

ASRA/ESRA/INS/AAPM/WIP/NANS guidelines for interventional spine and pain procedures in patients on antiplatelets and anticoagulants

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Introduction and background

A survey was conducted among participants at the “Anticoagulation/Antiplatelets and Pain Procedures” open forum held at the American Society of Regional Anesthesia and Pain Medicine (ASRA) annual fall meeting in 2012. The purpose of this survey was to determine the safe practice patterns of pain physicians regarding continuance of concurrently administered anticoagulants, timing schedules for cessation and resumption of use, and any use of “bridging” therapies when planning for various interventional pain procedures.

The survey items included specific practice characteristics, and whether active protocols were utilized. Additionally, the survey queried the frequency of adherence to specific elements of the current ASRA practice guidelines for regional anesthesia and/or if respondents incorporated different protocols for different pain procedures.

124 active participants attended the open forum. Responses were collected using an audience response system. 84% of respondents were anesthesiologists and the remainder were physical medicine and rehabilitation physicians, neurologists, orthopedists or neurological surgeons.

The vast majority of respondents (98%) followed ASRA regional anesthesia guidelines for anticoagulants but not for antiplatelet agents. Two thirds of the participants (67%) had separate protocols regarding aspirin (ASA) or non-steroidal 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 employed different protocols for cervical spine injections as compared to lumbar spine injections. Most did not express familiarity with selective serotonin reuptake inhibitors’ (SSRIs) effects on platelets. Only 36% knew that SSRIs may lead to a bleeding disorder.

The majority 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.

Based on these results, the need for separate ASRA guidelines, specifically for interventional pain procedures in patients on antiplatelets/anticoagulants, was self-evident. Hence, the Board of

Directors of ASRA recommended that the Regional Anesthesia and Pain Medicine journal (RAPM) appoint a committee to develop separate guidelines for pain.¹ The committee has an international representation, and was endorsed by the European Society of Regional Anesthesia and Pain Therapy (ESRA), American Academy of Pain Medicine (AAPM), the International Neuromodulation Society (INS), and the World Institute of Pain (WIP). The latest evidence was sought through extensive database search strategies. Although the guidelines may not always be based on randomized studies or on large numbers of patients from pooled databases, it is hoped that they will provide sound recommendations and the evidentiary basis for such recommendations.

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 pain procedures in patients receiving antiplatelet agents (ASA and NSAIDs).²⁻⁴

The current American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines for the placement of epidural and spinal catheters do not recommend cessation of these antiplatelet agents for epidural procedures, nor do the guidelines differentiate between interventional pain procedures and perioperative regional anesthesia blocks.¹

There are several reasons why pain procedures for chronic pain patients should be treated differently than regional anesthesia blocks. These factors can be divided into procedure-specific factors and patient-specific factors. The spectrum of interventional 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 (e.g., percutaneous spinal cord stimulation lead placement, vertebral augmentation, deep visceral blocks, and spine interventions) to low risk peripheral nerve blocks (Table 1). The ASRA regional anesthesia guidelines are appropriate for the low risk peripheral category, but the high risk targets require a more intensive look at the issues specific to patient safety and improved outcomes.

For example, spinal cord stimulation lead placement requires the use of large gauge needles with a long bevel and stiff stylet 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 a need to place more than one needle, replace the needles, or utilize multiple attempts at steering

and redirection of the leads.^{1,3} Further, trial and permanent implantation processes may be sequential (partial implantation) or separated depending on patient, continental, payor or physician preferences. This may lead to additional issues with starting/stopping anticoagulants.

Patients with neck or back pain undergoing epidural steroid injections or other spinal interventions may have significant spinal abnormalities including spinal stenosis, ligamentum flavum hypertrophy, spondylolisthesis, or spondylosis which may compact the epidural venous plexus within tight epidural spaces.⁴ Moreover, patients, after various spine surgeries, may develop fibrous adhesions and scar tissue, thus further compromising the capacity of the epidural space and distorting the anatomy of the epidural vessels. The risk of bleeding is further increased in pain patients taking several concomitant medications with antiplatelet effects including NDAIDs, ASA, and SSRIs.¹

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.^{6,7} The stress model for chronic pain is well established in humans and animals as evidenced by the high level of stress hormones compared to control subjects. The sustained endocrine stress response in pain patients may contribute to persistent pain states.^{8,9} In clinical studies, altered hypothalamic-pituitary-adrenal (HPA) axis function has been associated with chronic widespread body pain. These results may be explained by the associated high rates of psychological stress.¹⁰

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^{11,13}. Stress might also affect coagulation activity via an influence on the regulation of genes coding for coagulation and fibrinolysis molecules.¹⁴ Chronic stress increases many stress hormone levels.^{15,17} and catecholamine and cortisol surges might underlie the hypercoagulability observed with chronic psychological distress.^{18,19} The situation stimulates

the sympathetic nervous system and inhibits fibrinolysis through a β 1-mediated effect. Stimulation of vascular endothelial β 1 adrenoreceptors leads to reduced intracellular prostacyclin synthesis, which eventually impairs the release of tissue-type plasminogen activator (t-PA).²⁰

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

Table 1:**Pain procedures classification according to the potential risk for serious bleed**

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

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

*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 use of other anticoagulants/antiplatelets, liver cirrhosis or advanced liver disease, and advanced renal disaes.

Anatomical Considerations for the Development of a Hematoma in Spinal and Non-spinal Areas

Although most cases of a spinal hematoma have a multifactorial etiology, certain anatomical features may pose higher risks secondary to the anatomy and vascular supply of that specific spinal location.²¹ It is important for interventional pain physicians to apply knowledge of spinal and epidural anatomy during pre-procedural planning. Contents of the epidural space include the epidural fat, dural sac, spinal nerves, extensive venous plexuses, lymphatics, and connective tissue (e.g. plica mediana dorsalis and scar tissue following previous surgical intervention). Epidural fat is not uniformly distributed throughout the epidural space and is concentrated around the exiting nerve roots at the intervertebral foraminae and midline recesses.²² In addition, the amount of epidural fat in the posterior epidural space is directly related to age but not overall obesity.^{23,24} Epidural fat decreases with age. The amount of epidural fat according to spinal location increases with caudal progression, being absent in the cervical spine and highest in the lumbosacral spinal region.²⁵ The size of the epidural space also varies based on anatomical level with the posterior epidural space measuring approximately 0.4 mm at C7 – T-1, 7.5 mm in the upper thoracic spine, 4.1 mm at the T11 – T12 and 4 to 7 mm in the lumbar regions.²⁶

The epidural space has extensive thin-walled valveless venous plexi (plexus venous vertebralis interior, anterior and posterior) which are vulnerable to damage during needle puncture and advancement of spinal cord stimulator leads and intrathecal catheters. These epidural veins are mainly found in anterior and lateral aspects of the epidural space.²⁷⁻²⁹ Furthermore, the fragility of these vessels increases with age. Previous studies have demonstrated blood vessel trauma at the site of Tuohy needle entry. Igarashi et al.²⁴ demonstrated blood vessel trauma in 28% of patients who underwent an epidural puncture at L2 – L3. The size of the venous plexus changes with the segmental localization of the anastomoses.²¹ Large diameter anastomoses exist at the C6 – C7, superior thoracic, and entire lumbar regions. These vessels often occupy sites of common interventional pain procedures. In addition, venous plexus distention can occur with anatomical changes in the spinal canal including adjacent level spinal stenosis. The size of venous plexi is also dependent on intra-thoracic and intra-abdominal pressure (e.g. ascites and pregnancy).

Radiographic imaging should be reviewed prior to performing interventional pain procedures in order to assess for central and foraminal stenosis, disc herniations which compromise canal diameter, ligamentum flavum hypertrophy, epidural fibrosis, and previous surgical scar which can alter the level of procedural difficulty.³⁰ Furthermore, previous surgical and epidural interventions (e.g. epidural blood patch) at the targeted level may alter the epidural space and surrounding tissue. Previous epidural entry may result in inflammatory changes that cause proliferation of connective tissue, adhesions between the dura mater and the ligamentum flavum, and granulation changes in the ligamentum flavum.³¹ In addition, it has been suggested that previous surgical intervention, resulting in scarring at the targeted site, may be an independent risk factor for the subsequent development of an epidural hematoma secondary to reduced ability to absorb blood and blood products.³² Further research on these topics is warranted.

Other locations associated with significant undesirable vascularity include the target ganglia of the middle cervical, stellate, lumbar sympathetic, and celiac plexus. For example, surrounding the location for stellate ganglion blockade, multiple vascular structures exist including the vertebral, ascending cervical, and inferior thyroid arteries.³³⁻³⁵ The inferior thyroid artery originates from the thyrocervical trunk. The ascending cervical artery arises from the inferior thyroid artery and passes in front of the anterior tubercles of the cervical vertebral bodies. Inadvertent needle damage to these structures has resulted in retropharyngeal hematomas.³⁵

Nonsteroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) derive their anti-inflammatory effects through their ability to inhibit prostaglandin production by inhibiting cyclooxygenase (COX). The two main forms of cyclooxygenase 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, thus blocking access of arachidonic acid to the catalytic site. By inhibiting COX-1, NSAIDs prevent the formation of prostaglandin H₂ (PGH₂). Prostaglandin H₂ is required for the synthesis of thromboxane A₂ (TXA₂). Thromboxane A₂ is produced by platelets and has prothrombotic effects including

vasoconstriction.³⁶ There are multiple classes of NSAIDs including salicylates, acetic acid derivatives, enolic acid derivatives, and selective COX-2 inhibitors.

Aspirin's (acetylsalicylic acid) Effects on Hemostasis

Aspirin is rapidly absorbed from the gastrointestinal tract with peak levels occurring approximately 30 to 40 minutes following ingestion, resulting in platelet inhibition at one hour.^{37,38} The peak plasma levels for enteric-coated aspirin may be delayed until 3 to 4 hours after ingestion.^{39,40} Aspirin has 170- fold greater affinity for COX-1 over COX-2 and irreversibly inactivates COX-1 through the acetylation of the amino acid serine.^{41,42} By irreversibly inactivating COX-1 and blocking thromboxane production for the lifespan of a platelet, aspirin is very effective at inhibiting platelet activation, platelet aggregation, and thrombosis. Aspirin, within one hour after ingestion, results in greater than 90% reduction in thromboxane levels.⁴³ In addition to affecting platelets for their lifespan, aspirin also inactivates COX-1 in mature megakaryocytes (the bone marrow cell type responsible for platelet production). After a single dose of aspirin (100 to 400 mg), it has been demonstrated that cyclooxygenase activity does not return for approximately 48 hours. This delay in return of the activity of cyclooxygenase has been interpreted as the influence of aspirin on megakaryocytes.^{36,43,44} The average lifespan of a platelet is 7 to 10 days.⁴⁵ Each day, approximately 10% of the circulating platelet pool is replaced. At 5 to 6 days approximately 50% of platelets function normally. Also, platelet turnover and aspirin's antiplatelet effects display significant interindividual variability that is influenced by age, body mass and specific medical conditions, including diabetes.^{46,47}

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

The antiplatelet effects have also been studied in healthy volunteers through platelet aggregation tests including optical aggregometry and aspirin reaction units (ARU).^{40,49} Aspirin reaction units is a whole blood assay test to aid in the detection of platelet inhibition. In individuals not taking aspirin, ARUs are ≥ 550 .⁴⁰ When examining ARU changes following administration of four aspirin dosing regimens (enteric-coated 81 mg, uncoated 81 mg, enteric-coated 325 mg, and uncoated 325 mg in normal volunteers) the maximal reductions in ARUs ranged from 37% to 41% from baseline values.⁴⁰ When examining the induced- inhibition of platelet aggregation in healthy volunteers taking an 81 mg dose, aspirin demonstrated a $66.0\% \pm 18.6\%$ inhibition measured with optical aggregometry with the agonist arachidonic acid.⁴⁹

Aspirin also influences coagulation through non-TXA₂- mediated effects, including dose-dependent inhibition of platelet function, suppression of plasma coagulation, and enhancement of fibrinolysis.^{39,50-61} Secondary hemostasis and thrombus stability is also impaired, due to aspirin's acetylation of fibrinogen and its enhancement of fibrinolysis.³⁹ Aspirin, unlike non-aspirin NSAIDs such as indomethacin, decreases thrombin formation in clotting blood.⁶⁰ Aspirin at higher doses prevents endothelial cell prostacyclin production by inhibiting COX-2.³⁹ Prostacyclin inhibits platelet coagulation and stimulates vasodilation.

Phosphodiesterase Inhibitors

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

Phosphodiesterase inhibitors influence cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels which are inhibitory intracellular secondary second messengers that influence fundamental platelet processes. Phosphodiesterase -3 inhibitors (cilostazol) increase cAMP levels while phosphodiesterase- 5 inhibitors increase cGMP levels.

Dipyridamole Combined with Aspirin

Aspirin may be combined with other drugs to synergistically effect coagulation. One of these drugs is dipyridamole, which acts in vivo to modify several biochemical pathways involved in

platelet aggregation and thrombus formation.^{50,62-65} The extended release (ER) form of dipyridamole (200 mg ER) and aspirin (25 mg) are often used in combination for the management of cerebral vascular disease including secondary prevention for stroke and transient ischemic attacks.⁶⁶ Dipyridamole inhibits PDE-3 and PDE-5. By inhibiting cAMP and cGMP PDEs, cAMP and cGMP levels increase which result in a reduction in platelet aggregation and an increase in vasodilation. Also, extracellular adenosine levels are increased by blocking adenosine reuptake by vascular and blood cells. An increase in adenosine levels leads to further vasodilation.^{63,64} Thromboxane synthase and the thromboxane receptor are also blocked with the use of dipyridamole.⁶⁷ The final pathway by which dipyridamole affects coagulation is through its negative effects on the formation and accumulation of fibrin.⁶⁸ The plasma concentration decline of dipyridamole follows a two-compartment model with an alpha half-life of 40 minutes and a beta half-life of approximate 10 hours. The extended release component of dipyridamole used in combination with aspirin has an apparent half-life of 13.6 hours.⁶³ In conclusion, when aspirin is combined with dipyridamole there is an increased risk of bleeding.^{38,69}

Cilostazol

Another PDE-3 inhibitor that also has antiplatelet aggregation and arterial vasodilator properties is cilostazol.^{38,62} Cilostazol's antiplatelet properties include the inhibition of both primary and secondary platelet aggregation. Cilostazol also has other effects including decreasing the expression of P-selectin which is a cell adhesion molecule found on activated endothelial cells and platelets.⁷⁰ It also reduces thromboxane production and platelet factor 4 and platelet derived growth factor release.⁷¹ Some ex-vivo tests indicated that cilostazol may inhibit platelet aggregation to a greater degree than aspirin.⁷² Cilostazol is used to treat lower extremity claudication.^{38,62} It has also been used to prevent stent thrombosis, and for the prevention of stroke.⁷³ In the field of cardiology, cilostazol is used to augment the inhibition of platelet aggregation in clopidogrel low responders.^{74,75,76} 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. The cilostazol's anti-aggregatory effects increase with successive and continuous dosing. After 4 weeks of continuous administration with 100 mg and 200 mg daily dosing,

platelet adenosine diphosphate (ADP) –induced platelet aggregation rates were decreased by 21% to 38%, respectively.⁷⁸ The drug is hepatically metabolized and metabolites are renally excreted. The drug has an elimination half-life of 10 hours. Cilostazol does not increase bleeding time when used alone or in combination with aspirin.^{79,80} One case report described a spinal epidural hematoma after epidural catheter removal in an individual with a low platelet count that had been taking cilostazol following vascular surgery.⁸¹ Limited data exists 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 48 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 utilization 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 employment in the absence of established cardiovascular disease as defined by history, exam, 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 (e.g. diabetes mellitus).

Significant evidence exists supporting the use of aspirin for secondary prophylaxis for cardiovascular disease and guidelines recommend initiation and indefinite continuation unless contraindicated in this patient population.^{41,84,85} Low-dose aspirin when used for secondary prophylaxis has been shown to reduce the risk of stroke and myocardial infarction in the range of 25% to 30%.⁸⁶⁻⁸⁸ Furthermore, the discontinuation of aspirin for secondary prophylaxis is associated with significant risk.⁸⁹⁻⁹¹ Although some patients have aspirin resistance, the lowest effective aspirin daily dose for the prevention of TIA and ischemic stroke is 50 mg. For men at high risk for cardiovascular disease, the recommended dose increases to 75 mg.^{28,29,83,924} The routine long-term use of doses greater than 75 to 81 mg per day 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 for 14.3 ± 11.3 days for acute cerebral events.^{88,93-96} When aspirin is discontinued, a platelet rebound phenomenon may occur, which results in a prothrombotic state characterized by increased thromboxane production, enhancement of thrombus stability, improvement in fibrin cross-link networks, and decreased fibrinolysis.^{41,97-99}

When aspirin is utilized 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. Since aspirin irreversibly inhibits cyclooxygenase, it would take 10 days to completely restore a fully functioning platelet pool. Burch et al.⁴⁴ confirmed that the return of enzyme activity followed platelet turnover with an average platelet lifespan of 8.2 ± 2 days, although, platelet function may occur earlier.¹⁰³⁻¹⁰⁵ Burch et al. also confirmed that new unacetylated enzyme did not appear in circulation for 2 days suggesting that aspirin also acetylates cyclooxygenase in the megakaryocytes. As considerable individual specific variation exists, partial recovery of platelet function has been shown to occur when approximately one third of the circulating platelet pool has been replaced by uninhibited platelets.¹⁰⁴ A study that examined healthy men demonstrated that complete recovery of platelet aggregation occurred in

50% of the subjects by the 3rd day after discontinuation of taking 325 mg of aspirin every other day for 14 days.¹⁰⁵ Eighty percent of subjects demonstrated normal platelet aggregation by the fourth day. Another study examining platelet functional recovery after cessation of aspirin in volunteers and surgical patients, demonstrated that the majority of volunteers and patients experienced recovery of platelet function at day 3 and within 4 to 6 days, respectively.¹⁰⁶ By day 6, all of the subjects had restored platelet aggregation to at least 85% of baseline level. Also, studies examining the effect of aspirin on platelet aggregation in cardiac surgery patients demonstrate earlier platelet recovery, and as early as 3 days post-discontinuation.^{107,108} Gibbs et al¹⁰⁷ examined the effects of recent aspirin ingestion on platelet function in cardiac surgical patients. Patients were grouped into 3 categories based on time of last aspirin use: ≤ 2 days, 3 to 7 days and >7 days. A significant difference existed in platelet function between cardiac surgical patients who ingested aspirin ≤ 2 days preoperatively in comparison to the 3 to 7 days and > 7 days groups. No difference was found in platelet aggregation between the 3 to 7 days and > 7 days groups. Coleman et al.⁴⁰ demonstrated early recovery of platelet aggregation following 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 post-discontinuation.

Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs' Effects on Hemostasis

Non-aspirin NSAIDs bind reversibly and competitively inhibit the active site of the cyclooxygenase (COX) enzyme. The non-aspirin NSAIDs compete with arachidonic acid's binding to COX-1.³⁶ The degrees of reversible inhibition of COX-1 after single doses of frequently used NSAIDs are shown in Table 2. Besides indomethacin, non-aspirin NSAIDs do not achieve greater than 90% reversible inhibition of platelet enzyme activity.³⁶ 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-2.¹⁰⁹ The ratio of COX-2/COX-1 inhibition for meloxicam is approximately 80:25.¹¹⁰ This group of NSAIDs that is more selective for COX-2 inhibition may be associated with a lower procedural bleeding risk.

Unlike acetylsalicylic acid (ASA, aspirin), the platelet effects of these drugs are directly related to systemic plasma drug concentrations and influenced by the pharmacokinetic clearance of these medications. Once steady-state concentrations have been achieved, terminal half-life is a predictive time parameter to guide decision-making.¹¹¹ For NSAIDs, terminal half-lives and half-lives are interchangeable and equivalent. Because NSAIDs are well absorbed and absorption is not the limiting factor, half-life is more dependent on the plasma clearance and the extent of drug distribution. NSAIDs are highly bound to plasma proteins; therefore, their volume of distribution is minimal and the terminal half-lives and half-lives are similar.¹¹² It takes approximately 5 half-lives for systemic elimination (Table 3).^{113,114} NSAIDs are excreted either by glomerular filtration or tubular secretion. After 5 half-lives approximately 3% of the drug remains in the body. Although, repeat dosing with aspirin has been shown to have cumulative inhibition of platelet COX-1 activity, this has not been demonstrated with NSAIDs such as ibuprofen.¹¹⁵

The effect of platelet aggregation with the administration of one dose of 10 different NSAIDs has been studied in healthy volunteers.¹¹⁶ Some conventional NSAIDs that were studied included aspirin, diclofenac, ibuprofen, indomethacin naproxen, acetaminophen, and piroxicam. The non-aspirin NSAIDs were found to abolish the 2nd wave of platelet aggregation for variable time periods based on the pharmacokinetics associated with each drug. At 24 hours, greater than 50% of tested subjects had return of the 2nd wave of platelet aggregation except for piroxicam which took until day 3. Acetaminophen did not have any effect on the 2nd wave of platelet aggregation and aspirin's effects lasted between days 5 to 8 after the administration of the single-dose. Another study examined the effect of taking ibuprofen 600 mg every 8 hours for 7 days on platelet function in 11 patients. All 11 patients had return of normal platelet function 24 hours after the last dose of ibuprofen.¹¹⁷

Non-aspirin Nonsteroidal Anti-Inflammatory Drugs' Influence on the Cardiovascular Protective Effects of Aspirin

Nonselective COX inhibitors, such as ibuprofen, may limit aspirin's cardioprotective effects by impeding access of aspirin to the serine 529 target.¹¹⁸ A clinical dose (400 mg) of ibuprofen given 2 hours before aspirin ingestion has been shown to block aspirin's inhibition of serum

thromboxane formation and platelet aggregation. Delayed-release diclofenac was not found to limit the cardioprotective effects of aspirin. In addition, meloxicam, which is more selective for COX-2, has not been shown to negatively affect aspirin's ability to reduce thromboxane levels and prevent platelet aggregation.¹¹⁰

Cyclooxygenase 2 Inhibitors' Effects on Hemostasis

Unlike drugs that inhibit the enzyme cyclooxygenase -1 (COX-1), NSAIDs that inhibit only the enzyme cyclooxygenase -2 (COX-2) do not alter platelet function.¹¹⁹ The expression of COX-2 increases with inflammation.¹²⁰ Celecoxib is a COX-2 inhibitor. Multiple studies have demonstrated that celecoxib does not interfere with the normal mechanisms of platelet aggregation and hemostasis.^{119,121} Leese et al.¹¹⁹ in a randomized controlled trial demonstrated that supra-therapeutic doses (600 mg bid) of celecoxib given over a 10 day duration did not alter platelet aggregation, thromboxane B2 levels (thromboxane B2 is an inactive metabolite of thromboxane A2 which is excreted in the urine and a surrogate marker of thromboxane A2), or bleeding time. A limited number of studies suggest that COX-2 inhibitors are not associated with increased surgical blood loss.^{122,123}

Extra caution should be exercised when individuals are taking both celecoxib and warfarin. While 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 INR elevations and bleeding complications when both drugs are coadministered.^{126,130} Both celecoxib and warfarin are metabolized by the CYP 2C9 enzyme.

Procedural Recommendations: Overview

The ASRA¹²⁷ and European¹²⁸ guidelines recommend that central neuraxial blocks may be performed in individuals utilizing aspirin or NSAIDs. The Scandinavian¹²⁹ guidelines for the

performance of central neuraxial blocks in individuals utilizing aspirin, based their recommendations on the indication for aspirin utilization 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 per day for which the discontinuation time is extended to one week. For NSAIDs, the Scandinavian guidelines recommendations are guided by the specific half-life for each drug.

Data specifically defining the risk of bleeding with interventional pain medicine procedures with NSAID continuation is limited¹³¹; 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.¹³²⁻¹³⁶ Furthermore, low-dose aspirin utilization prior to spine surgery even when discontinued for at least 7 days, has been suggested to lead to further blood drainage after surgery.¹³⁷ In an extensive review, low-dose aspirin has also been shown to increase the rate of bleeding complications by a factor of 1.5 (median, interquartile range: 1.0 to 2.5).⁸⁸ The baseline risk of bleeding varied based on surgical type (cataract surgery versus transurethral prostatectomy).

Bleeding complications may also occur after the performance of interventional pain procedures. Spinal hematoma is a very rare complication that has been associated with spinal cord stimulator trials, implants with percutaneous placed cylindrical leads and laminotomy placed paddle leads, lead migration, revisions and lead removal.^{30,46,3,1,138-139} Aspirin has been suggested as a risk factor in some of the cases.^{46,3,1} Case reports of subdural hematomas following spinal anesthesia have also questioned aspirin's continuation prior to a spinal anesthetic.^{141,142} In addition, spinal hematomas have occurred after cervical epidural steroid injections in individuals taking non-aspirin NSAIDs.^{143,144} Other studies examining the performance of lumbar epidurals for pregnancy have not demonstrated an increased risk of bleeding complications with aspirin.¹⁴⁵ 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.¹⁴⁶⁻¹⁵⁵

Procedural Recommendation for Non-aspirin Nonsteroidal Anti-Inflammatory Drugs

- Non-aspirin-NSAIDs are utilized 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 the consequences of hematoma development may be higher (e.g. high risk procedures, see 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).
- Rather than discontinue all NSAIDs for a global period of time, 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.

Procedural 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, the vascular anatomy surrounding the target area, the degree of invasiveness of the procedure, and the potential sequelae associated with perioperative bleeding (Table 3).
- In addition, a complete review of the patient’s medical record should occur to identify additional medications that may heighten aspirin’s anticoagulant effect (e.g. selective serotonin norepinephrine reuptake inhibitors and dipyridamole).
- If aspirin is being taken for primary prophylaxis, aspirin discontinuation is recommended for procedures in which there is a heightened risk for perioperative bleeding and sequelae.
- In individuals utilizing aspirin for secondary prophylaxis, shared assessment, risk stratification, and management decisions should involve the interventional pain physician, patient, and physician prescribing aspirin. The risk of bleeding while continuing aspirin needs to be weighed against the cardiovascular risks of stopping aspirin. Documentation of decision-making should occur. If a decision is made to discontinue chronic aspirin therapy, the time of discontinuation should be determined individually.
- When aspirin is not being utilized for cardiovascular prophylaxis in an individual with overt cardiovascular disease or having medical conditions that confer particular risk, aspirin may be discontinued for a longer period of time, 6 days, to ensure platelet functional recovery.¹⁰⁶
- If aspirin is being discontinued in an individual taking aspirin for secondary prophylaxis, the length of discontinuation may be altered to a shortened time period in an effort to balance the risks of perioperative bleeding and cardiovascular events. Zisman et al.¹⁰⁶ demonstrated that in most aspirin treated patients, platelet function recovers 4 days after drug discontinuation.
- When performing elective pain procedures where there is either a high risk (Table 1) of potential bleeding and/or the possibility of significant sequelae in an individual taking aspirin for secondary prophylaxis, aspirin should be discontinued for a minimum of 6

days.¹⁰⁶ In individuals taking aspirin for secondary prophylaxis who are undergoing low or medium risk procedures for which aspirin will be discontinued, the length of discontinuation can be shortened to 4 days in an effort to balance the risks of procedural bleeding and cardiovascular events.^{40,106}

Procedural Recommendations for Phosphodiesterase Inhibitors

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

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

Procedural Recommendations Regarding Duration of Spinal Cord Stimulator Trials

Currently, no consensus exists regarding the required duration for a spinal cord stimulator trial.

- The length of the trial should be sufficient to demonstrate improvement in pain control and allow prospective patients the ability to determine if they desire to progress forward to the implantation stage. Chincholkar et al.¹⁵⁶, in a prospective trial examining 40 patients who underwent a spinal cord similar trial, demonstrated that a majority of patients are able to make a decision at a mean duration of 5.27 days. Furthermore, most individuals who had a successful trial arrived at a decision earlier than those with an unsuccessful trial.
- Since a platelet rebound phenomenon occurs with the discontinuation of aspirin and the time intervals between aspirin discontinuation and the occurrence of an acute cardiovascular event is in the range of 8 to 14 days, in individuals taking aspirin for secondary prevention it is recommended that the length of the trial be

minimized with a risk benefit ratio considered for adequate trialing verses the possibility of cardiovascular sequelae.

Timing of Therapy Restoration

- Since NSAIDs are not essential for cardiovascular protection, for high risk procedures we recommend withholding these drugs for 24 hours post procedure.
- For elective pain procedures associated with a high risk for bleeding complications, aspirin can be resumed 24 hours post procedure if required for secondary prevention.
- For primary prevention, aspirin should not be restarted for at least 24 hours. We recommend a delay because aspirin rapidly and significantly affects platelet function after ingestion. Aspirin also influences thrombus stability and fibrinolysis. Clot stabilization occurs at 8 hours.

Table 2: The Reversible Inhibition Effect of Commonly Utilized Non-aspirin NSAIDs on Cyclooxygenase Activity as Demonstrated by Changes in Serum Thromboxane Levels

Drug	Dose (mg)	Percentage of Initial Enzyme Activity		
		1 hr.	3 hr.	24 hr.
Diclofenac	50	19 ± 7	34 ± 6	57 ± 3
Ibuprofen	300	33 ± 14	12 ± 4	59 ± 39
Indomethacin	75	2 ± 2	2 ± 1	50 ± 23
Naproxen	250	11 ± 3	12 ± 3	22 ± 12
Piroxicam	20	68 ± 22	41 ± 16	27 ± 18

Adapted and modified with permission.³⁸

Table 3: Half-Lives of Commonly Administered Non-aspirin NSAIDs

Agent	Half-Life (hours)	Discontinuation Time 5-Half-Lives (hours)	Recommended Discontinuation Time (Day)
Diclofenac ¹⁵⁷	1 to 2	5 to 10	1
Etodolac ¹⁵⁸	6 to 8	30 to 40	2
Ibuprofen ¹⁵⁹	2 to 4	10 to 20	1
Indomethacin ¹⁶⁰	5 to 10	25 to 50	2
Ketorolac ¹⁶¹	5 to 6	25 to 30	1
Meloxicam ¹⁶²	15 to 20	75 to 100	4
Nabumetone ¹⁶³	22 to 30	110 to 150	6
Naproxen ¹⁶⁴	12 to 17	60 to 85	4
Oxaprozin ¹⁶⁵	40 to 60	200 to 240	10
Piroxicam ¹⁶⁶	45 to 50	225 to 250	10

Table 4: Procedural Anticoagulation Patient-Specific Management Checklist

Procedural Anticoagulation Management Checklist
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Evaluate baseline patient specific risk factors from history, physical examination & chart review

- Family history of bleeding disorders
- Physical examination → signs of easy bruising including petechiae, mucosal bleeding, and ecchymoses
- Renal & hepatic disease → order laboratory tests to evaluate coagulation status
- Evaluate coagulation tests if required (CBC, PT, aPTT)
- Screening for antiplatelet, antithrombotic or thrombolytic therapy
- Identify non-aspirin NSAIDs use

Categorize individual reason for aspirin utilization

- Primary prophylaxis → absence of established cardiovascular disease or risk factor
- Secondary prophylaxis → presence of cardiovascular disease
 - Informed decision-making involving procedural physician, prescribing medical physician, and patient

Identify and manage pharmacologic coagulopathies

- Understand drug elimination and appropriate discontinuation time
- Recognize other drugs that may alter coagulation (e.g. SSRIs, SNRIs)

Process the anatomical location of procedural intervention into decision-making

- Cervical/thoracic vs lumbar/sacral neuraxial area
- High risk, intermediate, or low risk procedures

Review appropriate radiographic imaging to identify/ understand anatomical challenges

- Cervical, thoracic, lumbar spinal stenosis that alter spinal canal anatomy
- Epidural fibrosis and significant scar tissue from previous surgical intervention

Appropriate timing for re-initiation of anticoagulation

Appropriate post-procedure surveillance and monitoring

SNRIs = Serotonin norepinephrine reuptake inhibitors

SSRIs = Selective serotonin reuptake inhibitors

P2Y₁₂ inhibitors clopidogrel, prasugrel, ticagrelor

The thienopyridines, ticlopidine and clopidogrel, block the ADP receptor, P2Y₁₂ subtype. In the presence of vessel injury, thromboxane A₂ and adenine nucleotides (which contain P2 receptors) are released. Of the P2Y₁₂ receptors, P2Y₁ initiates, while P2Y₁₂ completes the process of platelet aggregation. P2Y₁₂ receptor inhibitors have become widely used in the treatment of coronary syndromes, cerebrovascular ischemic events, and even peripheral vascular disease. P2Y₁₂ receptor inhibitors are used in combination with aspirin; so-called dual antiplatelet therapy, to reduce thrombotic events in the setting of acute coronary syndromes and in patients who undergo percutaneous coronary intervention.^{167,168} Ticlopidine is rarely used, as its antiplatelet effect is delayed^{169,171,172} 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 percent of patients and its susceptibility to drug-drug interactions and to genetic polymorphisms.^{170,171,172} Clopidogrel is a pro-drug, requiring two metabolic steps to form the active drug.¹⁷³ The time to peak effect of clopidogrel takes as long as 24 hours. However, a loading dose of 300-600 mg clopidogrel shortens the time to 4-6 hours.¹⁷⁴ The maximum percentage of platelet inhibition by clopidogrel is 50 to 60%, which normalizes seven days after it is discontinued.¹⁷⁵ The current ASRA guidelines on regional anesthesia recommended a seven-day cessation of clopidogrel,¹²⁹ while the American College of Cardiology (ACC) recommended 7-10 days in most patients and 5 days for patients who are at high risk for angina.^{176,177} The CURE trial specifically showed less perioperative bleeding when clopidogrel was stopped 5 days before surgery.¹⁷⁷ The five-day recommendation is probably acceptable for neuraxial injections as there have been case reports of uneventful neuraxial anesthesia 5 days after stoppage of clopidogrel.^{178,179} 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.¹⁸⁰ In a study on the decay of the antiplatelet effect of clopidogrel, Benzoni and colleagues noted no difference in the percent platelet inhibition and in the platelet reaction units (PRU) between five and seven days after discontinuation of clopidogrel.¹⁸¹ Unfortunately, the two studies involved only a small number of patients.^{180,181} Most pain procedures are elective and clopidogrel should preferably be stopped for seven days. In cases of spinal cord stimulation trial in patients at high risk for thromboembolic events, we

recommend consultation with the treating physician and stopping clopidogrel for five days before the trial of spinal cord stimulation, 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 five days prior to the procedure, a test of platelet function such as the VerifyNow P2Y12 assay or platelet mapping portion of the thrombelastograph should be performed.^{182,183,181}

Prasugrel is a pro-drug similar to clopidogrel and also causes irreversible inhibition of the P2Y12 receptor.¹⁸⁴ Unlike clopidogrel, it requires only one metabolic step to form its active drug¹⁷³. It is reliably converted to its active metabolite, is not involved in drug-drug interactions and is not susceptible to genetic polymorphisms.^{185,186} Prasugrel has a rapid onset of effect, the median time to peak effect being one hour.¹⁷⁵ Peak plasma concentration occurs in 30 minutes,¹⁸⁶ with a median half-life of 3.7 hours. Prasugrel causes 90% inhibition of platelet function compared to 60-70% for clopidogrel.¹⁷⁵ The superior antiplatelet effect of prasugrel is secondary to its improved metabolism, resulting in more active metabolites being delivered to the platelet.^{188,189} Patients over 75 years of age, those with history of transient ischemic attack or stroke or those with small body mass index are at risk for increased bleeding.^{190,191} Platelet activity does not normalize until seven days after it is stopped.¹⁹² A 7-10 day interval before a neuraxial injection has been recommended by the ASRA¹²⁷ and European guidelines for regional anesthesia,¹²⁸ while the Scandinavian guidelines stated that 5 days stoppage may be sufficient.¹²⁹ In view of its reliable conversion to its active metabolite, potency, reports of increased bleeding, and studies showing platelet activity normalizing at 7 days, a 7-day interval before medium and high risk interventional pain procedures is recommended.

Unlike clopidogrel and prasugrel, ticagrelor is a direct-acting P2Y12 receptor inhibitor.¹⁹³ While both the parent compound and the active metabolite have antiplatelet activities, the parent drug is responsible for the majority of the in-vivo platelet inhibition.^{194,195} 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.¹⁹⁶ There are no known drug interactions with ticagrelor and its pharmacokinetics is predictable, and not affected by genetic polymorphisms.¹⁹⁷

The antiplatelet effect of ticagrelor is rapid, with peak platelet inhibition occurring 2 to 4 hours after intake, compared to 24 hours with clopidogrel.¹⁹⁸ The mean platelet inhibition by ticagrelor is 90%, compared to 50-60% for clopidogrel.¹⁹⁹ 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.¹⁹⁹ Platelet recovery is more rapid with ticagrelor as platelet inhibition is similar to placebo 5 days after discontinuation.¹⁹⁹

Intervals between stoppage of the P2Y12 receptor inhibitors and pain procedures and subsequent resumption of the drugs

The ASRA and the European guidelines on regional anesthesia recommended a 7-day interval for clopidogrel while the Scandinavian guidelines noted that 5 days is probably adequate. The Scandinavian guidelines are based on the 10 to 15% formation of new platelets every day,²⁰⁰ resulting in 50 to 75% of the circulating platelet pool being unaffected by platelets 5 days after stoppage of the antiplatelet drug.¹⁷⁹ We recommend 7-day cessation of clopidogrel prior to pain intervention. If 5 days is recommended by the treating cardiologist or vascular medicine physician, specifically prior to an extended SCS trial, then a test of platelet function should be performed to assure adequate recovery of platelet function.²⁶⁹ For prasugrel, 7-10 days is advisable while 5 days is adequate for ticagrelor.¹⁹¹

For resumption of the antiplatelet drug after a neuraxial procedure or catheter removal, the Scandinavian guidelines recommended that the drug be started after catheter removal¹⁹² while the European guidelines recommended 6 hours after catheter removal before prasugrel and ticagrelor can be started.¹⁹¹ Baron cautioned in restarting prasugrel and ticagrelor early because of their rapid effect and potent antiplatelet inhibition.²⁰¹

Clopidogrel can be restarted 12-24 hours after a spine procedure, in view of its slow onset. However, a 300-600 mg loading dose of clopidogrel takes effect within 4 to 6 hours. If a loading dose of clopidogrel or a low molecular weight heparin (LMWH) is employed, then a 24-hour interval is more appropriate²⁶⁹ (**Table 2**). For prasugrel and ticagrelor, a 24-hour interval is recommended in view of their rapid antiplatelet effects.

Procedural 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 (see Table 1) can be safely done without stopping clopidogrel therapy*
- *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) of advanced 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.*
- *For prasugrel, the group recommends 7-10 days off therapy prior to pain procedures*
- *For ticagrelor, 5 days cessation is adequate for most pain procedures.*
- *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 then 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 gamma-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 International Normalized Ratio or 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 three days for acenocoumarol and five 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)^{202,203} so the initial anticoagulation from warfarin is secondary to a decrease in clotting factor VII. However, this is antagonized by a decrease in anticoagulant protein C,²⁰³ making the INR unreliable during the early phase of warfarin therapy.²⁰⁴ The full anticoagulant effect of warfarin does not occur until four days, when the levels of factor II are significantly decreased. Concentrations of clotting factors of $\geq 40\%$ are considered adequate for hemostasis,²⁰⁵ levels below 20% are associated with bleeding.²⁰⁶

Warfarin is difficult to dose as it has a narrow therapeutic index and wide inter-patient dosing variability, with genetic factors accounting for a large proportion of the variations in dose requirements.²⁰⁷ Although patients with variations in their *CYP2C9* and/or *VKORC1* require lower doses of warfarin, the ACCP recommended against pharmacokinetic based dosing pending clinical studies.²⁰⁴ Recent studies on genetic-based dosing did not settle this issue, as the results were not uniform. A trial that compared an algorithm-based warfarin dosing regimen versus dosing based on clinical variables did not show any difference in terms of the percentage of time the INR was in the therapeutic range (45% in both groups).²⁰⁸ A similar trial on acenocoumarol or phenprocoumon (coumarin anticoagulants used in Europe) showed the same results, i.e. the percentage of time the INR was in the therapeutic range was not better in the patients whose dosing was guided by genotype testing (62% vs 60% in the group where dosing was based on clinical variables).²⁰⁹ In contrast, another group of investigators noted a greater percentage of time where the INR was in the therapeutic range with genotype-guided dosing of warfarin (67% vs 60%).²¹⁰ Common among these trials is the frequent monitoring of the INR, a routine practice in academic centers but not in some community practices, which allows for frequent adjustment of warfarin dosing.

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, who showed that the levels of clotting factor VII are greater than 40% (levels considered safe for hemostasis), during the first 12-16 hours after initial warfarin intake.²⁰³ 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 pre-operative 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.²¹¹ In the other case, the age or weight of the patient or the dose of warfarin was not mentioned.²¹² These reports are not surprising, as Garcia et al²¹³ showed that warfarin requirement progressively decreases with age in both men and women. For example, at age 50, 5 mg daily is needed to keep the INR therapeutic, whereas at age 70, only 3.5 mg is required. At all ages, women require less than men.²¹³

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.²⁰³ Two papers showed the absence of spinal hematoma when the epidural catheter was removed two²¹⁴ to three days after warfarin was started.²¹⁵ In these studies, concentrations of the clotting factors were not determined and the number of patients in whom the epidural catheter was removed at day three was only 140. Removal of the epidural catheter within 48 hours is probably safe, since the levels of factors X and II are probably adequate for hemostasis.¹²⁷ 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 of recommendations:

- *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)^{216,217}.*
- *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 five days and the INR normalized before high and intermediate risk pain procedures*
- *Acenocoumarol should be stopped for three 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 can be instituted in patients who are at high risk for thrombosis after consultation with the treating vascular medicine physician.*

Heparin

Unfractionated heparin inactivates thrombin (factor IIa), factor Xa, and IXa.¹²⁷ The anticoagulant effect of intravenous heparin is immediate while subcutaneous heparin takes 1 hour.²¹⁸ Heparin has a half-life of 1.5–2 h and its therapeutic effect ceases 4 to 6 h after its administration. The effect of heparin is not linear but its half-life increases with increased dose. Monitoring is via the aPTT, therapeutic anticoagulation is achieved when the aPTT is 1.5 to 2.5 times the initial value.²¹⁹ Reversal is achieved with protamine, with the dose being 1 mg of protamine per 100 units of heparin.

The risk factors for the development of spinal hematoma in patients who had a neuraxial procedure and subsequent anticoagulation include: heparinization within one hour of dural puncture; concomitant aspirin therapy; and traumatic spinal punctures.²²⁰ In the study by Ruff and Daugherty, seven of 342 patients who were subsequently heparinized within one hour developed spinal hematoma while none in their control group of another 342 patients did.

The ASRA regional anesthesia guidelines recommended that intravenous heparin be stopped for 2 to 4 hour hours before a neuraxial procedure.¹²⁷ For pain interventional procedures, the longer 4-hour interval is recommended, especially for SCS placements, intrathecal drug delivery catheter placements, or vertebral augmentation, e.g. kyphoplasty. The elective nature of pain procedures makes this scenario very unlikely. Opioids and adjunct analgesics may be given during the heparin administration and the pain procedure performed after the patient has discontinued intravenous heparin.

ASRA recommended an interval of at least one hour after a spinal or epidural (or catheter removal) before IV heparin is administered.²²¹ If the neuraxial procedure is bloody, cancellation of surgery has been recommended.^{222,223} 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 one recommended by Chaney.²²³

Again, 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 of recommendations:

- *Intravenous heparin should be stopped for at least 4 hours before a low-, medium-, or high-risk procedure is performed.*
- *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 intravenous heparin should rarely exist since 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 units every 8–12 h) is via heparin-mediated inhibition of activated factor Xa. After subcutaneous injection of heparin, maximum anticoagulation is observed in 40 to 50 min which dissipates within 4 to 6 h. The aPTT of most patients remain in the normal range²²⁴ during subcutaneous mini-dose heparin, only a small percentage of patients' PTT exceed 1.5 times normal. The safety of neuraxial anesthesia in the presence of anticoagulation with twice-a-day subcutaneous doses of unfractionated heparin has been documented by several publications.²²¹ The ASRA guidelines on regional anesthesia considered mini-dose twice-a-day subcutaneous heparin not a contraindication to neuraxial injections. Although rare (no spinal hematoma in over 9000 patients,²²¹ cases of spinal hematoma have been reported in this setting.^{225,226,227} *It is for this reason that we recommend discontinuation of subcutaneous heparin for at least 8 hours before a planned neuraxial procedure including epidural steroid injections (ESIs).*

Thrice-a-day subcutaneous heparin regimens have become popular in reducing the incidence of postoperative thromboembolism (VTE).²²⁸ This practice has been associated with spontaneous hematomas.²²⁹ In a meta-analysis, King et al noted that while TID subcutaneous

heparin is superior to two-a-day regimen in preventing VTE, it is also associated with more bleeding.²²⁹ Most of the major bleeds involved the gastrointestinal tract, retroperitoneal space, or intracranial locations. The absence of prospective studies prompted the previous iterations of ASRA guidelines on regional anesthesia to recommend against neuraxial procedures in patients on three times a day regimen.¹²⁷ We make the same recommendation as it pertains to pain procedures.

Summary of recommendations:

- *Interventional pain procedures should not be performed in patients on TID subcutaneous heparin.*
- *If pain procedures are to be performed, then an interval of 8-10 hours from the last dose of sc heparin should be observed.*
- *The sc heparin can be restarted a minimum of 2 hours after the pain procedure.*
- *These scenarios should be avoided if possible. The patient's pain can be relieved by alternative analgesics (opioids, anticonvulsants, antidepressants) until the procedure can be performed after the patient has discontinued sc heparin.*

Low molecular weight heparin

The plasma half-life of the LMWHs ranges from 2 to 4 h after an intravenous injection and 3–6 h after a subcutaneous injection. LMWH has a higher and more predictable bioavailability than standard heparin and dose adjustment for weight is not necessary. 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%,²³⁰ 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.²³¹

Although the LMWH constitute a relatively homogeneous pharmacological group, the most studied and referred 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 LMWH 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 h when used as thromboembolic prophylaxis while dalteparin is given once daily. The drugs appear to have comparable efficacy in the treatment and prevention of venous thromboembolism.²³² 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. As therapeutic dose, 1mg/kg/12 h is prescribed. Generally speaking, three regimens of administration of LMWH as thromboprophylaxis are used daily, and are summarised below:²³³

Preoperative protocol, administration of the first dose of LMWH about 12 hours before surgery, followed 24 hours after the first administration and so on. *Postoperative protocol*, in which the 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). *Perioperative protocol*, with thromboprophylaxis starting between 12 hours before and 12 hours after surgery.

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

The ASRA guidelines for regional anesthesia recommended a minimum of two hours after epidural catheter removal, before LMWH is restarted. A FDA Drug Safety Communication on November 6, 2013 recommended a *four-hour interval* based on data provided to them by the manufacturer of enoxaparin, Sanofi-Aventis.²³⁵ 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), concomitant medications affecting hemostasis (antiplatelet, anticoagulant, NSAIDs, etc). The

identification of administration of LMWH within 12 hours after removal of the epidural catheter as a risk factor made us recommend a 12- 24 hour interval between medium and high-risk procedures and resumption of LMWH. It should be noted that the administration of enoxaparin within 24 to 48 hours after a cerebral embolic clot did not enlarge the hematoma.²⁵¹

The occurrence of spine abnormalities has been noted to be a risk factor for spinal hematoma by several publications.^{236,237,235} 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 stoppage 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 on regional anesthesia, which recommended a 24-hour interval when blood is noted in the epidural catheter,¹²⁷ a situation similar to high risk pain procedures (kyphoplasty, SCS placement, intrathecal catheter placements).

Summary of recommendations:

- *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.*
- *When a therapeutic dose of enoxaparin is employed 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 12-24 hours after medium and high-risk pain procedures.*
- *Concomitant drugs that affect hemostasis (antiplatelet, NSAIDs, SSRIs, other anticoagulants) should be used with extreme caution in patients on LMWH.*

Fibrinolytic Agents

Thrombolytic agents convert plasminogen and thrombi to plasmin, the enzyme that causes fibrinolysis. Recombinant tissue-type plasminogen activator (r-TPA), 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 anaesthetic technique in patients that have received fibrinolytic medication would lead to an increased risk of spinal haematoma 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.^{238,239,240,241,242,243,244} There are also cases of spinal hematoma in patients who had neuraxial procedures and had subsequent thrombolytic therapy.^{245,246,247} In some case reports, the patients were also given heparin. The risk of spinal hematoma in patients who receive thrombolytic therapy is not well defined because of the understandable lack of prospective studies. Because of sparse data, the ASRA guidelines on regional anesthesia did not specify the duration of discontinuation of thrombolytics before a neuraxial procedure. The Scandinavian guidelines recommend a 24-hour interval between discontinuation of the drug and neuraxial procedure,¹²⁹ based on the short half-lives of the different thrombolytic drugs. Conversely, avoidance of the drug for 10 days has been recommended.²⁴⁸ This interval is probably too long. Since 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. Since the fibrinolytic effect of the drugs can occur up to 27 hours, a minimum of 48 hours before a pain procedure should be observed. Longer intervals should be considered to avoid unnecessary bleeding. Alternative analgesics can be used until the procedure is safer. Note that blood clots are not completely stable until approximately 10 days 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, e.g. 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} Hopefully the administration of the fibrinolytic agent occurs more than

6 hours after the pain procedure so as not to lyse the clots from the pain intervention. For pain patients with an intrathecal catheter, the ASRA guidelines on regional anesthesia suggested measuring the fibrinogen level to assess the state of thrombolysis and in guiding the timing of removal of an epidural catheter. The European guidelines recommend leaving the epidural catheter during thrombolysis and removing the catheter when the effect of the drug is gone.¹²⁸ *In patients who just had a percutaneous SCS lead trial or an epidural/intrathecal catheter was placed, the catheter/leads can be left in place if the thrombolytic agent has already been given, a practice recommended by the European guidelines.* Fibrinogen levels can be intermittently determined. Frequent neurologic monitoring, e.g. every 2 hours, is recommended for an appropriate length of time in patients who have had 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. Alternatively, the catheter can be removed after 2 half-lives of the drug have elapsed.*

Summary of recommendations:

- *Interventional pain procedures should be avoided in patients who just had 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.*
- *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 spinal cord stimulation lead, the device can be left in place. Fibrinogen levels can be determined and the device removed after 48 hours or after two half-lives of the drug has elapsed.*

Fondaparinux

Fondaparinux is a synthetic anticoagulant that selectively inhibits factor Xa. The drug is 100% bioavailable, attains maximum concentration within 1.7 h of administration, and has a half-life of 17-21 hours Xa.)²⁵² Its extended half-life allows once-daily dosing. It is usually administered 6 hours after surgery.²⁵³ Fondaparinux is recommended as an antithrombotic agent after major orthopedic surgery,²⁵⁴ and as initial treatment of pulmonary embolism.²⁵⁵

The actual risk of spinal hematoma with fondaparinux is unknown. A study showed no complications in patients who had neuraxial catheters.²⁵⁶ In this study, 1553 of 1603 patients had neuraxial catheters (the rest had deep peripheral nerve catheters). Fondaparinux 2.5 mg was given 6-12 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 three attempts), the procedure was complicated by bleeding, if they were taking antiplatelet drugs, or the plan was to withdraw the epidural catheter the day after surgery. Because of the 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 These 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 Singelyn study,²⁵⁶ the authors observed a 2 half-life interval between stoppage of drug and removal of catheter. With two half-lives, only 75% of the drug is eliminated,²⁶⁶ a situation that is probably not safe in elderly pain patients who have spinal stenosis. A 5 half-life is more acceptable.

Summary of recommendations:

- *We recommend 5 half-lives, wherein 97% of the drug is already eliminated, between stoppage of the drug and medium and high risk pain procedures. This corresponds to 3-4 days.*

- *For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with treating physician(s) should guide whether Fondaparinux should be stopped. Many of these procedures may be safe without interrupting treatment. However, if a more conservative approach is needed, then two half-lives interval is probably adequate.*
- *We recommend resuming the drug after 24 hours as fondaparinux has a very short onset of effect.*

The time intervals between discontinuation of the anticoagulant and neuraxial procedure and between epidural catheter removal and resumption of the drug are summarized in table 5.

New anticoagulants: Dabigatran, Rivaroxaban, Apixaban

Interval between discontinuation of the anticoagulant and neuraxial pain procedures and subsequent resumption of the drug

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

There are no published studies on the intervals between stoppage 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, while the European and the Scandinavian guidelines based their recommendations on the half-life of the drug. The European and Scandinavian guidelines adopted a two half-life interval between discontinuation of the drug and neuraxial injection.^{128,129} based on the recommendation of Rosencher et al. Rosencher and her colleagues recommended two half-lives as an adequate compromise between prevention of venous thromboembolism and spinal hematoma.¹⁹⁴ But there is no consensus on the “exact” time for this management. Moreover, for selected patients at high thrombotic risk (defined as a CHA₂DS₂-VASc score more than 4²⁶⁶ or as

CHADS₂ more than 2²⁵⁹ or, with moderate to severe renal impairment (defined as a creatinine clearance <50 ml/min), a periprocedural bridging strategy for DOAC has been proposed.^{258,259,260}

The reasons for allowing residual anticoagulation include the occurrence of pulmonary embolism during the initial phase of warfarin therapy²⁰³ and subclinical deep vein thrombosis (DVT) soon after surgery,²²⁹ and to facilitate full anticoagulation.²⁶² However, the pharmacokinetics of the new anticoagulants were studied in young healthy individuals, not the elderly patients (degenerative spine abnormalities and multiple medical comorbidities) common to pain practices. Also, concomitant antiplatelet therapy was an exclusion criterion in some of the total joint surgery trials,²⁶³ and antiplatelet therapy has been implicated in case reports of spinal hematoma.^{2,3} There has been no post-marketing surveillance on the new anticoagulants except for dabigatran; such surveillance showed an increased incidence of gastrointestinal bleeding.²⁶⁴ Finally, a specific antidote for the new oral anticoagulants is not yet available.²⁶⁵

It should be noted that 25% of the drug still remains in the plasma after two half-lives, but only 3% remains after 5 half-lives.²⁶⁶ In view of the problems presented by patients with chronic pain and since some pain procedures involve more than an injection or insertion of a needle or catheter (e.g. spinal cord stimulation 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) so there is little justification to go beyond 5 half-lives. If the risk of VTE is high, then a bridge therapy with low molecular weight heparin may be instituted.

For resumption of new anticoagulants after removal of an epidural catheter or neuraxial injection, the Scandinavian guidelines recommended 8 hours minus the time it takes for the anticoagulant to reach peak effect.¹²⁹ This was based on the paper by Rosencher et al wherein they stated that it takes approximately 8 hours for a platelet plug to become a stable clot.²⁵⁷ The basis for this statement is not well documented, but the recommendation may be acceptable in regional anesthesia. A study showed that enoxaparin given 24-48 hours after intracerebral hemorrhage did not enlarge the size of the hematoma.²⁵¹ Although still effective when given within 6 hours of a cerebral embolic clot,²⁴⁹ *thrombolytics* are more effective when given within 3 hours after the onset of stroke.²⁵⁰ These studies^{249,250} imply that *anticoagulants* (not

thrombolytics) may have a hard time lysing a clot if given after 6 hours and most probably will not lyse a clot if given 24-48 hours after a neuraxial injection. Other authors noted that the reinstitution of antithrombotic therapy within 24 hours after a major procedure might increase the risk of bleeding after the procedure.²⁶⁵ Liew and Douketis²⁶⁸ 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 recommended 48 hours²⁶⁵ while Connolly and Spyropoulos recommended 24 hours but at half the usual dose.²⁷⁰ The risks posed by the elderly with spine abnormalities make us recommend a 24 hour interval after epidural steroid injections, spinal cord stimulation, kyphoplasty, or intrathecal catheter/pump placement before resumption of the new anticoagulants. If the risk of VTE is very high, a 24-hour interval, at half the baseline dose, may be considered. Such decisions should be made on an individual basis and in consultation with the treating physician(s). Dabigatran, rivaroxaban, and apixaban have short onsets of action and should hopefully make up for the delay in reinstitution of these drugs.

Procedural recommendations for the new anticoagulants:

- *We recommend a 5 half-life interval between discontinuation of one of the new anticoagulants before medium and high risk pain procedures. For low-risk procedures, a shared assessment, risk stratification, and management decision in conjunction with the treating physician(s) should guide whether these new anticoagulants should be stopped. These procedures may be safe without interrupting treatment. If a more conservative approach is needed, then a two half-lives interval is probably adequate.*
- *If the risk of VTE is high, then a LMWH bridge therapy can be instituted during stoppage of the anticoagulant and the LMWH can be discontinued 24 hours before the pain procedure.²⁶⁹*
- *We recommend a 24-hour interval after low, medium and high risk 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 substrates²⁷² (Figure 1), 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%,²⁷³ and peak plasma concentrations are attained 1.5-3 hours after intake of the prodrug.^{273,274,275} Dabigatran has a half-life of 14-17.^{276,277} The pharmacokinetic profile of dabigatran is predictable and not affected by sex, body weight or obesity, ethnic origin, or mild-to-moderate hepatic impairment.²⁸¹ Renal clearance accounts for 80% of the clearance of dabigatran,²⁷⁸ elimination half-life of the drug is doubled from 14 hours to 28 hours in patients with end-stage renal disease.^{278,279} The drug is contraindicated in patients with creatinine clearance <30.²⁸¹

Dabigatran is effective in the prevention of stroke in patients with non-valvular atrial fibrillation²⁸⁰ and has been approved for such use in the USA, 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 USA. This is probably because dabigatran was noted to be superior to enoxaparin in a European study²⁸² but not in a North American study.²⁸³ A meta-analysis of the trials noted no differences between dabigatran and enoxaparin in any of the endpoints that were analyzed.²⁸⁴

In the studies on dabigatran's use as VTE prophylaxis after total joint surgery, the drug was started after surgery.^{285,282,286,286,283,288} 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.²⁶⁹ Although there was no instance of spinal hematoma, the small number in relation the incidence of spinal hematoma,²⁸⁹ makes it hard for one to make a definitive conclusion on the interval between a neuraxial procedure and resumption of the drug. It should be noted that the manufacturer states that epidural catheters should not be placed in patients receiving dabigatran.¹²⁸

The activated partial thromboplastin time (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).^{290,291} The thrombin time (TT), also known as thrombin clotting time (TCT) is highly sensitive to the effects of dabigatran;^{291,292,293} the test is more appropriate to detect the presence of an anticoagulant effect of dabigatran and not to quantify its effect.²⁹³ A dilute TT (Hemoclot Thrombin Inhibitory assay) has become available and has linearity across pharmacologically relevant plasma dabigatran concentrations.^{290,292} The ecarin clotting time (ECT), which directly measures thrombin generation, is prolonged by dabigatran²⁹³ and is linearly related to dabigatran concentrations.²⁹⁰ 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.²⁹⁰

It is unlikely that fresh frozen plasma (FFP) is effective in the reversal of dabigatran.²⁹⁴ Activated charcoal prevents absorption of the dabigatran but needs to be given within two hours of ingestion of the drug. Dialysis might speed drug elimination of the drug. Recombinant Factor VIIa (NovoSeven, Princeton, NJ) has been recommended to control hemorrhage. Prothrombin complex concentrates (PCCs) or concentrated pooled plasma products contain either three (Factors II, IX, and X) or four (Factors II, VII, IX, and X) clotting factors. The use of four-factor PCCs has been suggested, but may not be able to reverse the anticoagulant effect of dabigatran.^{292,293} A dabigatran-directed neutralizing antibody is under development.²⁹⁵

Procedural recommendations with dabigatran:

- *We recommend a 5 half-life interval between discontinuation of dabigatran and medium or high risk pain procedure. This corresponds to four days (half-life of dabigatran is 12-17 hours).*
- *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. These procedures may be safe without interrupting treatment. If a more conservative approach is desired, then a two half-lives interval is probably adequate.*

- *For patients with end-stage renal disease, we recommend a 6-day interval since the half-life of dabigatran increases to 28 hours in this condition.*
- *For resumption of dabigatran after a pain intervention, we recommend 24 hours after low, intermediate, and high risk pain procedures (Table 3).*
- *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 (**Figure**), has a rapid onset of action. Peak plasma concentrations are observed within 2.5 to 4 hours^{296,297} and maximum inhibition of Factor Xa (up to 68%) occurs 3 hours after dosing. Factor Xa inhibition occurs for 12 hours²⁹⁷ or 24-48 hours when higher doses are given in the elderly²⁹⁸. The half-life of rivaroxaban is 5.7 to 9.2 hour,^{298,297} and can be as long as 13 hours in elderly patients^{300,299} secondary to the age-related decline in renal function.^{299,300} A third of the drug is eliminated each by the kidneys and the fecal/biliary route, with the remaining one-third being metabolized to inactive metabolites.^{296,301} The renal clearance of rivaroxaban decreases with increasing renal impairment.³⁰² Rivaroxaban is partly metabolized by the liver and its use is to be avoided in patients with severe liver disease.^{300,303} 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.³⁰⁴ Risks for increased bleeding include the elderly, patients with low body weight, and those with renal insufficiency.

Rivaroxaban is as effective as enoxaparin in the treatment of symptomatic VTE³⁰⁵ and non-inferior to warfarin for the prevention of embolic stroke during atrial fibrillation.³⁰⁶ Because of the efficacy of rivaroxaban in these conditions, it has been approved in the US, Canada, and Europe for the treatment of VTE. It has been approved for the prevention of stroke in non-valvular atrial fibrillation since Factor Xa inhibitors have been associated with fewer strokes and embolic events, fewer intracranial hemorrhages and lower all-cause mortality compared with warfarin.³⁰⁷ Rivaroxaban is also approved for prevention of VTE after orthopedic surgery in the US, Canada, and Europe as the drug was noted to be as effective or superior to enoxaparin in

preventing VTE after total joint surgery.^{308,309,310,311,312} In all four RECORD studies, 10 mg rivaroxaban was given 6 to 8 hours after surgery. Although the number of patients who had neuraxial anesthesia or epidural catheters was not stated in the RECORD studies, there was no spinal hematoma in the 4622 patients who received rivaroxaban and had “regional anesthesia”. According to Rosencher et al, the epidural catheters were not removed until at least two half-lives after the last dose of rivaroxaban, and the next rivaroxaban dose was given 4-6 hours after catheter removal.³¹³ None of the 1141 patients who were given rivaroxaban and had neuraxial anesthesia developed spinal hematoma.³¹³ This small number of patients does not provide assurance as to the safety of the two 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.³⁰³

A minimum of 18 hours between the last dose of rivaroxaban and removal of an indwelling catheter, and a minimum of 6 hours before resumption of the drug has been recommended by the Scandinavian Society guidelines.¹²⁹ The European Society guidelines recommended an interval of 22–26 hours between the last dose of rivaroxaban and removal of an indwelling catheter and an interval of 4–6 hours between epidural catheter removal and the next dose of rivaroxaban.¹²⁸ These two recommendations represent a two half-life interval between rivaroxaban discontinuation and epidural catheter placement or removal. The 4-6 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,²⁵⁷ 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.^{291,293} The INR however is not recommended as a monitor of rivaroxaban activity because the INR is dependent on the thromboplastin reagent, and thromboplastins vary greatly in their sensitivity to rivaroxaban.²⁹⁰ Factor Xa may be used as a surrogate for the plasma concentrations of rivaroxaban.³¹⁴ Overall, the PT and the anti-Xa are the tests best suited for monitoring the effects of rivaroxaban.²⁹⁰ Activated charcoal may be effective in removing

rivaroxaban if given within eight hours of rivaroxaban ingestion.²⁹³ Rivaroxaban may not be dialyzable because of high protein binding.³¹⁶ A four-factor PCC has been shown to reverse the in-vitro anticoagulant activity of rivaroxaban in healthy volunteers.³¹⁵ Recombinant Factor VIIa has been shown to be effective in reversing the effect of fondaparinux²⁹³ but has no demonstrated efficacy for reversing bleeding from the new oral anticoagulants.³¹⁶

Procedural 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.*
- *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. These procedures may be safe without interrupting treatment. If a more conservative approach is needed, then a two half-lives interval is probably adequate.*
- *For resumption of the drug after a pain procedure, we recommend 24 hours after low, medium, and high risk pain procedures.*
- *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 (Figure). It is also rapidly absorbed, attaining peak concentrations in 1-2 hours. Studies showed the half-life of apixaban to be 13.5 +/- 9.9 hours after a single 20 mg-dose,³¹⁷ 15.2 +/- 8.5 hours after a single 5 mg dose and 11.7 +/- 3.3 after multiple 5 mg doses.^{318,319} 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 three.³¹⁸ Apixaban has an oral bioavailability of more than 45%. It is eliminated via multiple elimination pathways and direct renal and intestinal excretion.³²⁰ 24% to 29% of the dose is excreted via the kidneys and 56% of the dose is recovered in the feces.³¹⁷

For the treatment of acute VTE, apixaban was found to be non-inferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) and was associated with significantly

less bleeding.³²¹ Apixaban was also noted to reduce the risk of recurrent VTE without increasing the rate of major bleeding.³²² In patients with atrial fibrillation, apixaban is superior to aspirin or warfarin in preventing stroke or systemic embolism.^{323,324} The drug has been approved in the US, 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.^{325,326,327,328} In these studies, apixaban was given 12-24 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.³²⁸

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. While the Scandinavian guidelines did not make recommendation on the interval between cessation of apixaban and neuraxial injection because of lack of available data,¹²⁹ the European guidelines recommended a 26-30 hour interval.¹²⁸ The Scandinavian guidelines recommended 6 hours after a neuraxial injection or catheter removal before resumption of the drug while the European guidelines recommended a 4-6 hour interval. Other recommendations ranged from 2-3 days stoppage of the drug and 24 (1/2 the usual dose on the first 24h) to 48 hours before resumption of the drug.^{265,270,268} In the absence of adequate data, we recommend a five 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.²⁹¹ The dilute PT assay, wherein the thromboplastin reagent is diluted sixteen times, has improved sensitivity over the conventional PT.²⁹¹ Apixaban can be evaluated with the anti-Xa assay.³²⁹ The anti-Xa assay is more sensitive than the PT and as sensitive as the dilute PT assay,^{316,330} and appears to be the best choice for clinical monitoring of the anticoagulant effect of apixaban.²⁹⁰ 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.²⁹³

Procedural recommendations with apixaban:

- We recommend stopping apixaban 5 half-lives, or 3 days, before high or intermediate risk pain procedures.
- 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. These procedures may be safe without interrupting treatment. If a more conservative approach is needed, then a two half-lives interval is probably adequate.
- For resumption of apixaban, we recommend 24 hours (or the next day) after low, medium, and high risk pain procedures.
- 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).

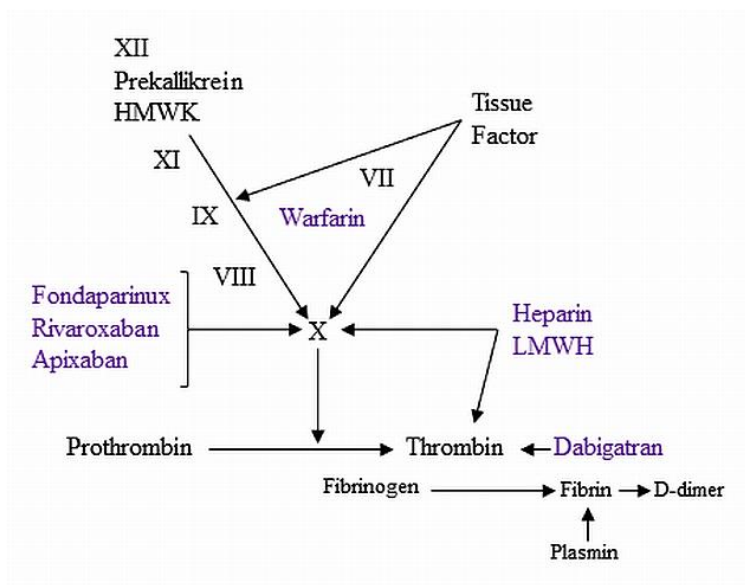


Figure 1: Coagulation scheme to show sites of action of anticoagulant drugs. Clotting factors are indicated by Roman Numerals. Warfarin affects the production of factors VII, IX, X, and

prothrombin. Heparin and LMWH inhibit factor Xa and thrombin. Fondaparinux, rivaroxaban, and apixaban are direct factor Xa inhibitors and dabigatran is a direct thrombin inhibitor.

Abbreviations: HMWK=high molecular weight kininogen; LMWH=low molecular weight heparin.

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Table 5

Recommended Intervals between Discontinuation of the Anticoagulants and Pain Procedure and Between Spine Procedure or Catheter Removal and Resumption of the Anticoagulant

Anticoagulant	Recommended interval between stoppage of drug and pain procedure	Recommended interval between low risk pain procedures and resumption of drug	Recommended interval between intermediate and high risk pain procedures and resumption of drug
Coumadin	5 days, normalization of INR	24h	24h
IV heparin	4h	24h	24h
Subcutaneous heparin, BID & TID	24h	24h	24h
LMWH	24h	24h	24h
Fibrinolytic agents	At least 48h*	At least 48h***	At least 48h***
Fondaparinux	4d	24h	24h

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

Table 6

Recommended Intervals between Discontinuation of the New Anticoagulants and Pain Procedure and Between Spine Procedure or Catheter Removal and Resumption of the Anticoagulant

Drug	Half-life	Recommended interval between stoppage of drug and pain procedure (5 half-lives)*	Recommended interval between peripheral and neuraxial pain procedures and resumption of drug**
Dabigatran	12-17 hours	4d	24h
	28h (renal disease)	6d (patients with renal disease)	
Rivaroxaban	9-13h	65h (3d)	24h
Apixaban	15.2 +/- 8.5 h	75h (3d)	24h

*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 procedures include medium and high risk interventional pain procedures. For low risk procedures, a shared decision making should be followed, a two-half-life interval maybe adequate.

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 sub-endothelial 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 pro-aggregatory and pro-thrombotic processes are excessive or inappropriate.

Platelet aggregation is initiated by extrinsic agonists such as sub-endothelial collagen exposure, thrombin, and also by intrinsic agonists such as ADP. Such agonists incite intracytoplasmic reactions leading to rearrangement of two 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.^{334,335} As such, drugs that inhibit GPIIb/IIIa prevent platelet aggregation.

Pharmacology and pharmacokinetics:

The drugs are usually administered intravenously (IV). Abciximab causes a noncompetitive but irreversible inhibition of the glycoprotein GP IIb-IIIa. It does not need dose adjustment in patients with renal failure, unlike the small molecule eptifibatide.³³¹ Its onset is rapid as it binds to platelets in minutes and platelet aggregation is almost completely inhibited after 2 hours. Although its half-life is short (10-30 minutes), its dissociation from glycoprotein is measured in hours resulting in slow recovery of platelet function (24-48 hours).^{332,331} Platelet recovery is noted by 48 hours after stoppage although platelet-bound abciximab can be detected up to 10 days.³³³ Similar to abciximab, eptifibatide and tirofiban have rapid onsets of

action. Unlike abciximab which takes several hours to dissociate, dissociation of these two drugs occurs in 10 to 15 seconds. The half-lives are 2.5 hours for eptifibatide and 2 hours for tirofiban. Recovery of platelet function occurs in 4 hours with eptifibatide and 4-8 hours with tirofiban. Following IV eptifibatide the bleeding time normalizes 15–30 minutes after drug discontinuation, and in-vitro platelet function begins to recover 4 hours after drug discontinuation.³³⁸ After tirofiban administration, both bleeding time and platelet aggregation normalize by 3–8 hours after stopping treatment.³³⁵

Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving GPIIb/IIIa antagonists has been noted.³⁴¹ In general, the cardiac surgical and interventional radiology literature recommend that elective surgery be delayed 24 to 48 hrs after abciximab and 4 to 8 hrs after eptifibatide or tirofiban. For semi-urgent surgery, if possible, delay until the antiplatelet effects have significantly dissipated (approximately 12 to 24 hours for abciximab, and 4 to 6 hours for peptidomimetic agents like eptifibatide or tirofiban) is advocated.³⁴² 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.³⁴¹

Although rare, abciximab, eptifibatide and tirofiban can produce thrombocytopenia immediately after drug administration in a small proportion of patients. Reactions usually occur within hours but may occasionally be delayed.³³⁹ In randomized controlled trials, mild thrombocytopenia (platelet count $<100,000/\mu\text{l}$) developed in about 5% of treated patients compared with about 2% of controls. Severe thrombocytopenia (platelet count $<20,000/\mu\text{l}$) occurred in about 0.7% of patients receiving abciximab for the first time, more often than with either eptifibatide or tirofiban (0.2%).³⁴⁰ A pooled analysis of 8 placebo-controlled studies concluded that abciximab, but not eptifibatide or integrilin, increased the incidence of thrombocytopenia in patients also treated with heparin.³⁴⁰

Interventional Pain Procedures in Patients Receiving GPIIb/IIIa inhibitors:

The pharmacologic differences make it impossible to extrapolate between these drugs regarding the coagulation profile for patients undergoing interventional pain procedures. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial.¹²⁷ No series involving the performance of epidural injections in the presence of GPIIb/IIIa receptor antagonists have been performed.

Generally surgery or interventional procedures, would require adequate platelet function and therefore procedures of high or intermediate risk category of interventional pain procedures (outlined above) should be delayed until platelet function has returned to normal which is at least 48 hours for abciximab.³³⁵ The European Society guidelines noted that a minimum of 48 hours for abciximab, and 8-10 hours for eptifibatide or tirofiban may be adequate.^{128,334}

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 7-10 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 surgery³⁴² 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.

Procedural 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 GP IIb/IIa inhibitor are rare since 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 24-48 hours. However, platelet-bound abciximab is noted up to 10 days and it causes irreversible binding, making recommendations on the interval between discontinuation of the drug and interventional procedures. A minimum interval is 48 hours is recommended even for low risk procedures. As there has been no study of platelet function after discontinuation of the drug, five days is probably adequate, based on daily formation of new platelets, for intermediate and high-risk procedures.*
- *For eptifibatide and tirofiban, an 8-hour stoppage before a low-risk interventional procedure is probably adequate. For intermediate and high-risk procedures, a 24-hour interval is ideal.*
- *The GPIIb/IIa inhibitors have rapid onsets of actions so an adequate time should be observed for the clot to stabilize. An 8-12 hour interval is probably adequate.*

Table 7

GP IIb/IIIa Inhibitors and Interventional Pain Procedures

Drug	Half-life	Recovery of platelet function	Interval Between Drug Discontinuation and Intervention*	Resumption of Drug after Intervention
Abciximab	10-30 min	48 hours	48-120 hours (2-5 days)	8-12 hours
Eptifibatide	2.5 hours	4 hours	8-24 hours	8-12 hours
Tirofiban	2 hours	4-8 hours	8-24 hours	8-12 hours

Data from:^{331,332}

* The shorter interval is for low risk while the longer interval is for intermediate & 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 while abciximab has a quick onset of action, it causes an irreversible binding with the glycoprotein IIb/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 GP IIb/IIIa inhibitors have rapid onsets of action.

Antidepressants and Serotonin Reuptake Inhibitors (SRIs)

Chronic pain patients frequently have concomitant depressive illnesses, and are often prescribed antidepressants to block reuptake of serotonin and norepinephrine for their adjuvant analgesic actions as well as activation of descending inhibitory pain pathways, amongst numerous beneficial effects. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), however, have been associated with increased bleeding risk. The tricyclic antidepressants and other non-serotonergic antidepressants seem not to be associated with bleeding.³⁴³⁻³⁴⁸

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.^{346,349} The bleeding risk is dependent on the potency of serotonin reuptake inhibition rather than selectivity.³⁴⁶ Other mechanisms have also been proposed including decreased platelet binding affinity, inhibition of calcium mobilization, and reduced platelet secretion in response to collagen.³⁵⁰

Fluoxetine, paroxetine, and fluvoxamine have a potent cytochrome P450 enzyme inhibitory effect, which, in turn, may inhibit the metabolism and increase blood levels of NSAIDs and other antiplatelets concomitantly metabolized by these enzymes. This may contribute to the increased bleeding risk associated with the concurrent use of SRIs and NSAIDs.³⁵¹ The added risk of increased gastrointestinal (GI) bleeding can be attributed to the SRI-induced increase in gastric acid secretion.^{343,344}

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.^{343,344,347,348}

The risk of re-operation 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 1.4-3.9). Comparatively, the risk of re-operation was 2.6% and 2.7% in never and former users respectively.³⁵² 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.³⁵³

SRI use was also associated with increased perioperative bleeding in orthopedic surgery.^{354,355} 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 non-users. (Adjusted odds ratio (OR) was 3.7, and 95% confidence interval (CI) was 1.4–10.2.) In contrast, patients using non-serotonergic antidepressants had no increased risk compared with nonusers (OR 0.7; CI, 0.1–6.0).³⁵⁴ 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.³⁵⁶

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.³⁵⁷

Conversely, few studies have reported a significant relationship between SRIs and perioperative bleeding risk in CABG surgery.³⁵⁸⁻³⁶⁰

SRIs and Antiplatelet Agents

The risk of gastrointestinal bleeding associated with SRIs increases with concurrent use of aspirin or antiplatelet medications.^{343,344,347} Similarly, patients taking SSRIs together with antiplatelet medications following acute myocardial infarction were at increased risk of bleeding.³⁶¹

A large epidemiologic study showed that combined use of an SSRI and non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin increased the risk of upper GI bleeding to 12.2 (95% confidence interval, 7.1-19.5) and 5.2 (95% confidence interval, 3.2-8.0),

respectively. Non-selective SRIs also increased the risk of upper GI bleeding to 2.3 (95% confidence interval, 1.5-3.4), while 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 unity after termination of SSRI use.³⁴⁴ Another population-based case-control study confirmed the increased bleeding risk with SSRIs and concurrent aspirin or NSAIDs use.³⁶² The adjusted odds ratio (OR) of upper gastrointestinal 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.³⁶² The increased risk of bleeding with SSRIs and NSAIDs combinations were greater than the additive risk of the individual drugs.³⁶³ A recent review article indicated that SSRI use is associated with approximately doubled odds of upper gastrointestinal (GI) bleeding. The risk of bleeding increased with the concurrent use of NSAIDs, anticoagulants, and antiplatelet agents and in patients with liver cirrhosis/ failure.³⁴⁷

SRIs and Anticoagulants

The risk of gastrointestinal bleeding associated with SRIs increases with concurrent use of anticoagulants.^{364,365} In a large population based study of approximately 2 million patients on warfarin, SSRI users were at significantly increased risk of hospitalization because of non-gastrointestinal tract bleeding (adjusted OR, 1.7; 95% CI, 1.1-2.5). NSAIDs users had a similar increased risk of non-gastrointestinal bleeding (adjusted OR, 1.7; 95% CI, 1.3-2.2).³⁶⁵

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 non-serotonergic antidepressants, manage drug discontinuation syndromes or treat worsening depression.

Because the absolute risk of abnormal bleeding with SSRIs is low and uncontrolled depression is associated with poorer surgical outcome,³⁶⁶ routine discontinuation of SRIs before pain procedures is not recommended.^{348,367} 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 in those with liver cirrhosis or failure.^{344,347,348}

However; in high risk patients with severe depression, suicidal risk, or history of uncontrolled discontinuation syndrome, switching from SRIs to non-serotonergic antidepressants (bupropion, mirtazapine, some tricyclic antidepressants) should be considered.^{348,356} This should involve shared decision -making with other treating physicians.

Few TCAs and most SSRIs and SNRIs, such as fluoxetine, sertraline, paroxetine, escitalopram, duloxetine, and venlafaxine, have intermediate to high degrees of serotonin reuptake inhibition (table 8).³⁶⁸ In contrast, non-serotonergic antidepressants such as bupropion, mirtazapine, and some tricyclic antidepressants don't inhibit serotonin reuptake.^{348,369} In fact, intraoperative bleeding risk was not higher in the non-serotonergic antidepressants users than nonusers.³⁵⁴⁻³⁵⁶ It has previously been shown that gastrointestinal bleeding induced by high-dose fluoxetine resolved after switching to mirtazapine.³⁷⁰

When to stop SRIs?

Antidepressant discontinuation can be associated with a significant risk of suicide attempts during the early period after discontinuation.³⁷¹ 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, gastrointestinal upset, dizziness, irritability, agitation, anxiety, and sleep disturbances. The 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.³⁷² However, these symptoms can be

minimized or avoided by gradually tapering off the antidepressant dose, and they improve or resolve after restarting the antidepressants.^{373,374}

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.³⁴⁷

SRI in general have relatively long half-lives (table xx). 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 1-2 weeks is required for most SRIs other than fluoxetine.^{375,376} In contrast, the half-life of fluoxetine and its active metabolite norfluoxetine is 2-4 days and 7-15 days respectively, requiring a washout period of about 5 weeks.^{376,377} Although, one case report showed that discontinuation of fluoxetine for 2 weeks was enough to restore abnormal bleeding and normalize bleeding time.³⁷⁸

Procedural recommendations with antidepressants

- *Routine discontinuation of SRIs before pain procedures is not recommended.*
- *Patients with stable depression who are at a high risk of bleeding associated with SRIs use (old age, advanced liver disease, concomitant ASA, NSAIDs, antiplatelets, or anticoagulants use) should undergo gradual tapering of the SRI dose and discontinue usage 1-2 weeks before the procedure. (See table xx 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 non-serotonergic antidepressants that do not or less potently inhibit serotonin reuptake (e.g., bupropion, mirtazapine, tricyclic antidepressants).*

- *SRI should be restarted as soon as possible after the disappearance of the bleeding risk from the procedure, usually next day.*
- *Perioperative management of SRI should be coordinated with the treating psychiatrist.*

Table 8:

The serotonergic effects of commonly used antidepressant in a ranking order

Antidepressants	Class	Receptor Occupancy (%) ³⁷⁹			t1/2 (hours)	5 - t1/2 (approx)	Active Metabolite
		5-HT-Transporter	Nor-epinephrine Transporter	5-HT _{2c} -Receptor			
Clomipramine ³⁸⁰	TCA	96.44	11.05	11.62	24	5 days	N-desmethyl
Paroxetine ³⁸¹	SSRI	95.7	4.7	0.06	21	5 days	
Escitalopram ³⁸²	SSRI	93.66	0.37	1.04	27-32	5-6 days	
Citalopram ³⁸³	SSRI	93.45	1.08	11.1	35	7 days	
Fluvoxamine ³⁸⁴	SSRI	92.74	3.33	1.35	16-26	5 days	
Fluoxetine ³⁸⁵	SSRI	88.96	7.37	19.74	24-72*	5-15 days	Norfluoxetine
Sertraline ³⁸⁶	SSRI	88.25	1.14	.062	24	5 days	N-desmethyl
Imipramine ³⁸⁷	TCA	86.17	38.59	35.69	24	5 days	Desipramine
Velafaxine ³⁸⁸	SNRI	84.52	12.47	14.83	5	1 day	O-desmethyl
Doxepin ³⁸⁹	TCA	67.08	82.44	94.03	15	3 days	
Amitriptyline ³⁹⁰	TCA	66.49	49.24	91.29	13-36	3-7 days	Nortriptyline
Duloxetine ³⁹¹	SNRI	56.25	15.35	0.17	12	2-3 days	
Nortriptyline ³⁹²	TCA	18.83	80.25	42.27	30	7 days	
Nefazodone ³⁹³	SSRI/Antag	4.22	3.05	40.6	4	1 day	
Maprotiline ³⁹⁴	Tetra	1.3	87.34	38.57	51	10 days	
Bupropion ³⁹⁵	Misc	0.74	0.71	0.71	15-22	5 days	Hydroxybupropion
Mirtazapine ³⁹⁶	Alpha-2	0.34	0.73	46.51	20-40	5-7 days	

Table 8: The serotonergic effects of commonly used antidepressant in a ranking order

Data from references 379-396

* t 1/2 in chronic use is 96-144 hours

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

Herbal/Alternative Therapies

The use of various natural botanical compounds and extracts has become more ubiquitous throughout the world, and many surveys suggest that up to 1/5 of western patients 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 these agents need not necessarily be stopped prior to neuraxial procedures.¹²⁷ The agents that appear to be most likely to cause significant bleeding or interact with other anticoagulants are garlic (*Allium sativum*), Ginkgo biloba, Ginseng (*Panax quinquefolius* L., Araliaceae), Asian ginseng (*Panax ginseng* C.A. Meyer), danshen (*Radix Salvia miltiorrhiza*), and Dong quai (*Radix Angelica sinensis*).

As per the remaining sections of this guideline, the authors are not convinced that interventional pain procedures are universally equivalent to perioperative perineural and neuraxial techniques. Certainly, higher risk interventional pain procedures, as previously defined in this guideline, may involve larger needles, multiple instrumentations and altogether different target endpoints. 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 doctor, even in the context of a thorough history and physical exam 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 (*Allium sativum*) has its primary effects on platelet aggregation. Previous studies have shown that garlic effects on bleeding are dose dependent.³⁹⁷ Allicin, the odiferous sulfinyl compound that provides garlic's flavor is formed from the crushing of garlic cloves. Ajoene, derived from allicin via extravasation in edible oils or solvents, effects platelet aggregation by inhibition of granule release and fibrinogen binding³⁹⁸ and also potentiates the inhibition of aggregation by prostacyclin, forskolin, indomethacin, and dipyridamole.³⁹⁹ 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/day of garlic were noted. His bleeding time was prolonged despite a normal platelet count, but later normalized after garlic cessation.⁴⁰⁰ Daily doses of 25 mg/day has been shown to result in significant inhibition of platelet aggregation.⁴⁰¹

As the antiplatelet effect of garlic is dose dependent, we recommend inquiry as to the daily dose of garlic intake. Test of platelet function should be ordered when patients with several co-morbidities take doses greater than 1000 mg/day or when there is concomitant intake with aspirin, NSAIDs, or SSRIs.

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 over 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.^{402,403} Typical case reports included a 46 year old African-American female on stable dosing of warfarin, who after starting dong quai, had prolongation of her international normalized ratio (INR) and prothrombin time (PT). These later normalized after discontinuation of the herb for one month. Other derivatives from the root including osthole and ferulic acid have effects on platelet aggregation and release through antagonism of cyclooxygenase and thromboxane synthetase in arachadonic acid and thromboxane A₂ metabolism.⁴⁰³ 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 appear 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 over-anticoagulation.⁴⁰⁴

Case reports of interactions between danshen and warfarin are described. A 62 year old man required mitral valve replacement and postoperatively was stabilized on warfarin with an INR of 3.0. Six weeks after discharge the patient was readmitted with anemia, lethargy and shortness of breath and was found to have pleural and pericardial effusions with an INR of 8.4. Rigorous history taking revealed the recent addition of danshen by a Chinese herbalist to help “mend” his heart. Upon cessation of the herbal preparation, his INR was re-established in the therapeutic range. The temporal relationships and lack of other causative factors suggested an interaction between danshen and warfarin.⁴⁰⁵

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

The clinically significant components of ginkgo biloba extracts producing the greatest physiologic effects are unknown; however the two considered most pharmacologically active are, flavonol glycosides and terpene lactones. Other constituents are quercetin, ginkgolic acids, proanthocyanidins, carboxylic acids and non-flavone glycosides.⁴⁰⁶ The chemical constituents can vary depending on the strain of ginkgo, as well growing conditions.⁴⁰⁷

Standardized extracts on the market contain 22–26% flavone glycosides (primarily quercetin, kaempferol and isorhamnetin) and 5–7% terpene lactones (ginkgolides A, B and C, and bilobalide).^{408,409} The most frequently included GBE formulations in clinical trials to date are EGb 761 and LI 1370.⁴⁰⁹ Inhibition of platelet activation factor (PAF) is considered to be the main mechanism of action resulting in ginkgo related biologic activity.^{410,411,412,413}

Spontaneous bleeding, including postsurgical bleeding, spontaneous subdural hematomas and hyphemas, subarachnoid hemorrhage and retrobulbar haemorrhage have been reported in multiple case reports in patients taking Ginkgo biloba extract. The hypothesized mechanism of toxicity is that antagonism of PAF and collagen lead to inhibition of platelet aggregation.⁴¹⁴ Many reported cases of spontaneous bleeding involved concurrent use of antiplatelet or anticoagulant therapies.⁴¹⁵ Diamond et al. concluded that adverse events, as described in case reports, occurred in patients that were taking additional medicines or had comorbid conditions.⁴¹⁶

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.

Panax Ginseng

Panax Ginseng (C.A. Meyer), Panax quinquefolium (American ginseng), and Panax notoginseng ((Burk) F.H.Chen (Araliaceae)) are but three 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), while ginseng literally means “man-root”.⁴¹⁷

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. 20 volunteers receiving warfarin during weeks 1 and 4 in combination with either ginseng or placebo noted significant declines in peak international normalized ratio (INR) levels as compared to the placebo group.⁴¹⁸ Studies using raw and steamed roots of *Panax notoginseng* with *Panax ginseng* and *panax quinquefolium* noted differences in effects, with *Panax notoginseng* in the steamed form having more potent effects on platelet aggregation and plasma anticoagulation. The steaming duration was correlated with increasing potency of effect. Rat bleeding times were prolonged by the use of either raw or steamed forms.⁴¹⁹ Other trials have shown little effect on warfarin resistance, with one randomized trial of ischemic stroke patients showing no effect of co-administered *Panax ginseng* on warfarin induced INR.⁴²⁰ Although isolated reports of increased vaginal bleeding after use of ginseng facial cream have been reported, the paucity of major adverse outcomes in large systematic reviews by Coon and others suggest that the adverse effects of this agent are less severe than many other agents.

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

Procedural recommendations for herbal medications:

- *Proceduralists should inquire about the use of herbal/alternative therapies and make this part of the reconciled medication list, with actual dosages of the agent, if possible.*
- *High risk procedures are most likely to have a significant bleeding risk. These include: spinal stimulation device placements, intrathecal drug delivery devices, vertebral body augmentation procedures and the like. Although there are no published cases, these completely elective procedures requiring extensive forethought and screening should be performed in idealized settings, i.e. with discontinuation of several known herbal agents.*
- *Lower and medium risk procedures are probably safe as long as other anticoagulants have been stopped according to the guidelines for those particular agents. However,*

patients who have other risk factors such as: advanced age, renal and or hepatic disease, history of major bleeding episodes from procedures, etc, should likewise have these preparations stopped, even if the procedures are low-medium risk.

- *Timing of cessation is likely variable, but a 1 week period seems appropriate, given that many of the involved agents pose risks due to effects on platelet aggregation and/or potentiation of warfarin effects.*
- *As the antiplatelet effect of garlic is dose dependent, we recommend inquiry as to the daily dose of garlic intake. Test of platelet function should be ordered when patients with several co-morbidities take doses greater than 1000 mg/day or when there is concomitant intake with aspirin, NSAIDs, or SSRIs.*
- *In patients taking warfarin and also dong quai, the INR should be checked. The herb should be discontinued when the INR is markedly elevated. Refer to the section on warfarin regarding recommendations regarding interventional procedures.*
- *In patients taking warfarin and also danshen, the INR should be checked. The herb should stopped be 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.*

Table 9.
Herbal Medications and their Effects on Coagulation*

Herb	Effect on coagulation	Time to normal hemostasis after stoppage, comments
Garlic	Inhibits platelet aggregation by reduction and inhibition of formation of thromboxane and lipogenase products, inhibition of phospholipase activity, and inhibition of incorporation of arachidonate into platelet phospholipids	7 days; test of platelet function recommended when there excessive doses are taken or in the presence of other antiplatelet drugs (aspirin, NSAIDs, SSRIs)
Dong quai	Contains natural coumarin derivatives; potentiates effect of warfarin	Check INR in patients on warfarin
Danshen	Decreases elimination of warfarin; inhibition of platelet aggregation	Check INR in patients on warfarin
Ginkgo biloba	Inhibition of platelet activation factor	36 hours, check platelet function in the presence of other antiplatelets
Panax ginseng	Reduces effect warfarin	

Modified from ¹²⁷ with permission

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