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.


A survey was conducted among participants at the Antiocoagulation/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 18, 2012, in Miami, Florida. The purpose of the survey was to determine the safe practice patterns of pain physicians regarding continuation 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 remainder 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. The committee has an international representation and was endorsed by 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. 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 antplatelet agents (ASA and NSAIDs). The current ASRA guidelines for the placement of epidural and spinal catheters do not recommend cessation of these antplatelet agents for epidural procedures, nor do the guidelines differentiate between interventional pain procedures and perioperative regional anesthesia blocks.

**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 styletted 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.

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 spondylodyplasia which may compact 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 antplatelet effects including NSAIDs, ASA, and SSRIs.

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

<table>
<thead>
<tr>
<th>High-Risk Procedures</th>
<th>Intermediate-Risk Procedures</th>
<th>Low-Risk Procedures</th>
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<tbody>
<tr>
<td>SCS trial and implant</td>
<td>Interlaminar ESIs (C, T, L, S)</td>
<td>Peripheral nerve blocks</td>
</tr>
<tr>
<td>Intrathecal catheter and pump implant</td>
<td>Transforminal ESIs (C, T, L, S)</td>
<td>Peripheral joints and musculoskeletal injections</td>
</tr>
<tr>
<td>Vertebral augmentation (vertebroplasty and kyphoplasty)</td>
<td>Facet MBNB and RFA (C, T, L)</td>
<td>Trigger point injections including piriformis injection</td>
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<tr>
<td>Epiduroscopy and epidural decompression</td>
<td>Paravertebral block (C, T, L)</td>
<td>Sacroiliac joint injection and sacral lateral branch blocks</td>
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<tr>
<td></td>
<td>Intradiscal procedures (C, T, L)</td>
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<td></td>
<td>Sympathetic blocks (stellate, thoracic, splanchnic, celiac, lumbar, hypogastric)</td>
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<td></td>
<td>Peripheral nerve stimulation trial and implant</td>
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<td></td>
<td>Pocket revision and IPG/ITP replacement</td>
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*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/antplatelets, 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.
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. 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. In clinical studies, altered hypothalamopituitary-adrenal axis function has been associated with chronic widespread body pain. These results may be explained by the associated high rates of psychological stress.

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. Stress may also affect coagulation activity via an influence on the regulation of genes coding for coagulation and fibrinolysis molecules. Chronic stress increases many stress hormone levels. Catecholamine and cortisol surges may underlie the hypercoagulability observed with chronic psychological distress.

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. The peak plasma levels for enteric-coated aspirin may be delayed until 3 to 4 hours after ingestion. 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. 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.

Aspirin also influences platelet function, COX activity, and thromboxane production is time and dose dependent. A single 20-mg dose of aspirin reduces COX activity by 82% as early as 5 minutes after dosing. Furthermore, a single dose of 100 mg of aspirin suppresses COX activity by 95% ± 4%. 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. After daily dosing with 20 to 40 mg of aspirin, 92% to 95% of COX activity is inhibited over 6 to 12 days.

Antplatelet effects have also been studied in healthy volunteers through platelet aggregation tests including optical aggregometry and aspirin reaction units (ARUs). Aspirin reaction units are 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. When examining ARU changes after administration of 4 aspirin dosing regimens (enteric-coated 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. When examining the induced inhibition of platelet aggregation in healthy volunteers taking an 81-mg dose, aspirin demonstrated a 66.0% ± 18.6% inhibition measured with optical aggregometry with the agonist arachidonic acid.

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

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 H2. Prostaglandin H2 is required for the synthesis of thromboxane A2 (TXA2). Thromboxane A2 is produced by platelets and has prothrombotic effects including vasoconstriction.

There are multiple classes of NSAIDs including salicylates, acetic acid derivatives, enolic acid derivatives, and selective COX-2 inhibitors.
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.46 Aspirin at higher doses prevents endothelial cell prostacyclin production by inhibiting COX-2.73 Prostacyclin inhibits platelet coagulation and stimulates vasodilatation.

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 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 vasodilatation. 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.70

The final pathway by which dipyridamole affects coagulation is through its negative effects on the formation and accumulation of fibrin.69 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.58,60

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 intermittent 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 heparically 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.84–88 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 ischaemic 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.80,95–96 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 al 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. Burch et al 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. 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. 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. 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. Gibbs et al 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 Alberts 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. 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. 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%. The degree of inhibition of COX-1 by specific NSAIDs influences the associated procedural bleeding risk. Traditional NSAIDs are nonselective and inhibit both COX-1 and COX-2, although some of the non–aspirin NSAIDs, including etodolac, nabumetone, and meloxicam, are associated with more selective inhibition of COX-2. The ratio of COX-2/COX-1 inhibition for meloxicam is approximately 80:25. 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. 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. It takes approximately 5 half-lives for systemic elimination (Table 3). 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.

The effect of platelet aggregation with the administration of 1 dose of 10 different NSAIDs has been studied in healthy volunteers. 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.

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. 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.

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. The expression of COX-2 increases with inflammation. Multiple studies have demonstrated that celecoxib, a COX-2 inhibitor, does not interfere with the normal mechanisms of platelet aggregation and hemostasis. At therapeutic doses, celecoxib does not inhibit COX-1. Leese et al 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. 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 An in 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).18 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 hematoa 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.1,3,30,38–40 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 Halves, h** | **Recommended Discontinuation Time, d** |
| Diclofenac156 | 1–2 | 5–10 | 1 |
| Etoxolac157 | 6–8 | 30–40 | 2 |
| Ibuprofen158 | 2–4 | 10–20 | 1 |
| Indomethacin159 | 5–10 | 25–50 | 2 |
| Ketorolac160 | 5–6 | 25–30 | 1 |
| Meloxicam161 | 15–20 | 75–100 | 4 |
| Nabumetone162 | 22–30 | 110–150 | 6 |
| Naproxen163 | 12–17 | 60–85 | 4 |
| Oxapozin164 | 40–60 | 200–240 | 10 |
| Piroxicam165 | 45–50 | 225–250 | 10 |
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 adenine nucleotides (which contain P2 receptors) are released. Of the P2Y12 receptors, P2Y1 initiates whereas P2Y12 promotes 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.66,105

Ticlopidine is rarely used, as its antiplatelet effect is delayed108 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 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.170 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, Benzoni 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 after discontinuing it.
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.\textsuperscript{180–182}

Prasugrel is a produg similar to clopidogrel and also causes irreversible inhibition of the P2Y12 receptor.\textsuperscript{183} Unlike clopidogrel, it requires only 1 metabolic step to form its active drug.\textsuperscript{122} It is reliably converted to its active metabolite, not involved in drug-drug interactions and not susceptible to genetic polymorphisms.\textsuperscript{184,185} Prasugrel has a rapid onset of effect, the median time to peak effect being 1 hour.\textsuperscript{124} Peak plasma concentration occurs in 30 minutes with a median half-life of 3.7 hours.\textsuperscript{185,186} Prasugrel causes 90% inhibition of platelet function compared with 60% to 70% for clopidogrel.\textsuperscript{174} The superior antiplatelet effect of prasugrel is secondary to its improved metabolism, resulting in more active metabolites being delivered to the platelet.\textsuperscript{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.\textsuperscript{189,190}

Platelet activity does not normalize until 7 days after prasugrel discontinuation.\textsuperscript{191} A 7- to 10-day interval before a neuraxial injection has been recommended by the ASRA\textsuperscript{127} and European guidelines for regional anesthesia,\textsuperscript{128} whereas the Scandinavian guidelines stated that 5-day stoppage may be sufficient.\textsuperscript{192} 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.\textsuperscript{193} 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.\textsuperscript{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.\textsuperscript{195} There are no known drug interactions with ticagrelor and its pharmacokinetics are predictable and not affected by genetic polymorphisms.\textsuperscript{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.\textsuperscript{197} The mean platelet inhibition by ticagrelor is 90%, compared to 50% to 60% for clopidogrel.\textsuperscript{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.\textsuperscript{198} Platelet recovery is more rapid with ticagrelor, as platelet inhibition is similar to placebo 5 days after discontinuation.\textsuperscript{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% forma-

tion of new platelets every day,\textsuperscript{199} resulting in 50% to 75% of the circulating platelet pool being unaffected by platelets 5 days after stoppage of the antiplatelet drug.\textsuperscript{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.\textsuperscript{178,181,182} For prasugrel, 7 to 10 days is advisable, whereas 5 days is adequate for ticagrelor.\textsuperscript{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,\textsuperscript{191} whereas the European guidelines recommended 6 hours after catheter removal before prasugrel and ticagrelor can be started.\textsuperscript{190} Baron et al\textsuperscript{190} 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), making 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,\textsuperscript{202} making the INR unreliable during the early phase of warfarin therapy.\textsuperscript{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,\textsuperscript{204} levels below 20% are associated with bleeding.\textsuperscript{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 pharmacokinetik-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 2 to 3 days after warfarin was started.213 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.211 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.215 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.216 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.211,221 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>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Recommended Interval Between Discontinuation of Drug and Pain Procedure</th>
<th>Recommended Interval Between Pain Procedures and Resumption of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumadin</td>
<td>5 d, normalization of INR</td>
<td>24 h</td>
</tr>
<tr>
<td>IV heparin</td>
<td>4 h</td>
<td>2 h†</td>
</tr>
<tr>
<td>Subcutaneous heparin, BID and TID</td>
<td>8–10 h</td>
<td>2 h†</td>
</tr>
<tr>
<td>LMWH</td>
<td>24 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Fibrinolytic agents</td>
<td>At least 48 h*</td>
<td>At least 48 h*</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>4 d</td>
<td>24 h</td>
</tr>
</tbody>
</table>

*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 range during subcutaneous minidose heparin; only a small percentage of patients’ PT 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.

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. 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). This practice has been associated with spontaneous hematomas. In a meta-analysis, King et al noted that while TID subcutaneous heparin is superior to a one-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. 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%, 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.

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. 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: (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. 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.

The presence of spine abnormalities has been noted to be a risk factor for spinal hematoma in several publications. 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, 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 thromb 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 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 safe. 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.125 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 if the patient 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,111 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, 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. Based on the recommendation of Rosencher et al, Rosencher and her colleagues 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 CHADS2-VASc score more than 4) or as CHADS2 more than 2 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.

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

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. 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. This was based on the paper by Rosencher et al 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. A study showed that enoxaparin given 24 to 48 hours after intracerebral hemorrhage did not enlarge the size of the hematoma. Although thrombolytics are still effective when given within 6 hours of a cerebral embolic clot, thrombolytics are more effective when given within 3 hours after the onset of stroke. These studies 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 reinstatement of antithrombotic therapy within 24 hours after a major procedure might increase the risk of bleeding after the procedure.

Liew and Douketis recommended a minimum of 24 hours in patients with low bleeding risk, and 48 hours in those with a high bleeding risk, before resuming dabigatran, rivaroxaban, or apixaban. Baron et al recommended 48 hours, whereas Connolly and Spyropoulos 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).

**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 physician(s) should guide whether fondaparinux should be discontinued.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life</th>
<th>Recommended Interval Between Drug and Interventional Pain Procedure*</th>
<th>Recommended Interval Between Procedure and Resumption of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12–17 h</td>
<td>4–5 d</td>
<td>24 h</td>
</tr>
<tr>
<td></td>
<td>28 h (renal disease)</td>
<td>6 d (renal disease)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>9–13 h</td>
<td>3 d</td>
<td>24 h</td>
</tr>
<tr>
<td>Apixaban</td>
<td>15.2 ± 8.5 h</td>
<td>3–5 d†</td>
<td>24 h</td>
</tr>
</tbody>
</table>

*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; 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%, and peak plasma concentrations are attained 1.5 to 3 hours after intake of the prodrug. Dabigatran has a half-life of 14 to 17 hours. The pharmacokinetic profile of dabigatran is predictable and not affected by sex, body weight or obesity, ethnic origin, or mild-to-moderate hepatic impairment. Renal clearance accounts for 80% of the clearance of dabigatran, elimination half-life of the drug is doubled from 14 to 28 hours in patients with end-stage renal disease. The drug is contraindicated in patients with creatinine clearance less than 30. Dabigatran is effective in the prevention of stroke in patients with nonvalvular atrial fibrillation and has been approved for such use in the United States, Canada, and Europe. It has also been approved for use in Europe and Canada for the prevention of VTE after total hip or knee replacement but not in the United States. This is probably because dabigatran was noted to be superior to enoxaparin in a European study but not in a North American study. A meta-analysis of the trials noted no differences between dabigatran and enoxaparin in any of the end points that were analyzed.

In the studies on dabigatran’s use as VTE prophylaxis after total joint surgery, the drug was started after surgery. 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. Although there was no instance of spinal hematoma, the small number in relation to the incidence of spinal hematoma 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.

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). The thrombin time (TT) also known as thrombin clotting time is highly sensitive to the effects of dabigatran. The test is more appropriate to detect the presence of an anticoagulant effect of dabigatran and not to quantify its effect. A dilute TT (Hemoclot Thrombin Inhibitory assay) has become available and has linearity across pharmacologically relevant plasma dabigatran concentrations. The ecarin clotting time (ECT), which directly measures thrombin generation, is prolonged by dabigatran and is linearly related to dabigatran concentrations. 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.

It is unlikely that fresh frozen plasma is effective in the reversal of dabigatran. Activated charcoal prevents absorption of the dabigatran but needs to be given within 2 hours of ingestion of the drug. Dialysis might speed elimination of the drug. Recombinant factor VIIa (NovoSeven, Princeton, New Jersey) has been recommended to control hemorrhage. Prothrombin complex concentrates (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. A dabigatran-directed neutralizing antibody is under development.

**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 and maximum inhibition of factor Xa (up to 68%) occurs 3 hours after dosing. Factor Xa inhibition occurs for 12 hours or 24 to 48 hours when higher doses are given in the elderly. The half-life of rivaroxaban is 5.7 to 9.2 hours, and can be as long as 13 hours in elderly patients secondary to the age-related decline in renal function. 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. The renal clearance of rivaroxaban decreases with increasing renal impairment. Rivaroxaban is partially metabolized by the liver and its use is to be avoided in patients with severe liver disease. 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. Risks for increased bleeding include the advanced age, patients with low body weight, and those with renal insufficiency.

Rivaroxaban is as effective as enoxaparin in the treatment of symptomatic VTE and noninferior to warfarin for the prevention of embolic stroke during atrial fibrillation. 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. 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. 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., 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. 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.

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. 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. These 2 recommendations represent a 2 half-life interval between rivaroxaban discontinuation and epidural catheter placement or removal. The 4- to 6-hour interval before resumption of the next dose is also in agreement with the recommendation of Rosencher et al. 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. The INR is dependent on the thromboplastin reagent, and thromboplastins vary greatly in their sensitivity to rivaroxaban. Factor Xa may be used as a surrogate for the plasma concentrations of rivaroxaban. Overall, the PT and anti-Xa are the tests best suited for monitoring the effects of rivaroxaban. Activated charcoal may be effective in removing rivaroxaban if given within 8 hours of rivaroxaban ingestion. Rivaroxaban may not be dialyzable because of high protein binding. A 4-factor PCC has been shown to reverse the in vitro anticoagulant activity of rivaroxaban in healthy volunteers. Recombinant factor VIIa has been shown to be effective in reversing the effect of fondaparinux but has not demonstrated efficacy for reversing bleeding from the new oral anticoagulants.

**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, 15.2 ± 8.5 hours after a single 5-mg dose, and 11.7 ± 3.3 after multiple 5-mg doses. 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. Apixaban has an oral bioavailability of more than 45%. It is eliminated via multiple elimination pathways and direct renal and intestinal excretion. A 24% to 29% of the dose is excreted via the kidneys and 56% of the dose is recovered in the feces.

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. Apixaban was also noted to reduce the risk of recurrent VTE without increasing the rate of major bleeding. In patients with atrial fibrillation, apixaban is superior to aspirin or warfarin in preventing stroke or systemic embolism. 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. 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.

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, the European guidelines recommend a 26- to 30-hour interval. 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. 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. The dilute PT assay, wherein the thromboplastin reagent is diluted 16 times, has improved sensitivity over the conventional PT. Apixaban can be evaluated with the anti-Xa assay. The anti-Xa assay is more sensitive than the PT and as sensitive as the dilute PT assay, and seems to be the best choice for clinical monitoring of the anticoagulant effect of apixaban. 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.

**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. 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 epifibatide. 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). Platelet recovery is noted 48 hours after stoppage, although platelet-bound abciximab can be detected up to 10 days. Similar to abciximab, epifibatide 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 epifibatide and 2 hours for tirofiban. Recovery of platelet function occurs in 4 hours with epifibatide and 4 to 8 hours with tirofiban. After IV epifibatide, the bleeding time normalizes 15 to 30 minutes after drug discontinuation, and in vitro platelet function begins to recover 4 hours after drug discontinuation. After tirofiban administration, both bleeding time and platelet aggregation normalize by 3 to 8 hours after stopping treatment. Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving GPIIb/IIIa antagonists has been noted. 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 epifibatide or tirofiban. For semirurgent 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 epifibatide or tirofiban) is advocated. 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.

Although rare, abciximab, epifibatide, 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. In randomized controlled trials, mild thrombocytopenia (platelet count <100,000/µL) developed in approximately 5% of treated patients compared with approximately 2% of controls. Severe thrombocytopenia (platelet count <20,000/µL) occurred in approximately 0.7% of patients receiving abciximab for the first time, more often than with either epifibatide or tirofiban (0.2%). A pooled analysis of 8 placebo-controlled studies concluded that abciximab, but not epifibatide or tirofiban, increased the incidence of thrombocytopenia in patients also treated with heparin.

**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. 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. The European Society guidelines note that a minimum of 48 hours for abciximab, and 8 to 10 hours for epifibatide or tirofiban may be adequate.

**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 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 epifibatide 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 angesic 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 antplatelets 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life</th>
<th>Recovery of Platelet Function, h</th>
<th>Interval Between Drug Discontinuation and Interventiona</th>
<th>Resumption of Drug After Intervention, h†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>10–30 min</td>
<td>48</td>
<td>48–120 h (2–5 d)</td>
<td>8–12</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>2.5 h</td>
<td>4</td>
<td>8–24 h</td>
<td>8–12</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>2 h</td>
<td>4–8</td>
<td>8–24 h</td>
<td>8–12</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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.\textsuperscript{148}

**SRIs and Anticoagulants**

The risk of GI bleeding associated with SRIs increases with concurrent use of anticoagulants.\textsuperscript{357,358} In a large population-based study of approximately 2 million patients on warfarin, SRI 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).\textsuperscript{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,\textsuperscript{359} routine discontinuation of SRIs before pain procedures is not recommended.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{149} In contrast, nonserotonergic antidepressants such as bupropion, mirtazapine, and some TCAs do not inhibit serotonin reuptake.\textsuperscript{345,361} In fact, intraoperative bleeding risk was not higher in the nonserotonergic antidepressant users than nonusers.\textsuperscript{152,154,350} It has previously been shown that GI bleeding induced by high-dose fluoxetine resolved after switching to mirtazapine.\textsuperscript{362}

**When to stop SRIs**

Antidepressant discontinuation can be associated with a significant risk of suicide attempts during the early period after discontinuation.\textsuperscript{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.\textsuperscript{364} However, these symptoms can be minimized or avoided by gradually tapering off the antidepressant dose and improve or resolve after restarting the antidepressants.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{368,369} Although one case report showed that discontinuation of fluoxetine for 2 weeks was enough to eliminate abnormal bleeding and normalize bleeding time.\textsuperscript{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 discontinuation 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.\textsuperscript{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), daneshen (Radix Salvia miltiorrhiza), and dong quai (Radix Angelicae 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
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>
<thead>
<tr>
<th>TABLE 6. The Serotonergic Effects of Commonly Used Antidepressants in a Ranking Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Receptor Occupancy, %**371</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td><strong>5-HT1 transporter</strong></td>
</tr>
<tr>
<td><strong>Norepinephrine transporter</strong></td>
</tr>
<tr>
<td><strong>5-HT2c Receptor</strong></td>
</tr>
<tr>
<td><strong>t1/2, h</strong></td>
</tr>
<tr>
<td><strong>5-t1/2 (Approx), d</strong></td>
</tr>
<tr>
<td><strong>Active Metabolite</strong>371</td>
</tr>
<tr>
<td><strong>t1/2, h</strong></td>
</tr>
<tr>
<td>**5-t1/2 (Approx)</td>
</tr>
<tr>
<td>Clomipramine372 TCA 96.44 11.05 11.62 24 5  N-desmethylclomipramine 69 2 wk</td>
</tr>
<tr>
<td>Paroxetine373 SSRI 95.7 4.7 0.06 21 5</td>
</tr>
<tr>
<td>Escitalopram374 SSRI 93.66 0.37 1.04 27–32 5–6</td>
</tr>
<tr>
<td>Citalopram375 SSRI 93.45 1.08 11.1 35 7</td>
</tr>
<tr>
<td>Fluvoxamine376 SSRI 92.74 3.33 1.35 16–26 5</td>
</tr>
<tr>
<td>Fluoxetine377 SSRI 88.96 7.37 19.74 24–72* 5–15  Norfluoxetine 7–15 d 5–10 wk</td>
</tr>
<tr>
<td>Sertraline378 SSRI 88.25 1.14 0.062 24 5  N-desmethysertraline 64–104 2–3 wk</td>
</tr>
<tr>
<td>Imipramine379 TCA 86.17 38.59 35.69 24 5  Desipramine 21 4–5 d</td>
</tr>
<tr>
<td>Velpaxfaine380 SNRI 84.52 12.47 14.83 5 1  O-desmethylvenlafaxine 11 2 d</td>
</tr>
<tr>
<td>Doxepin381 TCA 67.08 82.44 94.03 15 3</td>
</tr>
<tr>
<td>Amitriptyline382 TCA 66.49 49.24 91.29 1–36 3–7  Nortriptyline 22–88 1–3 wk</td>
</tr>
<tr>
<td>Duloxetine383 SNRI 56.25 15.35 0.17 12 2–3</td>
</tr>
<tr>
<td>Nortriptyline384 TCA 18.83 80.25 42.27 30 7</td>
</tr>
<tr>
<td>Fluvoxamine376 SSRI/ Antag 4.22 3.05 40.6 4 1</td>
</tr>
<tr>
<td>Maprotiline386 Tetra 1.3 87.34 38.57 51 10</td>
</tr>
<tr>
<td>Bupropion387 Misc 0.74 0.71 0.71 15–22 5  Hydroxybupropion 20 4–5 d</td>
</tr>
<tr>
<td>Mirtazapine388 α-2 0.34 0.73 46.51 20–40 5–7</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>TABLE 7. Herbal Medications and Their Effects on Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herb</strong></td>
</tr>
<tr>
<td><strong>Effect on Coagulation</strong></td>
</tr>
<tr>
<td><strong>Time to Normal Hemostasis After Stoppage, Comments</strong></td>
</tr>
<tr>
<td>Garlic</td>
</tr>
<tr>
<td>Inhibits platelet aggregation by reduction and inhibition of formation of thromboxane and lipoygenase products, inhibition of phospholipase activity, and inhibition of incorporation of arachidonate into platelet phospholipids</td>
</tr>
<tr>
<td>7 d; test of platelet function recommended when excessive doses are taken or in the presence of other antiplatelet drugs (aspirin, NSAIDs, SSRI)</td>
</tr>
<tr>
<td>Dong quai</td>
</tr>
<tr>
<td>Contains natural coumarin derivatives; potentiates effect of warfarin</td>
</tr>
<tr>
<td>Check INR in patients on warfarin</td>
</tr>
<tr>
<td>Danshen</td>
</tr>
<tr>
<td>Decreases elimination of warfarin; inhibition of platelet aggregation</td>
</tr>
<tr>
<td>Check INR in patients on warfarin</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
</tr>
<tr>
<td>Inhibition of PAF</td>
</tr>
<tr>
<td>36 h, check platelet function in the presence of other antiplatelets</td>
</tr>
<tr>
<td>Panax ginseng</td>
</tr>
<tr>
<td>Reduces effect of warfarin</td>
</tr>
</tbody>
</table>

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.
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. 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. Case reports of interactions between danshen and warfarin are described. A 62-year-old man required mitral valve replacement and postoperatively was stabilized on warfarin with an
INR of 3.0. Six weeks after discharge, the patient was re-admitted 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 terpine lactones. Other constituents are quercetin, ginkgolic 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 antplatelet 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.599

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<table>
<thead>
<tr>
<th>Drug</th>
<th>High risk procedures</th>
<th>Intermediate risk procedures</th>
<th>Low risk procedures</th>
<th>When to stop</th>
<th>When to restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA and ASA combinations</td>
<td>- Primary prophylaxis: 6 days secondary prophylaxis shared assessment and risk stratification</td>
<td>- No</td>
<td>- 24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>3 half-lives No</td>
<td>No</td>
<td>24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2 days</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>4 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogran</td>
<td>3 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticlopidin</td>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogran</td>
<td>2 days</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>24 hours</td>
</tr>
<tr>
<td>ASA combinations</td>
<td>- No shared assessment and risk stratification*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>High risk procedures</th>
<th>Intermediate risk procedures</th>
<th>Low risk procedures</th>
<th>When to stop</th>
<th>When to restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>- Low pharmacologic effectiveness</td>
<td>- No shared assessment and risk stratification*</td>
<td>- No</td>
<td>- 24 hours</td>
<td></td>
</tr>
<tr>
<td>Ximelagran</td>
<td>3 days, normal INR</td>
<td>3 days, normal INR</td>
<td>- No shared assessment and risk stratification*</td>
<td>- 24 hours</td>
<td></td>
</tr>
<tr>
<td>LMWH: prophylactic</td>
<td>12 hours</td>
<td>12 hours</td>
<td>12 hours</td>
<td>4 hours after low risk</td>
<td>12-24 hours after median/low risk pain procedures</td>
</tr>
<tr>
<td>LMWH: therapeutic</td>
<td>24 hours</td>
<td>24 hours</td>
<td>24 hours</td>
<td>4 hours after low risk procedures</td>
<td>12-24 hours after median/low risk pain procedures</td>
</tr>
</tbody>
</table>

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.
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.”

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.

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.

• 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 be important. A procedural anticoagulation management checklist is strongly recommended for clinicians, taking these factors into consideration (Figure 1). Periprocedural management of antiplatelets 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 antiplatelet 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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for thromboprophylaxis after knee replacement (ADVANCE-2): a


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