those patients concomitantly using aspirin, NSAIDs, other antiplatelets or anticoagulants, and those with liver cirrhosis or failure.^{148,342,345}

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.^{152,345} 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 (Figure 1).¹⁴⁹ In contrast, nonserotonergic antidepressants such as bupropion, mirtazapine, and some TCAs do not inhibit serotonin reuptake.^{345,361} In fact, intraoperative bleeding risk was not higher in the nonserotonergic antidepressant users than nonusers.^{152,154,350} It has previously been shown that GI bleeding induced by high-dose fluoxetine resolved after switching to mirtazapine.³⁶²

When to stop SRIs

Antidepressant discontinuation can be associated with a significant risk of suicide attempts during the early period after discontinuation.³⁶³ Moreover, rapid tapering or abrupt discontinuation of SRIs can result in the development of discontinuation syndrome. This syndrome is characterized by a constellation of various physical and psychological symptoms, including flu-like 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.³⁶⁴ However, these symptoms can be minimized or avoided by gradually tapering off the antidepressant dose and improve or resolve after restarting the antidepressants.^{365,366}

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.¹⁴⁸

The SRIs in general have relatively long half-lives (Table 6). Animal studies have indicated that most SRIs required 5 half-lives of washout period to normalize serum levels. In general, a discontinuation period of about 1 to 2 weeks is required for most SRIs other than fluoxetine.^{367,368} In contrast, the half-life of fluoxetine and its active metabolite norfluoxetine is 2 to 4 and 7 to 15 days, respectively, requiring a washout period of about 5 weeks.^{368,369} Although one case report showed that discontinuation of fluoxetine for 2 weeks was enough to eliminate abnormal bleeding and normalize bleeding time.³⁷⁰

Summary recommendations: 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 SRIs use (old age, advanced liver disease, concomitant ASA, NSAIDs, antiplatelets, or anticoagulants use) should undergo gradual tapering of the SRI dose and discontinue usage 1 to 2 weeks before the procedure (see Table 6 for the individual recommended time).
- Gradual tapering of the dose is especially important in SRIs with known serious discontinuation symptoms (paroxetine or venlafaxine).
- Fluoxetine is an exception, as 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 SRIs use, should be switched to nonserotonergic antidepressants that do not or less potently inhibit serotonin reuptake (eg, bupropion, mirtazapine, TCAs).
- The SRIs 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 Therapies

The use of various natural botanical compounds and extracts has become ubiquitous, and many surveys suggest that up to 1 in 5 patients in the United States and Europe may be using these agents. Some of the compounds have significant biological effects, including the ability to affect platelet aggregation or inhibit or augment warfarin effects. Previous guidelines that have examined the risks of these agents suggest they need not necessarily be stopped before neuraxial procedures.¹²⁷ The 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*).

As per the remaining sections of this guideline, the authors are not convinced that interventional pain procedures are universally equivalent to perioperative perineural and neuraxial techniques. 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

TABLE 6. The Serotonergic Effects of Commonly Used Antidepressants in a Ranking Order

Antidepressants†	Class	Receptor Occupancy, % ³⁷¹			t1/2, h	5-t1/2 (Approx), d	Active Metabolite ³⁷¹	t1/2, h	5-t1/2 (Approx)
		5-HT Transporter	Norepinephrine Transporter	5-HT2c-Receptor					
Clomipramine ³⁷²	TCA	96.44	11.05	11.62	24	5	N-desmethylclomipramine	69	2 wk
Paroxetine ³⁷³	SSRI	95.7	4.7	0.06	21	5			
Escitalopram ³⁷⁴	SSRI	93.66	0.37	1.04	27–32	5–6			
Citalopram ³⁷⁵	SSRI	93.45	1.08	11.1	35	7			
Fluvoxamine ³⁷⁶	SSRI	92.74	3.33	1.35	16–26	5			
Fluoxetine ³⁷⁷	SSRI	88.96	7.37	19.74	24–72*	5–15	Norfluoxetine	7–15 d	5–10 wk
Sertraline ³⁷⁸	SSRI	88.25	1.14	0.062	24	5	N-desmethylsertraline	64–104	2–3 wk
Imipramine ³⁷⁹	TCA	86.17	38.59	35.69	24	5	Desipramine	21	4–5 d
Velafaxine ³⁸⁰	SNRI	84.52	12.47	14.83	5	1	O-desmethylvenlafaxine	11	2 d
Doxepin ³⁸¹	TCA	67.08	82.44	94.03	15	3			
Amitriptyline ³⁸²	TCA	66.49	49.24	91.29	1–36	3–7	Nortriptyline	22–88	1–3 wk
Duloxetine ³⁸³	SNRI	56.25	15.35	0.17	12	2–3			
Nortriptyline ³⁸⁴	TCA	18.83	80.25	42.27	30	7			
Nefazodone ³⁸⁵	SSRI/ Antag	4.22	3.05	40.6	4	1			
Maprotiline ³⁸⁶	Tetra	1.3	87.34	38.57	51	10			
Bupropion ³⁸⁷	Misc	0.74	0.71	0.71	15–22	5	Hydroxybupropion	20	4–5 d
Mirtazapine ³⁸⁸	α-2	0.34	0.73	46.51	20–40	5–7			

Data from several references.^{371–388}

*t1/2 in chronic use is 96 to 144 hours.

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

these agents in these settings. One of the major problems with use of these herbal agents is that patients may not report them to their 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 products and dosages. Practitioners, logically then, should be prepared to thoroughly research the contents of these products to identify constituents and doses.

Garlic

Garlic (*A. sativum*) has its primary effects on platelet aggregation. Previous studies have shown that garlic effects on bleeding are dose dependent.³⁸⁹ 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, affects platelet aggregation by inhibition of granule release and fibrinogen binding³⁹⁰ and also potentiates the inhibition of aggregation by prostacyclin, forskolin, indomethacin, and dipyridamole.³⁹¹ 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 about 2000 mg/d of garlic were noted. His bleeding time was prolonged despite a normal platelet count, but later normalized after garlic cessation.³⁹² Daily doses of 25 mg/d have been shown to result in significant inhibition of platelet aggregation.³⁹³

TABLE 7. Herbal Medications and Their Effects on Coagulation

Herb	Effect on Coagulation	Time to Normal Hemostasis After Stoppage, Comments
Garlic	Inhibits platelet aggregation by reduction and inhibition of formation of thromboxane and lipoxygenase products, inhibition of phospholipase activity, and inhibition of incorporation of arachidonate into platelet phospholipids	7 d; test of platelet function recommended when excessive doses are taken or in the presence of other antiplatelet drugs (aspirin, NSAIDs, SSRIs)
Dong quai	Contains natural coumarin derivatives; potentiates effect of warfarin	Check INR in patients on warfarin
Danshen	Decreases elimination of warfarin; inhibition of platelet aggregation	Check INR in patients on warfarin
Ginkgo biloba	Inhibition of PAF	36 h, check platelet function in the presence of other antiplatelets
Panax ginseng	Reduces effect of warfarin	

Modified from Horlocker et al¹²⁷ with permission. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Procedural Anticoagulation Management Checklist
<p><u>Evaluate baseline patient specific risk factors for perioperative bleeding:</u></p> <ul style="list-style-type: none"> • History and physical examination signs suggestive of a bleeding disorder: <ul style="list-style-type: none"> - History of unexplained nosebleeds (epistaxis) or menorrhagia - Examination signs including petechiae, mucosal bleeding, purpura, or ecchymoses • Family history of bleeding disorders. • Screen for antiplatelet, antithrombotic, or thrombolytic therapy. • Screen for SNRIs, SSRIs, and herbal therapies that may influence coagulation status. • Order coagulation tests when needed based on history and physical examination and/or medication use. • Identify aspirin and non-aspirin NSAIDs utilization.
<p><u>For individuals on aspirin categorize reason for utilization:</u></p> <ul style="list-style-type: none"> • Primary prophylaxis → absence of established cardiovascular disease or risk factor. • Secondary prophylaxis → presence of cardiovascular disease.
<p><u>Process the anatomical location of procedural intervention into decision-making.</u></p> <ul style="list-style-type: none"> • Intracanal vs extracanal spinal procedures • Cervicothoracic neuraxial area or lumbosacral neuraxial area. • Surrounding vascular structures at risk for penetration.
<p><u>Review appropriate radiographic imaging to identify and understand anatomic challenges</u></p> <ul style="list-style-type: none"> • Cervical, thoracic, and lumbar spinal stenosis that alter spinal canal anatomy • Epidural fibrosis and significant scar tissue from previous surgical intervention
<p><u>Identify and manage pharmacologic coagulopathies</u></p> <ul style="list-style-type: none"> • Understand drug elimination and appropriate discontinuation time. • Determine appropriate timing for reinitiation of anticoagulation and antiplatelet therapy. • Practice Informed decision-making involving procedural physician, prescribing medical physician, and patient.
<p><u>Employ post-procedure surveillance for the detection of bleeding complications</u></p>

SNRIs = Selective serotonin norepinephrine reuptake inhibitors

SSRIs = Selective serotonin reuptake inhibitors

FIGURE 1. Procedural management for antiplatelet and anticoagulant therapy.

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 aspirin, NSAIDs, or SRIs.

Dong Quai

Dong quai is from *Radix Angelica 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 more than 2000 years and is marketed for painful menstrual cramps, 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.^{394,395} 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 TXA₂ metabolism.³⁹⁵ 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. The herb should be discontinued when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations regarding interventional procedures.

Danshen

Danshen (*Radix salvia miltiorrhiza*) is a popular traditional Chinese agent that is widely used for various cardiac ailments. Its pharmacologic 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.³⁹⁶

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

Drug	When to stop			When to restart
	High risk procedures	Intermediate risk procedures	Low risk procedures	
ASA and ASA combinations	-Primary prophylaxis: 6 days -secondary prophylaxis: shared assessment and risk stratification	Shared assessment and risk stratification* [†]	No	24 hours
NSAIDs	5 half-lives	No [‡]	No	24 hours
Diclofenac	1 day			
Ketorolac	1 day			
Ibuprofen	1 day			
Etodolac	2 days			
Indomethacin	2 days			
Naproxen	4 days			
Meloxicam	4 days			
Nabumetone	6 days			
Oxaprozin	10 days			
Piroxicam	10 days			
Phosphodiesterase Inhibitors				
Cilostazol	2 days	No	No	24 hours
Dipyridamole	2 days	No	No	
ASA combinations	Follow ASA recommendations	Shared assessment and risk stratification*		
Anticoagulants				
Coumadin	5 days, normal INR	5 days, normal INR	-No - shared assessment and risk stratification*	24 hours
Acenocoumarol	3 days, normal INR	3 days, normal INR	-No - shared assessment and risk stratification*	24 hours
IV heparin	4 hours	4 hours	4 hours	2 hours**
Subcutaneous heparin, BID & TID	8-10 hours	8-10 hours	8-10 hours	2 hours
LMWH: prophylactic	12 hours	12 hours	12 hours	-4 hours after low risk -12-24 hours after medium/high risk pain procedures
LMWH: therapeutic	24 hours	24 hours	24 hours	-4 hours after low risk procedures -12-24 hours after medium/high risk pain procedures

Drug	When to stop			When to restart
	High risk procedures	Intermediate risk procedures	Low risk procedures	
Fibrinolytic agents	48 hours	48 hours	48 hours	48 hours
Fondaparinux	4 days	4 days	shared assessment and risk stratification	24 hours
P2Y12 inhibitors				
Clopidogrel	7 days	7 days	No	12-24 hours
Prasugrel	7-10 days	7-10 days	No	12-24 hours
Ticagrelor	5 days	5 days	No	12-24 hours
New anticoagulants				
Dabigatran	4-5 days 6 days (impaired renal function)	4-5 days 6 days (impaired renal function)	shared assessment and risk stratification*	24 hours
Rivaroxaban	3 days	3 days	shared assessment and risk stratification*	24 hours
Apixaban	3-5 days	3-5 days	shared assessment and risk stratification*	24 hours
Glycoprotein IIb/IIIa inhibitors				
Abciximab	2-5 days	2-5 days	2-5 days	8-12 hours
Eptifibatid	8-24 hours	8-24 hours	8-24 hours	8-12 hours
Tirofiban	8-24 hours	8-24 hours	8-24 hours	8-12 hours
Antidepressants and Serotonin Reuptake Inhibitors (SRIs)	See text and table 6	No	No	See text and table 6

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

New medications since the latest ASRA guidelines for regional anesthesia are in blue boxes.

* See detailed text in the corresponding section.

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

[†]Consideration should be given to the discontinuation of aspirin for certain intermediate risk procedures including interlaminar cervical epidural steroid injections 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 epidural steroid injections 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 the Development of a Hematoma in Spinal and Nonspinal Areas).

FIGURE 2. Summary of periprocedural management of anticoagulants and antiplatelet medications. To view a full page version of this figure go to <http://links.lww.com/AAP/A142>.

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.³⁹⁷

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

Ginkgo Biloba

The ginkgo 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 has 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, ginkgolide acids, proanthocyanidins, carboxylic acids and non-flavone glycosides.³⁹⁸ The chemical constituents can vary depending on the strain of ginkgo as well as growing conditions.³⁹⁹

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).^{400,401} The most frequently included GBE formulations in clinical trials to date are EGb 761 and LI 1370.⁴⁰¹ Inhibition of platelet activation factor (PAF) is considered to be the main mechanism of action resulting in ginkgo-related biologic activity.⁴⁰²⁻⁴⁰⁵

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 PAF and collagen lead to inhibition of platelet aggregation.⁴⁰⁶ Many reported cases of spontaneous bleeding involved concurrent use of antiplatelet or anticoagulant therapies.⁴⁰⁷ Diamond et al⁴⁰⁸ concluded that adverse events, as described in case reports, occurred in patients that were taking additional medicines or had comorbid conditions.

In patients taking ginkgo biloba and other antiplatelets (aspirin, NSAIDs, SSRIs), platelet function test (whichever available) should be considered. Refer to the section on antiplatelets regarding guidelines on their discontinued or continued use.

Ginseng

Panax ginseng (C.A. Meyer), *P. 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.”⁴⁰⁹

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.⁴¹⁰ 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.⁴¹¹ Other trials have shown little effect on warfarin resistance, with one randomized trial of ischemic stroke patients showing no effect of coadministered *P. ginseng* on warfarin-induced INR.⁴¹² 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 suggest that the adverse effects of this agent are less severe than many other agents.

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

Summary recommendations for herbal medications

- Physicians should inquire about patients' use of herbal/alternative therapies and make this part of the reconciled medication list, with actual dosages of the agent, if possible. Practitioners should be aware that these agents are not regulated like other FDA-approved drugs, contributing to the potential for widely disparate doses.
- High-risk procedures are most likely to have a significant bleeding risk. Although there are no published cases, we recommend that elective procedures be performed in idealized settings (ie, with discontinuation of several known herbal agents).
- 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, and history of major bleeding episodes from procedures, should have these anticoagulants 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 (Table 7).
- 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 aspirin, NSAIDs, or SSRIs.
- In patients taking warfarin and also dong quai, the INR should be checked. The herb should be discontinued when the INR is

markedly elevated. Refer to the section on warfarin regarding recommendations regarding interventional procedures.

- In patients taking warfarin and also danshen, the INR should be checked. The herb should be stopped when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations regarding interventional procedures. As there can be inhibition of platelet aggregation, interaction between danshen and other antiplatelet drugs (aspirin, NSAIDs, SSRIs) should be kept in mind especially in patients with several comorbidities.
- In patients taking ginkgo biloba and other antiplatelets (aspirin, NSAIDs, SSRIs), a test of platelet function should probably be ordered. Refer to the section on antiplatelets regarding guidelines on their discontinued or continued use.

SUMMARY

This guideline was produced with the goal of being a significant clinical help to practicing interventional spine and pain physicians. The authors felt that stratification into procedural risk categories might improve the application of these guidelines. However, one should not construe that a high-risk procedure is necessarily “risky,” as this is rarely the case. Evidence where available was used, but many recommendations are based on pharmacologic principles 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 (Figure 1). Perioperative management of anticoagulants and antiplatelet agents are summarized in Figure 2. It is intended that the outcomes associated 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. Although this is understood, we implore the reader to strive to understand the reasoning behind the guideline recommendations (eg, “5 half-lives”) and the impact of possible patient and situational confounders on outcomes.

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