# Antithrombotic Therapy and Regional Anesthesia

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**THE AMERICAN SOCIETY OF REGIONAL** Anesthesia and Pain Medicine, in conjunction with the European Society of Anaesthesiology, published updated guidelines on antithrombotic therapy in the patient receiving neuraxial and peripheral regional anesthesia.[1] These guidelines aim to resolve international differences in the management of antithrombotic agents for neuraxial and peripheral nerve procedures and to incorporate new information and medications that have become available since the last guidelines were published in 2010. In the past 8 years many new antithrombotic medications have been approved by the US Food and Drug Administration (FDA) such as rivaroxaban (2011), apixaban (2012), edoxaban (2015), cangrelor (2015), and betrixaban (2017). In addition, there have been evolving standards for the prevention of perioperative venous thromboembolism and more frequent use of regional anesthesia techniques.

Antithrombotic medications include anticoagulant and antiplatelet agents. Anticoagulants slow down clotting, thereby reducing fibrin formation. Antiplatelet agents prevent platelets from aggregating. Both agents prevent blood clots from forming and expanding. Antithrombotic therapy is often necessary in managing common disease states such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, and acute coronary syndromes.[2-4] Although the prevention of thrombosis is important, a patient on antithrombotic therapy is at an increased risk for bleeding. Minor procedures may not require interruption of antithrombotic therapy; however, continuation in the setting of a major surgery increases bleeding risk. In many patients, therapy may safely be interrupted until surgical hemostasis is achieved. Reinitiating antithrombotic therapy is typically recommended 24 hours postoperatively for those at low risk of bleeding and 48 to 72 hours for those at high risk of bleeding.[1] In some instances, interruption of antithrombotic therapy greatly increases the risk of thromboembolism. If the surgical procedure cannot be delayed, shorter acting anticoagulant or antiplatelet agents may be used as bridging therapy during the time in which the long-acting antithrombotic regimen is subtherapeutic.

Regional anesthesia techniques in the perioperative setting are more commonly used because of enhanced surgical recovery pathways alongside the desire to implement multimodal analgesia regimens that ultimately reduce opioid consumption. Common regional anesthesia techniques include superficial peripheral nerve blocks (eg, supraorbital, digital, and ankle), deep peripheral nerve blocks (eg, sciatic nerve, lumbar plexus, and infraclavicular brachial plexus), and neuraxial blocks (eg, spinal and epidural).

Neurologic complications associated with regional anesthesia procedures are rare.[1,5] Bleeding risk associated with superficial peripheral techniques typically fall in the minor risk category. Generally, patients on antithrombotic agents may continue therapy, but block site, compressibility, vascularity, and consequences of bleeding should all be considered. Conversely, deep peripheral nerve blocks and neuraxial blocks have an intermediate to high bleeding risk. In this setting, the deep, fixed, noncompressible space imparts a higher risk for catastrophic outcomes such as long-term injury or permanent paralysis. The most feared complications of neuraxial anesthesia include spinal and epidural hematomas, defined as bleeding within the neuraxial space. The risk of hematoma development is increased with repeated epidural or spinal punctures or a traumatic regional block.[1] The use of antithrombotic therapy before, during, and after

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neuraxial or peripheral nerve blocks increases the risk for bleeding, although the actual incidence of neurologic dysfunction resulting from a hemorrhagic complication is unknown.[1] Reversal agents are available for some anticoagulants, but the only reversal for antiplatelet medications is that of a platelet transfusion. To prevent devastating neurologic injuries secondary to bleeding, antithrombotic therapy should be managed similarly in patients undergoing neuraxial, perineuraxial, deep plexus, or deep peripheral nerve blocks. With the vast array of antithrombotic agents available, four questions commonly arise.

1. What duration should the antithrombotic medication be held before the neuraxial or nerve procedure?
2. When can the antithrombotic medication be restarted after the neuraxial or nerve procedure?
3. What duration should the antithrombotic medication be held before neuraxial catheter removal?
4. When can the antithrombotic medication be restarted after the neuraxial catheter removal?

The classes of medications that are often questioned include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), factor Xa inhibitors, direct thrombin inhibitors, vitamin K antagonists, and antiplatelet medications (Table 1). Health care professionals in the perioperative setting should determine whether a patient is receiving an antithrombotic agent, and in the instance of neuraxial or peripheral nerve procedures, identify the appropriate time interval to hold and restart the agent in relation to catheter placement and removal. Time intervals in the guidelines, summarized in Table 1, should be interpreted cautiously in patients with significant renal insufficiency. In addition, concomitant use of other medications or disease states affecting hemostasis should also be considered.

## Unfractionated Heparin

UFH is an anticoagulant that imparts its effect by binding to antithrombin III, inducing a conformational change that potentiates the inhibition of factor IIa (thrombin), factor Xa, and factor IXa.[6] The inhibition of thrombin and other clotting factors prevents clots from forming and expanding. Heparin is available in an injectable formulation that may be administered by the subcutaneous or intravenous route. Intravenous administration results in immediate anticoagulant activity, whereas subcutaneous administration results in a 1 to 2 hour delay in effect. The anticoagulant activity of heparin is dose dependent, increasing disproportionately with higher doses. Therapeutic doses of heparin are most commonly monitored using the activated partial thromboplastin time, but may also be monitored with antifactor Xa testing or the activated clotting time. Administration of prophylactic doses of heparin via the subcutaneous route does not significantly prolong the activated partial thromboplastin time in most patients and therefore monitoring is not necessary. Factors associated with an increased risk of spinal hematoma in heparinized patients undergoing neuraxial blockade include less than a 60-minute time interval between the administration of heparin and lumbar puncture, traumatic needle placement, and concomitant use of other antithrombotic agents such as aspirin.[1] The anticoagulant effect of UFH may be neutralized with protamine.

## Low-Molecular-Weight Heparin

LMWHs are structurally similar, but shortened versions of the UFH molecule. The shorter molecules bind and induce a conformational change in antithrombin III that primarily accelerates the inhibition of factor Xa. Depending on the molecule length, some are able to also inhibit factor IIa.[6] Examples of LMWH include enoxaparin and dalteparin. The elimination half-life of LMWH in a patient with normal renal function is 4 to 7 hours. In patients with severe renal insufficiency, the anticoagulant effect is increased and the elimination half-life may be prolonged up to 16 hours. LMWH may be administered by a subcutaneous injection for both prophylaxis and treatment of thromboembolisms. Therapeutic anticoagulant activity of LMWH is assessed by the antifactor Xa level, although the level of residual antifactor Xa acceptable to safely place a neuraxial block remains undetermined.[1] Prophylactic doses do not require monitoring. Currently, there is no complete reversal agent for LMWH.

## Factor Xa Inhibitors

Fondaparinux, a synthetic pentasaccharide, has a mechanism similar to UFH and LMWH but only

**Table 1. Recommended Time Intervals to Hold and Restart Antithrombotic Therapy Surrounding Neuraxial and Peripheral Nerve Procedures per ASRA Guidelines[1]**

| | Before Procedure | When in Place | Before Removal | After Removal |
|---|---|---|---|---|
| **Antithrombotic Therapy** | **Hold Before Neuraxial/Nerve Procedure** | **Restart Postpuncture, When Neuraxial/ Nerve Catheter in Place** | **Hold Before Neuraxial/Nerve Catheter Removal** | **Restart After Neuraxial/Nerve Catheter Removal** |
| **UFH** | | | | |
| Heparin, subcutaneous, prophylaxis, 5,000 units, q8-12 h (low-dose UFH) | 4-6 h | 1 h | 4-6 h | 1 h |
| Heparin, subcutaneous, prophylaxis, 7,500-10,000 units, q12 h or a total dose ≤20,000 units/d (higher-dose UFH) | 12 h with verification of normal coagulation status | Safety not established, assess risks and benefits | Safety not established, assess risks and benefits | 1 h |
| Heparin, subcutaneous, prophylaxis, >10,000 units per dose or total dose >20,000 units/d (higher dose UFH) | 24 h with verification of normal coagulation status | Safety not established, assess risks and benefits | Safety not established, assess risks and benefits | 1 h |
| Heparin, intravenous infusion, therapeutic | 4-6 h with verification of normal coagulation status | 1 h | 4-6 h with verification of normal coagulation status | 1 h |
| **LMWH** | | | | |
| LMWH, subcutaneous, prophylaxis, q24 h | 12 h | 12 h (with next dose given no sooner than 24 h after first dose) | 12 h | 4 h |
| LMWH, subcutaneous, prophylaxis, q12 h | 12 h | Not recommended | Not recommended | 4 h |
| LMWH, subcutaneous, therapeutic, q12 or q24 h | 24 h<br>Consider verifying normal coagulation status | Not recommended | Not recommended | 4 h (if catheter placed ≥24 h before removal) |

*(Continued)*

**Table 1. Continued**

| Antithrombotic Therapy | Before Procedure: Hold Before Neuraxial/Nerve Procedure | When in Place: Restart Postpuncture, When Neuraxial/Nerve Catheter in Place | Before Removal: Hold Before Neuraxial/Nerve Catheter Removal | After Removal: Restart After Neuraxial/Nerve Catheter Removal |
|---|---|---|---|---|
| **Factor Xa inhibitors** | | | | |
| Apixaban | 72 h | Not recommended | Not recommended | 6 h |
| Betrixaban (CrCl > 30 mL/min) | ≥72 h | Not recommended | Not recommended | 5 h |
| Edoxaban | 72 h | Not recommended | Not recommended | 6 h |
| Rivaroxaban | 72 h | Not recommended | Not recommended | 6 h |
| Fondaparinux | Not recommended | Not recommended | Not recommended | 6 h |
| **Direct thrombin inhibitors** | | | | |
| Dabigatran (CrCl > 80) | 72-120 h | Not recommended | Not recommended | 6 h |
| Dabigatran (CrCl 50-79) | 96-120 h | Not recommended | Not recommended | 6 h |
| Dabigatran (CrCl 30-49) | 120 h | Not recommended | Not recommended | 6 h |
| Dabigatran (CrCl < 30) | Not recommended | Not recommended | Not recommended | 6 h |
| Argatroban | Not recommended | Not recommended | Not recommended | Not recommended |
| Bivalirudin | Not recommended | Not recommended | Not recommended | Not recommended |
| **Vitamin K antagonist** | | | | |
| Warfarin (chronic therapy) | 5 d with verification of normalized INR | Immediately<br>Low-dose therapy only with daily INR | Verify INR < 1.5 and within 24 h after initial warfarin dose | Immediately |
| Warfarin (one time, low dose, and < 24 h) | Consider verification of normal INR | Immediately<br>Low-dose therapy only with daily INR | Verify INR < 1.5 and within 24 h after initial warfarin dose | Immediately |
| Warfarin (one time, low dose, and ≥24 h or >1 dose) | Verify normal INR before procedure | Immediately<br>Low-dose therapy only with daily INR | Verify INR < 1.5; safety not established with initial warfarin dose given 24-48 h prior | Immediately |
| **Antiplatelet agents** | | | | |
| Nonsteroidal anti-inflammatory drugs | No restrictions | No restrictions | No restrictions | No restrictions |
| Aspirin | No restrictions | No restrictions | No restrictions | No restrictions |
| Clopidogrel | 5-7 d | Immediately, nonloading dose only and 24 h postoperatively | Verify within 1-2 d of initial postprocedure, nonloading dose | No loading dose: immediately<br>Loading dose: 6 h |
| Prasugrel | 7-10 d | Not recommended | Not recommended | No loading dose: immediately<br>Loading dose: 6 h |
| Ticagrelor | 5-7 d | Not recommended | Not recommended | No loading dose: immediately<br>Loading dose: 6 h |
| Cangrelor | 3 h | Not recommended | Not recommended | 8 h |

*(Continued)*

**Table 1. Continued**

| | Before Procedure | When in Place | Before Removal | After Removal |
|---|---|---|---|---|
| **Antithrombotic Therapy** | **Hold Before Neuraxial/Nerve Procedure** | **Restart Postpuncture, When Neuraxial/ Nerve Catheter in Place** | **Hold Before Neuraxial/Nerve Catheter Removal** | **Restart After Neuraxial/Nerve Catheter Removal** |
| Abciximab | 24-48 h* | Not recommended | Not recommended | Not recommended |
| Eptifibatide | 4-8 h* | Not recommended | Not recommended | Not recommended |
| Tirofiban | 4-8 h* | Not recommended | Not recommended | Not recommended |
| Cilostazol | 48 h | Not recommended | Not recommended | 6 h |
| Dipyridamole | 24 h | Not recommended | Not recommended | 6 h |

ASRA, American Society of Regional Anesthesia and Pain Medicine; INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

*Patients are typically on dual antithrombotic therapy and may have residual anticoagulant or antiplatelet effects.

has the capacity to potentiate factor Xa inhibition by antithrombin III because of its short length.[6] This inhibition disrupts the conversion of prothrombin (factor II) to thrombin (factor IIa), preventing the activation of platelets and the conversion of fibrinogen to fibrin. It is administered by a subcutaneous injection for thromboembolism treatment or prophylaxis. The major route of elimination is urinary excretion of unchanged drug. The elimination half-life of fondaparinux is 17 to 21 hours and is prolonged in patients with renal impairment. The anticoagulant effect of fondaparinux is irreversible and reports of spinal hematoma development during initial clinical trials have resulted in cautious use.[1]

Oral factor Xa inhibitors are anticoagulants that inhibit thrombin-induced platelet activation and fibrin clot formation by directly and reversibly inhibiting factor Xa in both the intrinsic and extrinsic coagulation cascades. The conversion of prothrombin (factor II) to thrombin (factor IIa) is subsequently disrupted, preventing the activation of platelets and the conversion of fibrinogen to fibrin. Examples of oral factor Xa inhibitors include apixaban (Eliquis), betrixaban (Bevyxxa), edoxaban (Savaysa), and rivaroxaban (Xarelto). The half-lives of the oral factor Xa inhibitors differ between each agent and can be prolonged in the setting of renal dysfunction. The oral factor Xa inhibitors may be used for treatment or prophylaxis of thromboembolisms. There are minimal data and clinical experience with the factor Xa inhibitors and neuraxial or peripheral nerve procedures. Reports of spinal hematoma development have resulted in cautious use surrounding regional anesthetic blocks. Currently, there are no FDA-approved assays to measure the anticoagulant effects of the factor Xa inhibitors. Reversal of apixaban and rivaroxaban may be accomplished with recombinant coagulation factor Xa (Andexxa), although nationwide availability is currently limited. There is currently no complete reversal agent for betrixaban or edoxaban.

## Direct Thrombin Inhibitors

Direct thrombin inhibitors are anticoagulants whose mechanism of action is to inhibit both free and clot-bound thrombin, in addition to thrombin-induced platelet aggregation. Intravenous direct thrombin inhibitors include bivalirudin (Angiomax) and argatroban (Acova). These formulations are commonly administered as a continuous, titratable, infusion for the treatment and prophylaxis of thrombosis. They are primarily useful in patients with or at risk for heparin-induced thrombocytopenia. The half-life of bivalirudin is prolonged in the setting of renal dysfunction and the half-life of argatroban is prolonged with hepatic dysfunction. This often results in unpredictable therapeutic responses. The lack of clinical data, absence of an antidote, and likelihood that therapeutic anticoagulation is needed in patients receiving intravenous direct thrombin inhibitors is the impetus behind the recommendation that neuraxial techniques should be avoided in patients receiving intravenous direct thrombin inhibitors.[1,6]

Dabigatran (Pradaxa) is an oral direct thrombin inhibitor. There is limited clinical experience with the use of neuraxial techniques in dabigatran-treated patients. Recommendations in the guidelines are based on expert opinion and on the pharmacokinetics of the drug. The typical half-life of dabigatran is 12 to 17 hours and is significantly prolonged with renal dysfunction. Therapy adjustments in preparation for neuraxial or peripheral nerve procedures may be based on the patient's creatinine clearance if felt to be a reliable indicator of renal function and there are no additional risk factors for bleeding such as age greater than 65 years, hypertension, and concomitant antiplatelet medications.[1] Currently, there are no FDA-approved assays to measure the anticoagulant effects of dabigatran. Dissimilar to the intravenous thrombin inhibitors, a reversal agent for dabigatran is available. Idarucizumab (Praxbind) is a monoclonal antibody fragment that binds specifically to dabigatran and neutralizes the anticoagulant effect within minutes.[7]

## Warfarin

Warfarin is an anticoagulant whose mechanism of action is to antagonize vitamin K to prevent the formation of clotting factors II, VII, IX, and X, as well as proteins C and S.[6] The half-life of warfarin is dependent on the half-lives of the inhibited clotting factors. A therapeutic dose of warfarin decreases the total amount of each vitamin K-dependent clotting factor by 30% to 50%.[6] As a result of the long half-life of some clotting factors, the full antithrombotic effect may not be achieved for several days. The anticoagulant effect of warfarin is measured by the international normalized ratio (INR). Whether the INR needs to be normalized or less than 1.5 before neuraxial procedures remains to be controversial. Caution is advised when performing neuraxial procedures in patients recently discontinued from warfarin therapy. Low-dose therapy may be initiated in the presence of indwelling catheters along with daily INR monitoring and frequent neurologic assessments. The catheter should be removed before the onset of therapeutic anticoagulation occurs.[1] In the instance of bleeding or in the case of urgent or emergent procedures, warfarin can be reversed with administration of fresh frozen plasma, supplementation with oral or intravenous vitamin K, or administration of prothrombin complex concentrate.[6]

## Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin have an antiplatelet effect by inhibiting platelet cyclooxygenase 1.[6,8] As a result, synthesis of thromboxane A2, which plays a major role in platelet aggregation, is reduced. The effect of aspirin on the platelet is irreversible and lasts for the life of the platelet (7 to 10 days). Non-aspirin NSAIDs reversibly inhibit cyclooxygenase 1, resulting in a duration that is reflective of the dose and half-life of the drug. Some common examples of non-aspirin NSAIDS are ibuprofen, naproxen, diclofenac, and meloxicam. The use of NSAIDs or aspirin does not pose a significant risk with respect to performance of neuraxial blocks or peripheral nerve procedures and therefore may be continued. Caution, however, is advised if there is concurrent use of other anticoagulant or antiplatelet medications secondary to the increased risk of bleeding complications.[1]

## $P2Y_{12}$ Inhibitors

Thienopyridines are antiplatelet medications that irreversibly block $P2Y_{12}$ adenosine diphosphate (ADP)-receptors on the surface of the platelet, which in turn inhibits platelet activation and aggregation.[6] Examples of thienopyridines are clopidogrel (Plavix) and prasugrel (Effient). Thienopyridines demonstrate both time-dependent and dose-dependent therapeutic effects. Clopidogrel has a slow onset of action with platelet inhibition detected in approximately 48 hours of a 75 mg dose and within 2 hours of a 300 to 600 mg loading dose. Prasugrel has a quicker onset of action with the ability to inhibit platelet aggregation in less than 30 minutes after a 60 mg loading dose. The differing pharmacokinetics of each agent and each dose becomes extremely relevant when adjusting or initiating thienopyridine therapy in the perioperative setting. With both agents, platelet function gradually returns to baseline over the course of 5 to 10 days because of their irreversible mechanism.

Ticagrelor (Brilinta), unlike the thienopyridines, reversibly interacts with the platelet $P2Y_{12}$ ADP-receptor resulting in a reversible inhibition of platelet activation and aggregation. An antiplatelet affect is noted within 30 minutes of an oral loading dose. Ticagrelor has an equally active metabolite.

The half-lives of the active molecules are 7 and 9 hours. As per the manufacturer, discontinuation of ticagrelor increases the risk of myocardial infarction, stroke, and death.[9] However, if temporary discontinuation is required (eg, nonelective surgery with a major risk of bleeding), therapy should be held for 5 days before surgery and restarted as soon as hemostasis is achieved.[9] In relation to neuraxial procedures, timing of re-initiation after catheter removal is dependent on whether a loading dose is prescribed.[1]

Cangrelor (Kengreal) in an intravenous, selective, reversible $P2Y_{12}$ ADP-receptor inhibitor that results in the inhibition of platelet activation and aggregation. Platelet inhibition occurs within 2 minutes of initiating the continuous infusion and is maintained for the duration of the infusion. The half-life of 3 to 6 minutes results in an ultraquick offset.[10] Cangrelor may be used as a bridge therapy in situations in which thrombotic risk is high (eg, recent stent placement) and the surgical procedure cannot be delayed.[11]

## Glycoprotein IIb/IIIa Inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors are intravenous antiplatelet medications whose mechanism of action is to block the GP IIb/IIIa receptor on the platelet, which prevents platelet aggregation. The GP IIb/IIIa receptor is the binding site for fibrinogen, von Willebrand factor, and other ligands that are important in platelet aggregation.[6] The primary indication for use is in the management of acute coronary syndromes. Examples of GP IIb/IIIa inhibitors are abciximab (Reopro), eptifibatide (Integrilin), and tirofiban (Aggrastat). Contraindications to therapy include major surgery within the previous 4 to 6 weeks. After discontinuation of the intravenous infusion, platelet function generally recovers over the course of 48 hours with abciximab and 8 hours with eptifibatide and tirofiban.[1,6]

## Cilostazol

Cilostazol is an antiplatelet medication that inhibits phosphodiesterase III. As a result, cyclic adenosine monophosphate (AMP) is increased, which leads to reversible inhibition of platelet aggregation. The half-life of cilostazol is 11 to 13 and 21 hours for the active metabolite.[6] Cilostazol is indicated for intermittent claudication in patients with peripheral vascular disease. The risk of bleeding associated with neuraxial and peripheral nerve procedures or maintaining catheters in the presence of residual cilostazol activity is unknown. Recommendations within the practice guidelines are pharmacokinetically derived.

## Dipyridamole

Dipyridamole (Persantine) is an antiplatelet agent that inhibits the activity of adenosine deaminase and phosphodiesterase. Adenosine, adenine nucleotides, and cyclic AMP accumulate, resulting in the inhibition of platelet aggregation.[6] Although there is limited information to guide recommendations related to neuraxial procedures, extended release dipyridamole in combination with aspirin therapy was found to have a higher incidence of bleeding complications when compared with clopidogrel in a secondary stroke prevention study.[12,13] In addition, reports of hematoma development after deep peripheral nerve blocks have resulted in guideline recommendations to discontinue therapy preoperatively and remove catheters before reinstituting therapy postoperatively.[1,14,15]

## Conclusions

Recommendations published in the 2018 practice guidelines serve as a resource for health care clinicians involved in the care of patients receiving antithrombotic agents who are potential candidates for neuraxial or peripheral nerve blockade. The patient's coagulation status and platelet function should be optimized at the time of needle puncture or catheter placement and the level of anticoagulation should be carefully monitored when the catheters remain in place. Indwelling catheters should not be removed in the presence of therapeutic anticoagulation or platelet dysfunction. Neurologic testing of sensory and motor function should be performed routinely. Signs and symptoms of neurologic impairment (eg, numbness or weakness of the legs, or bowel or bladder dysfunction) warrant urgent evaluation and prompt intervention.

Although not discussed in this article, related publications issued in 2018 in collaboration with the American Society of Regional Anesthesia and Pain Medicine include *The Interventional Spine*

*and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition)*[16] and *The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants*.[17] These publications, in addition to the guidelines on *Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy*[1] reviewed in this article, provide instrumental guidance to health care clinicians related to the perioperative and periprocedural management of patients on antithrombotic therapy.

## References


1. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (Fourth Edition). *Reg Anesth Pain Med*. 2018;43:263-309.
2. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:7S-47S.
3. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315-352.
4. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154:1121-1201.
5. Neal JM, Barrington MJ, Brull R, et al. The second ASRA Practice advisory on neurologic complications associated with regional anesthesia and pain medicine: Executive summary 2015. *Reg Anesth Pain Med*. 2015;40:401-430.
6. Hilal-Dandan R, Brunton LL, eds. *Blood Coagulation and Anticoagulant, Fibrinolytic, and Antiplatelet Drugs. Goodman and Gilman's Manual of Pharmacology and Therapeutics*, 2ed. New York, NY: McGraw-Hill Education; 2016.
7. Pollack CV Jr., Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511-520.
8. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol*. 1995;35:209-219.
9. AstraZeneca. *Brilinta (ticagrelor) Tablets, for Oral Use. [Package Insert]*. 2018.
10. Farmaceutici C. *Kengreal (Cangrelor) for Injection, for Intravenous Use. [Package Insert]*. 2016.
11. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: A randomized controlled trial. *JAMA*. 2012;307:265-274.
12. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e89S-e119.
13. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238-1251.
14. Clendenen SR, Robards CB, Wang RD, Greengrass RA. Case report: Continuous interscalene block associated with neck hematoma and postoperative sepsis. *Anesth Analg*. 2010;110:1236-1238.
15. Parvaiz MA, Korwar V, McArthur D, Claxton A, Dyer J, Isgar B. Large retroperitoneal haematoma: An unexpected complication of ilioinguinal nerve block for inguinal hernia repair. *Anaesthesia*. 2012;67:80-81.
16. Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (Second Edition): Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med*. 2018;43:225-262.
17. Leffert L, Butwick A, Carvalho B, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. *Anesth Analg*. 2018;126:928-944.