

Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition)

Terese T. Horlocker, MD,* Erik Vandermeulen, MD,† Sandra L. Kopp, MD,* Wiebke Gogarten, MD,‡
Lisa R. Leffert, MD,§ and Honorio T. Benzon, MD||

(Reg Anesth Pain Med 2018;43: 263–309)

Evolving standards for the prevention of perioperative venous thromboembolism (VTE) and the introduction of increasingly potent antithrombotic medications have resulted in concerns regarding the heightened risk of neuraxial bleeding. Furthermore, societies and organizations seeking to address these concerns through guidelines in perioperative management have issued conflicting recommendations. In response to these patient safety issues and the need for a more international approach to management, the American Society of Regional Anesthesia and Pain Medicine (ASRA), in conjunction with the European Society of Anaesthesiology (ESA), convened its Fourth Consensus Conference on Regional Anesthesia and Anticoagulation. Portions of the material presented here were published in the 1998, 2003, and 2010 ASRA Consensus Documents as well as the 2010 ESA Guidelines.^{1–8} The information has been updated to incorporate data available since the time of its publication.

Based on limited clinical and animal data, these guidelines do not define standard of care. They are not intended to replace clinical judgment as applied to a specific patient scenario. Variances from recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. Importantly, the authors consistently tended toward conservative recommendations. The consensus statements are designed to encourage safe and quality patient care, but cannot guarantee a specific outcome. As with any clinical guideline recommendation, these are subject to revision as knowledge of specific complications advances.

The first 2 consensus conferences focused on neuraxial blocks and anticoagulants in surgical patients, with limited information on the management of thromboprophylaxis in the parturient. However, the hypercoagulability associated with pregnancy and the puerperium has resulted in an increased number of parturients receiving antithrombotic therapy for the treatment and prevention of thromboembolism.^{9–14} The third consensus conference, based on limited information, recommended that parturients be managed similarly to nonpregnant patients undergoing neuraxial block.⁷ More recently, the National Partnership for Maternal

Safety (NPMS)¹³ developed a consensus bundle on VTE, which will likely result in more parturients receiving thromboprophylaxis. Integration of these recommendations in a patient population where there is a lack of a comparable “alternative” analgesic technique has again raised concern regarding the timing of epidural catheter placement/removal and initiation of postpartum thromboprophylaxis and is addressed in this update. Of note, ASRA collaborated with the NPMS and Society for Obstetric Anesthesia and Perinatology (SOAP) to develop a unified set of recommendations.¹⁵

The 2010 consensus conference also addressed, for the first time, the risk of significant bleeding in patients undergoing plexus and peripheral neural blockade. This section also is extensively updated as more information regarding frequency and severity of bleeding complications associated with nonneuraxial techniques has become available.

Finally, recent publications of cases of epidural hematoma during interventional pain procedures in patients receiving antiplatelet agents suggested a need for separate recommendations for these patients,^{16–18} as the current ASRA guidelines for the placement of epidural and spinal catheters do not recommend cessation of these antiplatelet agents for epidural procedures, nor do the guidelines differentiate between interventional pain procedures and perioperative regional anesthesia blocks.⁷ A summary of the interventional spine and pain guidelines, highlighting the differences, is included. In addition, the guidelines consider the management of patients undergoing pain (both neuraxial and peripheral) procedures in combination with antithrombotic therapy.

These recommendations are intended for use by anesthesiologists and other physicians and health care providers performing neuraxial and peripheral regional anesthetic/analgesic blockade. However, these recommendations may also serve as a resource for other health care providers involved in the management of patients who have undergone similar procedures (eg, myelography, lumbar puncture).

METHODS

A systematic and general review of the relevant literature between 2010 and 2017 was performed. Published reports on pharmacokinetics and pharmacodynamics of antithrombotic medications, series of patient receiving these medications while undergoing neuraxial and peripheral blockade, and case reports of neuraxial and perineural bleeding (both spontaneous and regional anesthesia associated) were identified. Members of the task force represented the specialties of regional anesthesia/acute pain and interventional pain. The members represented ASRA, SOAP, and ESA.

Since the last consensus document, many new oral anticoagulant medications have been approved by the US Food and Drug Administration (FDA). Nearly all were released with a black box warning regarding the risk of spinal hematoma. In addition, many

From the *Mayo Clinic, Rochester, MN; †Katholieke Universiteit, Leuven, Belgium; ‡Bielefeld Hospital, Bielefeld, Germany; §Massachusetts General Hospital, Boston, MA; and ||Northwestern University, Chicago, IL.
Accepted for publication January 21, 2018.

Address correspondence to: Terese T. Horlocker, MD, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (e-mail: horlocker.terese@mayo.edu).

The authors declare no conflict of interest.

Copyright © 2018 by American Society of Regional Anesthesia and Pain Medicine

ISSN: 1098-7339

DOI: 10.1097/AAP.0000000000000763

have labeling that describes time intervals between discontinuation of the anticoagulant and a surgical procedure or neuraxial block, the timing of epidural catheter after administration of the anticoagulant, and the timing of subsequent dosing following neuraxial catheter removal. In the absence of larger series and case reports, these recommendations are often pharmacologically based. For example, recommended time intervals between discontinuation of drug during therapeutic anticoagulation and subsequent neuraxial block are 5 half-lives (and is dependent on renal function). This allows for resolution of 97% of the anticoagulant effect. With lower levels of anticoagulation associated with prophylaxis, only a 2-half-life interval is required. Similarly, a recent FDA Drug Safety Communication recommended a 4-hour time interval between catheter removal and subsequent low-molecular-weight heparin (LMWH) administration.¹⁹ The new recommendation is based on the work of Rosencher et al,²⁰ who proposed subsequent dosing of antithrombotic therapy based on 8 hours minus the time it takes for the anticoagulant to reach peak effect. Rosencher et al²⁰ cited the work of Bouma and Mosnier,²¹ who noted that it takes approximately 8 hours for a platelet plug to become stable. For example, the efficacy of thrombolytic therapy following a cerebral embolic clot markedly decreases after 6 to 8 hours.²² This implies that anticoagulants will have a hard time lysing a clot after 8 hours. Given the 4-hour time to peak effect with LMWH, the time to subsequent dosing following catheter manipulation would be 8 hours minus 4 hours, or 4 hours.²³ The American Society of Regional Anesthesia and Pain Medicine has consistently incorporated FDA-approved labeling into practice recommendations and as such adopted the changes. This time interval is also consistent with the ESA,⁸ Scandinavian,²⁴ and most recent German guidelines (all of which incorporate a pharmacologic approach to newer anticoagulants where data are sparse).^{8,23,25}

Recommendations are frequently made with a time interval, rather than an exact time (eg, 4–6 hours), representing normal variation in pharmacologic activity. In patients without additional comorbidities that affect metabolism, excretion, and/or distribution, the shorter time may be observed. Significant renal insufficiency (in a renally excreted medication) is not included in this time interval and will require longer periods. Also to be considered are a patient history of bruising/bleeding, the presence of multiple medications affecting hemostasis, and the proposed regional technique (deep vs superficial, continuous vs single injection).

Strength and Grade of Recommendations

The recommendations presented are based on a thorough evaluation of the available information using a grading system based on level of evidence and strength of recommendation. The level of evidence classification combines an objective description of the types of studies/expert consensus supporting the recommendation. Unfortunately, with a complication as rare as spinal hematoma, in randomized clinical trials and meta-analyses, the highest (A) level of evidence is not available. Numerous observational and epidemiologic series (typically, level of evidence B) have documented the conditions for safe performance of neuraxial anesthesia and analgesia in the anticoagulated patient. However, high-quality evidence may come from large observational/epidemiologic series yielding very large risk reduction.²⁶ Hence, depending on the risk reduction, recommendations from these sources may be categorized as level of evidence A or B. Recommendations derived from case reports or expert opinion merit a C level of evidence. Often, recommendations involving the anesthetic management of new antithrombotic agents, for which data involving safety and/or risk are sparse, are based on the pharmacology of hemostasis-altering drugs, risk of surgical bleeding, and expert opinion (C level of evidence).

The grade of recommendation indicates the strength of the guideline and the degree of consensus agreement. For example, grade 1 represents general agreement in the efficacy, grade 2 notes conflicting evidence or opinion on the usefulness, and grade 3 suggests that the procedure may not be useful (and possibly harmful). These guidelines do not contain any grade 3 recommendations. The phrase “we recommend” is used for strong recommendations (grades 1A, 1B, and 1C), and “we suggest” for weaker recommendations (grades 2A, 2B, and 2C). In cases where the evidence is scant (such as with the new oral anticoagulants), the authors highly valued patient safety and proposed conservative (ie, longer) times for interruption of therapy prior to neural blockade. These will likely be revised as additional information regarding blood levels and anticoagulant effect, as well as the introduction of reversal agents, is presented.

Finally, although there are several new sections representing the recently introduced antiplatelet and anticoagulant medications, as well as revised recommendations of previously included agents, in some cases the management has remained unchanged. In order to facilitate review, the status of the current recommendations is noted in each section.

Current Recommendations for the Prevention and Treatment of Venous Thromboembolism

Venous thromboembolism is an important health care problem and a significant source of morbidity and mortality. Nearly all hospitalized patients have at least 1 risk factor for thromboembolism; approximately 40% have 3 or more risk factors²⁷ (Table 1). Consequently, the majority of hospitalized patients are candidates for thromboprophylaxis.

The agent, dosing regimen, and duration of thromboprophylaxis are based on identification of risk factors, both individual (eg, age, sex, previous history of thromboembolism) and group-specific (eg, primary reason for hospitalization, surgery, medical illness)^{27,28}

TABLE 1. Risk Factors for Venous Thromboembolism

Surgery
Trauma (major trauma or lower-extremity injury)
Immobility, lower-extremity paresis
Cancer (active or occult)
Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Central venous catheterization
Inherited or acquired thrombophilia

Adapted from Geerts et al,²⁷ with permission.

(Tables 1 and 2). Depending on the risks of thromboembolism and bleeding, thromboprophylaxis may be achieved with compression stockings, intermittent compression devices, with medications (chemoprophylaxis), or a combination of both.^{28,29} Because an individualized approach to thromboprophylaxis is complex, most recommendations are group specific, with modifications based on the presence/absence of additional risk factors. Guidelines for antithrombotic therapy including appropriate pharmacologic agent, degree of anticoagulation desired, and duration of therapy continue to evolve.^{30,31}

A review of the evolution of practice guidelines and the strength/grade of recommendations noted that (1) the vast majority of guidelines are based on lower levels of evidence or expert opinion—level A recommendations (derived from randomized clinical trials) are rare; and (2) bias may exist due to funding of industry trials (in restricted patient populations), as well as conflict of interest by the guideline-writing groups.^{32,33} The American College of Chest Physicians (ACCP) thoroughly addressed these issues in their most recent edition of *The Antithrombotic Therapy and Prevention of Thrombosis*, ninth edition (AT9), in 2012. The lead investigator, Gordon H. Guyatt,³¹ noted AT9 of the evidence-based clinical practice guidelines differed substantially from the prior version both in process and in content. The most important changes in the content of AT9 resulted directly from a change in the process of reconciling intellectual and financial conflicts of interest. The new process gave primary leadership and responsibility for each article in the document not to a thrombosis expert but to a methodologist who, in almost all cases, also is a practicing physician without important conflicts of interest. In addition, there was a more rigorous reevaluation of the evidence that distinguished between a surrogate outcome (asymptomatic thrombosis detected on imaging) and patient important outcomes (symptomatic thrombosis vs bleeding). The more rigorous and critical evaluation of the literature resulted in many weak recommendations (2A–C) replacing the strong recommendations (1A–C) of previous editions. One remarkable result was a major change on the use of aspirin in thromboprophylaxis in orthopedic surgery. The authors of the eighth edition (AT8) had concluded that there was “high-quality evidence justifying a strong recommendation against aspirin as the sole agent for thromboprophylaxis in surgical patients.”^{27,31} After reevaluation of the evidence and inclusion of a very large

trial, the AT9 authors concluded “that the trial provides moderate-quality evidence supporting the use of aspirin in patients undergoing major orthopedic procedures, which is now offered as an option for thromboprophylaxis in patients undergoing major orthopedic procedures.”^{31,34} Thus, with AT8, for patients undergoing major orthopedic surgery, LMWH, fondaparinux, and vitamin K agonists were the only recommended agents of thromboprophylaxis.²⁷ However, with the AT9 guidelines, clinicians may now choose from LMWH, fondaparinux, vitamin K agonists, dabigatran, rivaroxaban, apixaban, low-dose unfractionated heparin (UFH), aspirin, or an intermittent pneumatic compressive device.²⁹ It is interesting to note that the American Academy of Orthopaedic Surgeons published guidelines in 2011 for the prevention of venous thromboembolic disease for patients undergoing elective hip and knee arthroplasty with essentially the same conclusion (http://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/VTE_full_guideline_10.31.16.pdf. Accessed March 4, 2017). The American Academy of Orthopaedic Surgeons evidence-based guidelines recommended “the use of pharmacologic agents and/or mechanical compressive devices for the prevention of VTE in patients undergoing elective hip or knee arthroplasty and who are not at elevated risk beyond that of the surgery itself for VTE or bleeding.” However, noting that “current evidence is unclear about which prophylactic strategy (or strategies) is/are optimal or suboptimal, we were unable to recommend for or against specific prophylactics in these patients.”

In general, AT9 represents a “less aggressive” set of guidelines with more options for thromboprophylaxis. Selection of antithrombotic agents that are efficacious but have less impact on hemostasis (such as aspirin compared with LMWH in orthopedic patients) will theoretically decrease the severity and frequency of serious bleeding implications—both surgical and anesthesia related—and improve patient safety.

As with previous advisories, ASRA recommendations incorporate the dosing regimen approved by the FDA, as well as the ACCP antithrombotic guidelines.

1.0 Administration of Thromboprophylaxis

1.1 For each of the antithrombotic agents, we recommend that clinicians follow the FDA-approved dosing and ACCP management guidelines (grade 1A).

Remarks: There is no change in this recommendation.

TABLE 2. Recommendations for Thromboprophylaxis in Nonorthopedic Surgical Patients

Risk of Symptomatic VTE	Risk of Major Bleeding Complications	
	Average Risk (~1%)	High Risk (~2%) or Severe Consequences
Very low (<0.5%)	No specific prophylaxis	
Low (~1.5%)	Mechanical prophylaxis, preferably with IPC	
Moderate (~3.0%)	LDUH, LMWH, or mechanical prophylaxis, preferably with IPC	Mechanical prophylaxis, preferably with IPC
High (~6.0%)	LDUH or LMWH plus mechanical prophylaxis with ES or IPC	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High-risk cancer surgery	LDUH or LMWH plus mechanical prophylaxis with ES or IPC and extended-duration prophylaxis with LMWH postdischarge	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High risk, LDUH, and LMWH contraindicated or not available	Fondaparinux or low-dose aspirin (160 mg); mechanical prophylaxis, preferably with IPC; or both	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added

ES indicates elastic stockings; IPC, intermittent pneumatic compression; LDUH, low-dose UFH.

Adapted from Gould et al,²⁸ with permission.

TABLE 3. Perioperative Management of Patients on Warfarin

Preoperative

- Discontinue warfarin at least 5 days before elective procedure
- Assess INR 1–2 d prior to surgery, if >1.5, consider 1–2 mg oral vitamin K
- Reversal for urgent surgery/procedure, consider 2.5–5 mg oral or IV vitamin K; for immediate reversal, consider PCCs, fresh frozen plasma
- Patients at high risk of thromboembolism
 - Bridge with therapeutic SC LMWH (preferred) or IV UFH
 - Last dose of preoperative LMWH administered 24 h before surgery, administer half of the daily dose
 - Intravenous heparin discontinued 4–6 h before surgery
- No bridging necessary for patients at low risk of thromboembolism

Postoperative

- Patients at low risk of thromboembolism
 - Resume warfarin on POD
- Patients at high risk of thromboembolism (who received preoperative bridging therapy)
 - Minor surgical procedure—resume therapeutic LMWH 24 h postoperatively
 - Major surgical procedure—resume therapeutic LMWH 48–72 h postoperatively or administer low-dose LMWH
- Assess bleeding risk and adequacy of hemostasis when considering timing of the resumption of LMWH or UFH therapy

Recommendations from Douketis et al.³⁶

Perioperative Management of Antithrombotic and Antiplatelet Therapy

Long-term anticoagulation with warfarin is often indicated for patients with a history of VTE, mechanical heart valves, and atrial fibrillation. In addition, patients with bare metal or drug-eluting coronary stents require antiplatelet therapy with aspirin and thienopyridine derivatives (eg, clopidogrel) for varying durations. These patients may present for elective or urgent surgical procedures. Perioperative management involves balancing the risks of surgical bleeding and thromboembolism. Minor procedures may not require interruption of antithrombotic or antiplatelet therapy. However, continuation of these medications in the setting of a major surgery increases the risk of bleeding. Thus, it is critical to determine whether the planned procedure necessitates interruption of antithrombotic/antiplatelet therapy and, if so, whether the patient will need bridging therapy to minimize the risk of thromboembolism during the time the antithrombotic effect is subtherapeutic. In many patients, antithrombotic therapy may be safely interrupted until adequate surgical hemostasis is achieved. In other patients, bridging anticoagulation with UFH or LMWH is required until the time of surgery (and reinitiated in the immediate postoperative period). It may also be necessary to postpone elective surgeries in patients where a suitable “bridge” has not been identified and antithrombotic therapy is critical; premature discontinuation of dual antiplatelet therapy in patients with coronary stents has been associated with stent thrombosis, myocardial infarction, and death^{35,36} (Tables 3 and 4).

Evidence-based guidelines for the perioperative management of antithrombotic therapy have been established by the ACCP.³⁶ In general, in patients at moderate to high risk of thromboembolism, bridging therapy is recommended (and the prevention of thromboembolism is valued over the potential for increased surgical bleeding). Notably, 3 different bridging regimens are presented;

selection is based on the potential consequences of perioperative bleeding. Conversely, no bridging therapy is recommended for patients at low risk of thromboembolism. While the recommendations for management are relatively simple, complexity arises in the determination of who is “high risk.” This evaluation is perhaps best performed within an integrated multidisciplinary clinic by thrombophilia experts.³⁷ Timing of resumption of antithrombotic therapy postoperatively also is based on the relative risks of bleeding and thrombosis. In general, it is recommended that patients at low risk of bleeding initiate antithrombotic therapy 24 hours postoperatively, whereas those at high risk of bleeding wait for 48 to 72 hours.^{36,38} These are longer time intervals than were previously recommended.³⁹

Incidence, Risk Factors, and Neurologic Outcome of Spinal Hematoma

Spinal hematoma, defined as symptomatic bleeding within the spinal neuraxis, is a rare and potentially catastrophic complication of spinal or epidural anesthesia. The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with central neural blockade is unknown. In an extensive review of the literature, Tryba⁴⁰ identified 13 cases of spinal hematoma following 850,000 epidural anesthetics and 7 cases among 650,000 spinal techniques. Based on these observations, the calculated incidence is approximated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics.⁴¹ However, the series involved in these calculations involved patients who were not receiving thromboprophylaxis. Recent case series and epidemiologic surveys suggest that the risk has increased.^{2,42,43} In addition, without a mandatory reporting system and/or centralized registry, it is likely that many spinal hematomas remain unreported, and the frequency is higher than calculated.

Hemorrhage into the spinal canal most commonly occurs in the epidural space, likely because of the prominent epidural venous plexus, although anesthetic variables, such as needle size and catheter placement, may also affect the site of clinically significant bleeding.^{44,45} In a review of the literature from 1906 through 1994, Vandermeulen et al⁴³ reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia; 60% of cases occurred in the last decade of the study period. In 42 (68%) of the 61 patients, the spinal hematomas associated with central neural

TABLE 4. Perioperative Management of Patients on Antiplatelet Therapy

Patients with coronary stents

- Elective surgery postponed for the following durations if aspirin and thienopyridine (eg, clopidogrel or prasugrel) therapy must be discontinued
 - Bare metal stents: 6 wk
 - Drug-eluting stents: 6 mo
- If surgery cannot be postponed, continue dual antiplatelet therapy throughout perioperative period

Patients at high risk of cardiac events (exclusive of coronary stents)

- Continue aspirin throughout the perioperative period
- Discontinue clopidogrel/prasugrel 5 d prior to surgery
- Resume thienopyridine 24 h postoperatively

Patients at low risk of cardiac events

- Discontinue dual antiplatelet therapy 7–10 d prior to surgery
- Resume antiplatelet therapy 24 h postoperatively

Recommendations from Douketis et al.³⁶

blockade occurred in patients with evidence of hemostatic abnormality. Twenty-five of the patients had received intravenous (IV) or subcutaneous (SC) (unfractionated or low molecular weight) heparin, whereas an additional 5 patients were presumably administered heparin as they were undergoing a vascular surgical procedure. In addition, 12 patients had evidence of coagulopathy or thrombocytopenia or were treated with antiplatelet medications (aspirin, indomethacin, ticlopidine), oral anticoagulants (phenprocoumon), thrombolytics (urokinase), or dextran 70 immediately before or after the spinal or epidural anesthetic. Needle and catheter placement was reported to be difficult in 15 (25%) or bloody in 15 (25%) patients. Overall, in 53 (87%) of the 61 cases, either a clotting abnormality or needle placement difficulty was present. A spinal anesthetic was performed in 15 patients. The remaining 46 patients received an epidural anesthetic, including 32 patients with an indwelling catheter. In 15 of these 32 patients, the spinal hematoma occurred immediately after the removal of the epidural catheter. Nine of these catheters were removed during therapeutic levels of heparinization. Neurologic compromise presented as progression of sensory or motor block (68% of patients) or bowel/bladder dysfunction (8% of patients), not severe radicular back pain. Importantly, although only 38% of patients had partial or good neurologic recovery, spinal cord ischemia tended to be reversible in patients who underwent laminectomy within 8 hours of onset of neurologic dysfunction⁴³ (Table 5).

The need for prompt diagnosis and intervention in the event of a spinal hematoma was also demonstrated in 2 reviews of the American Society of Anesthesiologists (ASA) Closed Claims database involving claims related to nerve injury.^{46,47} Cheney et al⁴⁶ examined the claims of nerve injury associated with general or regional block between 1990 and 1999 and noted that spinal cord injuries were the leading cause of claims in the 1990s. Furthermore, spinal hematomas accounted for nearly half of the spinal cord injuries. Patient care was rarely judged to have met standards because of delay in the diagnosis and resultant poor outcome. Consequently, the median payment was very high.⁴⁶ An in-depth analysis of the claims related to nerve injury following regional anesthesia between 1980 and 1999 reported 36 spinal hematomas, associated mainly with vascular or orthopedic surgical procedures. Three-fourths of patients had evidence of a preexisting or iatrogenic coagulation abnormality.⁴⁷ More than half of the patients received IV heparin during a vascular surgical or diagnostic procedure, often in combination with other medications that impair coagulation. Consistent with Vandermeulen et al,⁴³ the presenting symptom was increased motor block (83% of cases), rather than back pain (25% of cases). Importantly, the presence of postoperative numbness or weakness was typically attributed

to local anesthetic effect rather than spinal cord ischemia, which delayed the diagnosis. Although the symptoms were noted typically on postoperative day 1 (POD1), often 24 hours or more elapsed prior to diagnosis.⁴⁷ There were permanent deficits in 90% of patients.

It is impossible to conclusively determine the risk factors for the development of spinal hematoma in patients undergoing neuraxial blockade solely through review of the case series, which represent only patients with the complication and do not define those who underwent uneventful neuraxial analgesia. However, large inclusive surveys that evaluate the frequencies of complications (including spinal hematoma), as well as identify subgroups of patients with higher or lower risk, enhance risk stratification. Moen et al⁴² investigated serious neurologic complications among 1,260,000 spinal and 450,000 epidural blocks performed in Sweden over a 10-year period. Twenty-four of the 33 spinal hematomas occurred in the last 5 years of the decade surveyed. Among the 33 spinal hematomas, 24 occurred in females; 25 were associated with an epidural technique. A coagulopathy (existing or acquired) was present in 11 patients; 2 of these patients were parturients with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Pathology of the spine was present in 6 patients. The presenting complaint was typically lower-extremity weakness. Only 5 of 33 patients recovered neurologically (because of delay in the diagnosis/intervention). These demographics, risk factors, and outcomes confirm those of previous series. However, the methodology allowed for calculation of frequency of spinal hematoma among patient populations. For example, the risk associated with epidural analgesia in women undergoing childbirth was significantly less (1 in 200,000) than that in elderly women undergoing knee arthroplasty (1 in 3600, $P < 0.0001$). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (1 in 22,000) compared with all patients undergoing spinal anesthesia (1 in 480,000). A more recent review by Ehrenfeld et al⁴⁸ involving 43,000 orthopedic patients undergoing epidural blockade reported a similar frequency, 1.38/10,000 (95% confidence interval, 0–0.002).

Overall, these series suggest that the risk of clinically significant bleeding varies with age, associated abnormalities of the spinal cord or vertebral column, the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation (particularly with standard heparin or LMWH), perhaps in an additive versus synergistic multifactorial manner. They also consistently demonstrate the need for prompt diagnosis and intervention.

Fibrinolytic and Thrombolytic Therapy

Pharmacology of Fibrinolytics/Thrombolytics

The fibrinolytic system dissolves intravascular clots as a result of the action of plasmin. Plasmin is produced by the cleavage of a single peptide bond of the inactive precursor, plasminogen. The resulting compound is a nonspecific protease capable of dissolving fibrin clots and other plasma proteins, including several coagulation factors. Exogenous plasminogen activators such as streptokinase and urokinase not only dissolve thrombus but also affect circulating plasminogen. Endogenous t-PA formulations (alteplase, tenecteplase) are more fibrin-selective and have less effect on circulating plasminogen. Clot lysis leads to elevation of fibrin degradation products, which themselves have an anticoagulant effect by inhibiting platelet aggregation. Patients who receive fibrinolytic therapy frequently receive IV heparin to maintain an activated partial thromboplastin time (aPTT) of 1.5 to 2 times normal and often an antiplatelet agent such as aspirin or clopidogrel. While the plasma half-life of thrombolytic drugs is only hours, it

TABLE 5. Neurologic Outcome in Patients With Spinal Hematoma Following Neuraxial Blockade*

Interval Between Onset of Paraplegia and Surgery	Good (n = 15)	Partial (n = 11)	Poor (n = 29)
<8 h (n = 13)	6	4	3
Between 8 and 24 h (n = 7)	1	2	4
>24 h (n = 12)	2	0	10
No surgical intervention (n = 13)	4	1	8
Unknown (n = 10)	2	4	4

*Neurologic outcome was reported for 55 of 61 cases of spinal hematoma following neuraxial blockade.

Adapted from Vandermeulen et al,⁴³ with permission.

may take days for the thrombolytic effect to resolve; fibrinogen and plasminogen are maximally depressed at 5 hours after thrombolytic therapy and remain significantly depressed at 27 hours (Fig. 1). The decrease in coagulation factor levels is greater with streptokinase compared with t-PA therapy. However, the frequency of hemorrhagic events is similar.⁵⁰ Importantly, original contraindications to thrombolytic therapy included surgery or puncture of noncompressible vessels within 10 days.⁵¹

Case Reports of Spontaneous and Regional Anesthesia-Related Spinal Hematomas Related to Thrombolytic Therapy

There are no large series addressing regional anesthesia in the patient receiving fibrinolytic/thrombolytic therapy. The majority of published reports involve spontaneous spinal or epidural hematomas after thrombolytic therapy.^{52–68} Recent cases involve thrombolysis for myocardial infarction. Bleeding has been reported at all spinal levels—cervical, thoracic, and lumbar.

To date, there are 6 cases of spinal hematoma involving the concomitant use of neuraxial anesthesia and fibrinolytic/thrombolytic therapy. Five cases appeared in the literature^{69–73}; 1 additional case was reported through the MedWatch system. (The MedWatch program was initiated in 1993. Reporting of serious adverse events by health care professionals and hospitals is voluntary. Confidentiality is maintained. However, manufacturers and distributors of FDA-approved pharmaceuticals have mandatory reporting requirements. The FDA estimates that less than 1% of serious adverse drug reactions are reported.) Two of the spinal hematomas (including the MedWatch case) occurred in patients who underwent a neuraxial technique (epidural anesthesia for lithotripsy, epidural steroid injection [ESI]) and subsequently complained of myocardial ischemia and were treated with a thrombolytic.^{7,69} The potential for significant spinal bleeding was not appreciated by the interventional cardiologists, despite recent neuraxial needle placement in these 2 patients.

2.0 Anesthetic Management of the Patient Receiving Thrombolytic Therapy

Patients receiving fibrinolytic/thrombolytic medications are at risk of serious hemorrhagic events, particularly those who have undergone an invasive procedure. Recommendations are based on the profound effect on hemostasis, the use of concomitant heparin and/or antiplatelet agents (which further increase the risk of bleeding), and the potential for spontaneous neuraxial bleeding with these medications.

2.1 In patients scheduled to receive thrombolytic therapy, we recommend that the patient be queried and medical record reviewed for a recent history of lumbar puncture, spinal or epidural anesthesia, or ESI to allow appropriate monitoring. Guidelines detailing original contraindications to thrombolytic drugs suggest avoidance of these drugs for 10 days following puncture of noncompressible vessels (grade 1A).

Remarks: There is no change in this recommendation.

2.2 In patients who have received fibrinolytic and thrombolytic drugs, we recommend against performance of spinal or epidural anesthetics except in highly unusual circumstances (grade 1A).

Remarks: There is no change in this recommendation.

2.3 Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs. However, a 48-hour time interval and documentation of normalization of clotting studies (including fibrinogen) are suggested (grade 2C).

Remarks: There is no change in this recommendation.

2.4 In those patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy, we recommend that neurological monitoring should be continued for an appropriate interval. It may be that the interval of monitoring should not be more than 2 hours between neurologic checks. If neuraxial blocks have been combined with fibrinolytic and thrombolytic therapy and ongoing epidural catheter infusion, we recommend the infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurologic function (grade 1C).

Remarks: There is no change in this recommendation.

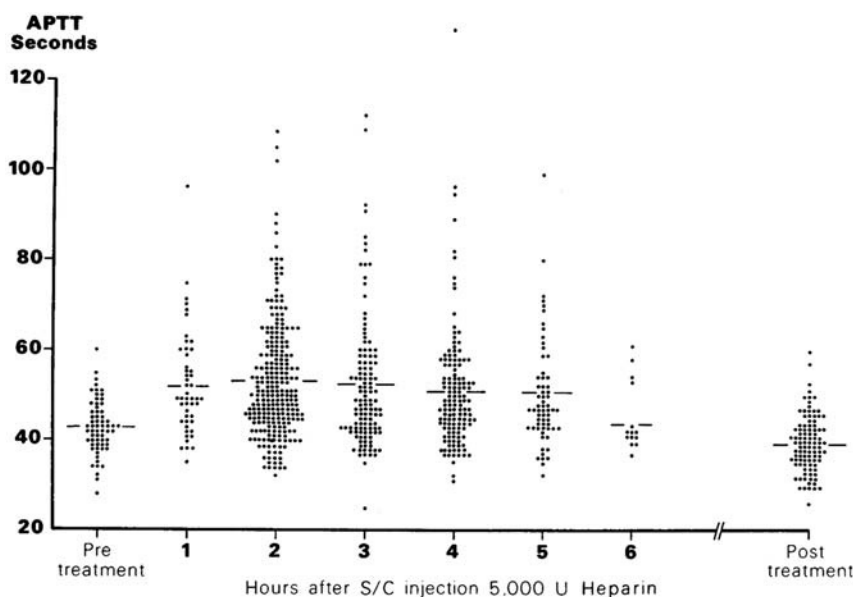


FIGURE 1. Activated partial thromboplastin time before treatment, 1 to 6 hours after SC injection of 5000 U of heparin, and after prophylactic heparin treatment of surgical patients. The horizontal bars show the mean values. The aPTT was significantly prolonged for 1 to 5 hours after injection of heparin. Adapted from Gallus et al,⁴⁹ with permission.

2.5 There is no definitive recommendation for removal of neuraxial catheters in patients who unexpectedly receive fibrinolytic and thrombolytic therapy during a neuraxial catheter infusion. We suggest the measurement of fibrinogen level (one of the last clotting factors to recover) to evaluate the presence of residual thrombolytic effect and appropriate timing of catheter removal (grade 2C).

Remarks: There is no change in this recommendation.

Intravenous and Subcutaneous Unfractionated Heparin

Pharmacology of Unfractionated Heparin

The major anticoagulant effect of heparin is due to a unique pentasaccharide that binds to antithrombin with high affinity and is present in approximately one-third of heparin molecules. Binding of this heparin pentasaccharide to antithrombin accelerates its ability to inactivate thrombin (factor IIa), factor Xa, and factor IXa. Anticoagulant activities of UFH depend on both the number of heparin molecules with the pentasaccharide chain and the size of the molecules containing the pentasaccharide sequence. Larger-molecular-weight heparins will catalyze inhibition of both factors IIa and Xa. Smaller-molecular-weight heparins will catalyze inhibition of only factor Xa.^{74,75} Intravenous injection results in immediate anticoagulant activity, whereas SC injection results in a 1- to 2-hour delay. The anticoagulant effect of heparin is both dose and molecular size dependent and is not linear, but increases disproportionately with increasing doses. For example, the biologic half-life of heparin increases from 30 minutes after 25 U/kg IV, to 60 minutes with 100 U/kg IV, and to 150 minutes with a bolus of 400 U/kg IV.^{75,76} When the SC route is selected for delivery of therapeutic anticoagulation, the dose of heparin is higher than the IV route to compensate for the reduced bioavailability associated with SC administration.

When given in therapeutic doses, the anticoagulant effect of heparin is typically monitored with the aPTT. However, this test does not directly measure heparin and is affected by physiologic and analytic variables. Anti-factor Xa testing offers improvements over aPTT testing for accurate measurement of heparin levels. Clinical data from the last 10 to 20 years suggest that anti-factor Xa monitoring may offer a smoother dose-response curve and require fewer blood samples and dosage adjustments.⁷⁷ The activated clotting time (ACT) is typically used to monitor higher doses given during cardiopulmonary bypass. Adequate therapeutic effect (in patients with VTE or unstable angina) is achieved

with a prolongation of the aPTT to between 1.5 and 2.5 times the baseline value,⁷⁴ heparin level of 0.2 to 0.4 U/mL, or anti-factor Xa level of 0.3 to 0.7 U/mL.⁷⁸ Administration of low-dose (5000 U) SC heparin for prophylaxis of deep venous thrombosis does not significantly prolong the aPTT in the majority of patients and is typically not monitored. However, it can result in unpredictable (10-fold variability) and therapeutic blood concentrations of heparin in some patients within 2 hours after administration.⁴⁹

One of the advantages of heparin anticoagulation is that its effect may be rapidly reversed with protamine. Each milligram of protamine can neutralize 100 U of heparin. Neutralization of subcutaneously administered heparin may require a prolonged infusion of protamine because of the continued absorption.⁷⁴ Finally, following administration of heparin for more than 5 days, there is a subset of patients who will develop a decrease in the platelet count.⁷⁶

Risk Factors for Spinal Hematoma in the Heparinized Patient Undergoing Neuraxial Blockade

The combination of spinal or epidural needle insertion in the presence of sustained therapeutic anticoagulation with heparin is associated with increased risk. Much of our information about this association comes from a report of 342 patients who deliberately received systemic therapeutic heparin after lumbar puncture.⁷⁹ Three factors associated with increased risk were identified: less than 60-minute time interval between the administration of heparin and lumbar puncture, traumatic needle placement, and concomitant use of other anticoagulants (aspirin). These risk factors have been verified in subsequent large reviews of case reports of hematomas associated with neuraxial procedures in the presence of UFH^{45,80,81} (Table 6).

Intravenous Unfractionated Heparin

Intraoperative heparinization typically involves injection of 5000 to 10,000 U of heparin intravenously during the operative period, particularly in the setting of vascular surgery to prevent coagulation during cross-clamping of arterial vessels.⁷⁵ Neuraxial anesthetic techniques are often attractive for these patients, but may be associated with an increased risk of epidural hematoma, as demonstrated by case series, epidemiologic surveys, and the ASA Closed Claims database.^{42,43,82,83} Maintaining a 1-hour interval between needle placement and heparinization, as well as avoidance of other hemostasis-altering medications, decreases the risk of significant bleeding.

TABLE 6. Risk Factors and Estimated Incidence for Spinal Hematoma and Neuraxial Anesthesia

	Relative Risk of Spinal Hematoma	Estimated Incidence for Epidural Anesthesia	Estimated Incidence for Spinal Anesthesia
No heparin			
Atraumatic	1.00	1:220,000	1:320,000
Traumatic	11.2	1:20,000	1:29,000
With aspirin	2.54	1:150,000	1:220,000
Heparin anticoagulation following neuraxial procedure			
Atraumatic	3.16	1:70,000	1:100,000
Traumatic	112	1:2000	1:2900
Heparin >1 h after puncture	2.18	1:100,000	1:150,000
Heparin <1 h after puncture	25.2	1:8700	1:13,000
With aspirin	26	1:8500	1:12,000

Data from Stafford-Smith,⁴⁵ with permission.

Management of a traumatic neuraxial procedure must also be considered. Previous case reports suggest that presence of a bloody tap or a traumatic regional block is an associated factor in approximately 50% of spinal hematomas.⁴³ Although some investigators have recommended cancellation of the surgical procedures should these events occur,⁸⁰ there are no clinical data to support this recommendation.^{67,84} Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case are warranted.

Heparinization may be continued into or initiated in the post-operative period. However, the removal of a neuraxial catheter in the presence of heparin therapy increases the risk of hematoma formation. In the series by Vandermeulen et al,⁴³ half of the spinal hematomas associated with systemic heparinization were detected at the time of catheter removal. The risk of hematoma resulting from catheter removal has led to the recommendation that, in patients who have undergone systemic heparinization, heparin should be discontinued for 2 to 4 hours, and the coagulation status assessed prior to neuraxial catheter manipulation or removal.

Heparinization During Cardiopulmonary Bypass

Since the publication of the initial ASRA guidelines in 1998,⁴ there have been continued discussions regarding the relative risk (and benefit) of neuraxial anesthesia and analgesia in the patient undergoing heparinization for cardiopulmonary bypass.^{85–89} Unfortunately, although there is improved analgesia, pulmonary function, and cardiac arrhythmia, there is no reduction in hospital stay, myocardial infarction, or mortality. To date, there is a single case of spinal hematoma following the full heparinization associated with cardiopulmonary bypass.⁹⁰ However, these series involve small numbers of patients. Using a mathematical analysis of the probability of predicting a rare event (based on the totals of 4583 epidural and 10,840 spinal anesthetics reported without complications), Ho et al⁹¹ estimated the risk of hematoma to be approximately 1:1528 for epidural and 1:3610 for spinal technique. Thus, this analgesic technique remains controversial in that the risk appears too great for the perceived benefits. A review has recommended certain precautions to be taken to minimize the risk⁸²:

- (1) Neuraxial blocks should be avoided in a patient with known coagulopathy from any cause.
- (2) Surgery should be delayed 24 hours in the event of a traumatic tap.
- (3) Time from instrumentation to systemic heparinization should exceed 60 minutes.
- (4) Heparin effect and reversal should be tightly controlled (smallest amount of heparin for the shortest duration compatible with therapeutic objectives).
- (5) Epidural catheters should be removed when normal coagulation is restored, and patients should be closely monitored postoperatively for signs and symptoms of hematoma formation.

Subcutaneous Unfractionated Heparin

Low-dose SC UFH is commonly used for prophylaxis against development of VTE in general and urologic surgery.⁹² Administration of 5000 U of heparin subcutaneously twice daily (BID) or thrice daily (TID) has been used extensively and effectively for prophylaxis against deep venous thrombosis. There is often no detectable change in the clotting parameters, as measured by the aPTT, anti-factor Xa level, or heparin level. However, there is a minority of patients, perhaps up to 15%, who may develop measurable changes in coagulation, although the aPTT rarely exceeds 1.5 times the normal level and normalizes within 4 to 6 hours

after administration.⁴⁹ There is a smaller subset (2%–4%) of patients who may become therapeutically anticoagulated during SC heparin therapy.

The widespread use of SC heparin and paucity of complications suggests that there is little risk of spinal hematoma associated with this therapy. There are 9 published series totaling more than 9000 patients who have received this therapy without complications.⁴ Two recent series, with a combined total of more than 4000 patients who received epidural analgesia in the presence of TID 5000 U heparin, reported no spinal hematomas.^{93,94} There are only 4 case reports of neuraxial hematomas, 3 epidural⁴³ and 1 spinal,⁹⁵ during neuraxial block with the use of SC heparin.

The safety of higher-dose SC UFH (doses >5000 U or total daily dose >15,000 U) remains controversial because of the marked variability in patient response to these dosing regimens. Specifically, because the anticoagulant effect of heparin is nonlinear and increases disproportionately with increasing doses, administration of more than 5000 U will increase the intensity and duration of the anticoagulant effect.⁷⁵ For example, in 1 study involving obstetric patients, 6 of 11 women receiving therapeutic SC UFH still had an elevated aPTT 12 hours after their last dose.¹⁰ Timing of assessment of coagulation status for residual heparin effect is based on dose and frequency of dosing. For example, for individual heparin dose of 7500 to 10,000 U BID or a daily dose of 20,000 U or less, it is suggested neuraxial block occur 12 hours after SC heparin administration and assessment of coagulation status. Likewise, for therapeutic UFH (eg, individual dose >10,000 U SC per dose or >20,000-U total daily dose), it is suggested neuraxial block occur 24 hours after SC heparin administration and assessment of coagulation status.

The updated ASRA recommendations on unfractionated SC heparin differ significantly from the previous guidelines. Specifically, the 2010 statements suggested the following:

In patients receiving prophylaxis with SC UFH with dosing regimens of 5000 U BID, there is no contraindication to the use of neuraxial techniques. The risk of neuraxial bleeding may be reduced by delay of the heparin injection until after the block and may be increased in debilitated patients after prolonged therapy. In patients receiving doses greater than 10,000 U of UFH daily or more than BID dosing of UFH, we suggest that neuraxial block be avoided (grade 2C).

The new guidelines allow for 5000 U TID but also suggest that the timing of needle placement and catheter removal—regardless of BID or TID dosing—coincide with lower levels of anticoagulant activity. These updated recommendations are not the result of additional case reports of spinal hematoma in this patient population but are consistent with recent trends/concepts of perioperative thromboprophylaxis, which recommend dosing regimens that minimize residual anticoagulant at the time of surgery as well as allow for a delay in initiation of postoperative thromboprophylaxis until hemostasis is ensured.^{10,28,29,36} These recommendations are based on the pharmacology of SC 5000-U dose of UFH, which results in an anticoagulant effect 1 hour after administration that persists 4 to 6 hours,^{76,96} hence the 4- to 6-hour delay after administration for needle placement. Finally, these recommendations are consistent with those of the ESA,⁸ (as well as British⁹⁷ and German guidelines,²⁵ which permit an international set of guidelines) (Table 7).

3.0 Anesthetic Management of the Patient Receiving Unfractionated Heparin

Anesthetic management of the heparinized patient was established more than 2 decades ago. Initial recommendations

TABLE 7. European Society of Anaesthesiology's Recommended Time Intervals Before and After Neuraxial Puncture or Catheter Removal*

	Time Before Puncture/Catheter Manipulation or Removal	Time After Puncture/Catheter Manipulation or Removal	Laboratory Tests
UFHs (for prophylaxis, $\leq 15,000$ IU/d)	4–6 h	1 h	Platelets during treatment for >5 d
UFHs (for treatment)	IV 4–6 h SC 8–12 h	1 h 1 h	aPTT, ACT, platelets
LMWHs (for prophylaxis)	12 h	4 h	Platelets during treatment for >5 d
LMWHs (for treatment)	24 h	4 h	Platelets during treatment for >5 d
Fondaparinux (for prophylaxis, 2.5 mg/d)	36–42 h	6–12 h	(Anti-factor Xa, standardized for specific agent)
Rivaroxaban (for prophylaxis, 10 mg daily)	22–26 h	4–6 h	(Anti-factor Xa, standardized for specific agent)
Apixaban (for prophylaxis, 2.5 mg BID)	26–30 h	4–6 h	(Anti-factor Xa, standardized for specific agent)
Dabigatran (for prophylaxis, 150–220 mg)	Contraindicated according to the manufacturer	6 h	TT
Coumarins	INR ≤ 1.4	After catheter removal	INR
Hirudins (desirudin)	8–10 h	2–4 h	aPTT, ECT
Argatroban	4 h	2 h	aPTT, ECT, ACT
Acetylsalicylic acid	None	None	
Clopidogrel	7 d	After catheter removal	
Ticlopidine	10 d	After catheter removal	
Prasugrel	7–10 d	6 h after catheter removal	
Ticagrelor	5 d	6 h after catheter removal	
Cilostazol	42 h	5 h after catheter removal	
NSAIDs	None	None	

*All time intervals refer to patients with normal renal function. Prolonged time interval in patients with hepatic insufficiency.

Adapted from Gogarten et al,⁸ with permission.

have been supported by in-depth reviews of case series, case reports of spinal hematoma, and the ASA Closed Claims Project.

3.1 We recommend daily review of the patient's medical record to determine the concurrent use of medications that affect other components of the clotting mechanisms. These medications include antiplatelet medications, LMWH, and oral anticoagulants (grade 1B).

Remarks: There is no change in this recommendation.

3.2 Since heparin-induced thrombocytopenia may occur during heparin administration, we recommend that patients receiving IV or SC UFH for more than 4 days have a platelet count assessed prior to neuraxial block or catheter removal (grade 1C).

Remarks: There is no change in this recommendation.

3.3 Intravenous heparin

3.3.1 Discontinue heparin infusion 4 to 6 hours and verify normal coagulation status prior to neuraxial blockade (grade 1A).

Remarks: There is no change in this recommendation.

3.3.2 Avoid neuraxial techniques in patients with other coagulopathies (grade 1A).

Remarks: There is no change in this recommendation.

3.3.3 Delay heparin administration for 1 hour after needle placement (grade 1A).

Remarks: There is no change in this recommendation.

3.3.4 Remove indwelling neuraxial catheters 4 to 6 hours after the last heparin dose (and after assessment of the patient's coagulation status); reheparinize 1 hour after catheter removal (grade 1A).

Remarks: There is no change in this recommendation.

3.3.5 Monitor the patient postoperatively to provide early detection of motor blockade and consider use of minimal concentration of local anesthetics to enhance the early detection of a spinal hematoma (grade 1A).

Remarks: There is no change in this recommendation.

3.3.6 Although the occurrence of a bloody or difficult neuraxial needle placement may increase risk, there are no data to support mandatory cancellation of a case. Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case are warranted (grade 1A).

Remarks: There is no change in this recommendation.

3.3.6 Currently, insufficient data and experience are available to determine if the risk of neuraxial hematoma is increased when combining neuraxial techniques with the full anticoagulation of cardiac surgery. We suggest postoperative monitoring of neurologic function and selection of neuraxial solutions that minimize sensory and motor block to facilitate detection of new/progressive neurodeficits (grade 2C).

Remarks: There is no change in this recommendation.

3.4 Subcutaneous heparin

3.4.1 Preoperative low-dose UFH for thromboprophylaxis.

We suggest, in patients receiving SC low-dose UFH with dosing regimens of 5000 U BID or TID, neuraxial block occur 4 to 6 hours after heparin administration, or coagulation status be assessed (grade 2C).

Remarks: There is no change in this recommendation.

3.4.2 Preoperative “higher-dose” UFH for thromboprophylaxis (eg, individual heparin dose of 7500–10,000 U BID or a daily dose of ≤20,000 U). We suggest neuraxial block occur 12 hours after SC heparin administration and assessment of coagulation status (grade 2C).

Remarks: This is a new recommendation that addresses the higher-dose UFH thromboprophylaxis in the pregnant patient.

3.4.3 Preoperative therapeutic UFH (eg, individual dose >10,000 U SC per dose or >20,000-U total daily dose). We suggest neuraxial block occur 24 hours after SC heparin administration and assessment of coagulation status (grade 2C).

Remarks: This is a new recommendation that addresses the higher-dose UFH therapeutic anticoagulation in the pregnant patient.

3.4.4 Postoperative low-dose UFH. There is no contraindication to maintaining neuraxial catheters in the presence of low-dose UFH. We suggest catheter removal occur 4 to 6 hours after heparin administration. Subsequent heparin administration may occur 1 hour after catheter removal (grade 2C).

Remarks: There is no change in this recommendation.

3.4.5 Postoperative “higher-dose” UFH. The safety of indwelling neuraxial catheters in patients receiving doses greater than 5000 U or greater than 15,000 U of UFH daily has not been established. We suggest that the risk and benefits be assessed on an individual basis and that techniques to facilitate detection of new/progressive neurodeficits (eg, enhanced neurologic monitoring occur and neuraxial solutions to minimize sensory and motor block) be applied (grade 2C).

Remarks: There is no change in this recommendation.

Low-Molecular-Weight Heparin

Pharmacology, Monitoring, and Reversal of the Anticoagulant Effect of LMWH

Low-molecular-weight heparins are used for both prophylaxis and treatment of arterial and VTE. The biochemical and pharmacologic properties of LMWH differ from those of UFH.^{74,98–101} Most relevant are the prolonged half-life and irreversibility with protamine. Anti-factor Xa levels peak 3 to 5 hours after administration. The elimination half-life of LMWH is 3 to 6 hours after SC injection in patients with normal renal function and is dose independent. In patients with severe renal insufficiency, the anticoagulant effect is exaggerated, and the elimination half-life may be prolonged up to 16 hours.⁹⁸ Prolonged LMWH therapy may be associated with an accumulation of anti-factor Xa activity and fibrinolysis.¹⁰²

The anticoagulant effect of LMWH is most readily assessed by the anti-factor Xa activity. However, the anti-factor Xa activity is typically not monitored except with high-dose (therapeutic) applications. Anti-factor Xa activity may be assessed prior to neuraxial blockade. Importantly, the clinical significance of the residual anti-factor Xa effect is unknown. For example, while targeted levels have been established for therapeutic anticoagulation, the level of residual anti-factor Xa acceptable for “safe” performance of neuraxial block remains undetermined.⁹⁸

While the anticoagulant effects of standard heparin are neutralized by an equimolar dose of protamine, because of reduced protamine binding to LMWH fractions, only the anti-factor IIa

activity of LMWH is completely reversed, whereas anti-factor Xa activity is not fully neutralized. Both anti-factor IIa and anti-factor Xa activity may return up to 3 hours after protamine reversal.

Low-molecular-weight heparins vary both biochemically and pharmacologically, including molecular weight, anti-factor IIa and anti-factor Xa activities, and plasma half-life. However, there are no adequate trials comparing the efficacy and safety of 1 LMWH to another, and it is not possible to recommend 1 specific LMWH over another.⁷⁴ Experience in Europe suggests that the rate of spinal hematoma is similar among LMWH preparations.¹⁰³

Spinal and Epidural Anesthesia in the Patient Receiving LMWH

In 1993, enoxaparin was the first LMWH to be introduced for general use in the United States. Labeled indications included thromboprophylaxis after major joint replacement. The initial dose scheduling was 30 mg every 12 hours, with the first dose administered as soon as possible after surgery. In the first 5 years, more than 40 spinal hematomas were reported through the MedWatch system.² The risk of spinal hematoma was estimated to be approximately 1 in 3000 continuous epidural anesthetics compared with 1 in 40,000 spinal anesthetics.¹⁰⁴ However, this was likely an underestimation; in addition to the spinal hematomas reported at the time of the first ASRA consensus conference, there were approximately 20 that had occurred but were not yet reported to the MedWatch system. The frequency was attributed to BID dosing (compared with once-daily dosing as administered in Europe) in the presence of an indwelling neuraxial catheter. However, 20 years later in Sweden, Moen et al⁴² reported a 1:3600 frequency of spinal hematomas among women undergoing total knee replacement (with once-daily LMWH), which is strikingly similar to the frequency associated with BID administered LMWH calculated by Horlocker and Wedel.²

Risk Factors for Spinal Hematomas With LMWH Thromboprophylaxis

Based on an examination of the published cases, MedWatch reports, and clinical experience in Europe and North America, specific risk factors have been proposed.^{2,3,42} It is not possible to stratify the individual risk factors or determine interactions between risk factors. In summary, age and sex appear to be significant patient factors, perhaps through vertebral canal compromise (smaller volume need to produce critical ischemic pressure) and/or drug effect (exaggerated response to LMWH, renal insufficiency). Finally, the additive, if not synergistic, effect of multiple hemostasis-altering medications cannot be overstated and may elevate the risk of once-daily LMWH to that of BID dosing.⁴²

On November 6, 2013, the FDA released a Drug Safety Communication regarding updated recommendations to decrease the risk of neuraxial bleeding and paralysis in patients on LMWHs¹⁹ (Table 8). The recommendations were based on a series of 100 confirmed spinal hematomas occurring between July 20, 1992, and January 31, 2013, which were associated with enoxaparin thromboprophylaxis and neuraxial anesthesia. The case series were submitted to the FDA by the manufacturer of enoxaparin (Lovenox; Sanofi-Aventis, Paris, France). Importantly, the majority of these were included in the series of spinal hematomas reported in the 1998 and 2002 ASRA recommendations. Although all 100 spinal hematomas involved enoxaparin, the new timing recommendations will be added to the labels of all LMWHs. Specifically:

- For enoxaparin, placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of

TABLE 8. Patient, Anesthetic, and LMWH Risk Factors* Associated With Spinal Hematoma

	n
Patient factors	
Female sex	72
Elderly (≥ 65 y)	70
Abnormalities of spinal cord or vertebral column	20
Patients at increased risk of hemorrhage†	47
Renal insufficiency	7
Anesthetic factors	
Traumatic needle/catheter placement	26
Epidural technique	54
Indwelling epidural catheter during LMWH administration	36
LMWH dosing factors	
Immediate preoperative administration (<12 h)	5
Intraoperative administration	7
Early postoperative administration (<12 h)	17
Administration close to indwelling catheter removal (<12 h)	1
Twice-daily administration (vs once daily administration)	48
Higher LMWH dose than that in the label	1
Concomitant medications affecting hemostasis	43

*More than 1 risk factor may have been present in a single case.

Adapted from the FDA Drug Safety Communication.¹⁹

prophylactic doses such as those used for prevention of deep vein thrombosis (30 mg BID or 40 mg once daily). Longer delays (24 hours) are appropriate to consider for patients receiving higher therapeutic doses of enoxaparin (1 mg/kg BID or 1.5 mg/kg once daily).

- A postprocedure dose of enoxaparin should usually be given no sooner than 4 hours after catheter removal.
- In all cases, a benefit-risk assessment should consider both the risk of thrombosis and the risk of bleeding in the context of the procedure and patient risk factors.

The first and third statements are compatible with previous ASRA guidelines. Conversely, the second recommends a 4-hour time interval prior to administration of a postprocedure dose of LMWH (rather than the 2-hour time interval recommended by ASRA). Importantly, among the 100 confirmed spinal hematomas, none were associated with a 0- to 4-hour time interval between catheter removal and subsequent LMWH dosing (Table 8).¹⁹ As previously mentioned, it appears that the new recommendation is based on the recommendation of Rosencher et al,²⁰ who proposed subsequent dosing of antithrombotic therapy based on 8 hours minus the time it takes for the anticoagulant to reach peak effect (which is 4 hours for LMWH).

Therapeutic (Off-label) Applications

Bridging anticoagulation aims to minimize the risk of arterial thromboembolism, such as stroke and systemic embolism, in patients with a mechanical heart valve or atrial fibrillation and to minimize the risk of recurrent thrombosis in patients with prior VTE. During bridging, either standard or LMWH is administered during the 10- to 12-day period that warfarin is discontinued and the prothrombin time (PT) allowed to normalize (Table 3). Low-molecular-weight heparin has been demonstrated to be efficacious as a “bridge therapy” for these patients.^{74,105} High-dose (therapeutic-dose) LMWH bridging involves administering a dose

that is similar to that used for the treatment of acute VTE or an acute coronary syndrome, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily. It is advisable to maintain peak anti-factor Xa levels between 0.5 and 1 U/mL (measured 3–4 hours after the LMWH dose, with the assay calibrated to the specific LMWH administered). With these doses, it is critical that the last preoperative dose should occur at least 24 hours preoperatively.³⁶ A recent series of 19 patients therapeutically anticoagulated with enoxaparin preoperatively demonstrated the likelihood of residual anti-factor Xa activity, even if the 24-hour interval is maintained.¹⁰⁶ Eleven of 19 patients still had anti-factor Xa activity that would place them at or above the lower limit for the peak target therapeutic range for VTE prophylaxis. One of these patients had an anti-factor Xa level within the target therapeutic range for thrombosis treatment. All but 1 patient, whose sample was drawn at 23.25 hours, would have met the ASRA-recommended time-based guideline (a minimum of 24 hours from the last dose). Although the small number of patients makes it difficult to definitively identify risk factors that may increase the possibility of residual anti-factor Xa level activity, this series validates previously reported results that suggest that patients with lower creatinine clearance (CrCl) values and increased age may be at particular risk of an exaggerated and/or prolonged response and are at risk of bleeding complications (including spinal hematoma)^{2,107} (Table 8).

Both the FDA and ACCP recommend a reduction in the therapeutic dosing in patients who have severe renal disease (CrCl <30 mL/min).¹⁰⁸ However, recent reviews have suggested that a reduction in LMWH dose should be made even with CrCl between 30 and 50 mL/min because of the bleeding risk.¹⁰⁷ It is also interesting that many of the patients in the series by Henshaw et al,¹⁰⁶ for example, an 85-year-old, 53-kg woman with a calculated CrCl of 45 mL/min, received 60 mg BID. Her anti-factor Xa activity was 0.54 international unit (IU)/mL—still within treatment therapeutic peak target range of 0.5 to 0.8 IU/mL. Of note, there have been no spinal hematomas reported in patients who have undergone bridging therapy with subsequent neuraxial block. However, these recent data, combined with the increased availability of the anti-factor Xa assay, suggest that in patients who may be at risk of significant residual LMWH effect an assessment may be made prior to neuraxial block. It is also important to determine when the first postoperative dose is anticipated because these patients are often aggressively anticoagulated postoperatively. It is recommended that therapeutic-dose LMWH be resumed 24 hours after non-high-bleeding-risk surgery and 48 to 72 hours after high-bleeding-risk surgery.³⁶

4.0 Anesthetic Management of the Patient Receiving LMWH

North American recommendations have drawn on the extensive European experience in the development of practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. Previous consensus recommendations have appeared to decrease the risk. Concern remains for higher-dose applications, where sustained therapeutic levels of anticoagulation are present, as well as early postprocedural dosing.

4.1 The anti-factor Xa level is not predictive of the risk of bleeding, although it may be useful in monitoring efficacy of therapy with therapeutic (high dose) regimens. We recommend against the routine use of monitoring of the anti-factor Xa level. An acceptable level of residual anti-factor Xa level for performance of neuraxial block remains undetermined (grade 1A).

Remarks: The increased availability of anti-factor Xa activity level allows for preoperative assessment of residual anticoagulant effect in patients on higher-dose LMWH.

4.2 Antiplatelet or oral anticoagulant medications administered in combination with LMWH increase the risk of spinal hematoma. Education of the entire patient care team is necessary to avoid potentiation of the anticoagulant effects. We recommend against concomitant administration of medications affecting hemostasis, such as antiplatelet drugs, standard heparin, or dextran, regardless of LMWH dosing regimen when there is an indwelling neuraxial catheter (grade 1A).

Remarks: There is no change in this recommendation.

4.3 Since heparin-induced thrombocytopenia (HIT) may occur during LMWH administration, we recommend that patients receiving LMWH for greater than 4 days have a platelet count assessed prior to neuraxial block or catheter removal (grade 1C).

Remarks: There is no change in this recommendation.

4.4 The presence of blood during needle and catheter placement does not necessitate postponement of surgery. We suggest that initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively and that this consideration be discussed with the surgeon (grade 2C).

Remarks: There is no change in this recommendation.

4.5 Preoperative LMWH

4.5.1 We recommend that needle placement should occur at least 12 hours after a prophylactic LMWH dose (grade 1C).

Remarks: Previously recommended was a 10- to 12-hour range. This recommendation incorporates labeling changes made by the FDA.

4.5.2 In patients administered a dose of LMWH 2 hours preoperatively (general surgery patients), we recommend against neuraxial techniques because needle placement would occur close to peak anticoagulant activity (grade 1A).

Remarks: There is no change in this recommendation.

4.5.3 In patients receiving higher (therapeutic) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hours, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hours, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily, we recommend delay of at least 24 hours prior to needle/catheter placement (grade 1C). Consider checking anti-factor Xa activity level, particularly in elderly patients and patients with renal insufficiency. An acceptable level of residual anti-factor Xa activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: Residual anti-factor Xa activity may be present even after 24 hours. Assessment, especially in patients with moderate to severe renal insufficiency, may be considered.

4.6 Postoperative LMWH

4.6.1 Twice-daily prophylactic dosing. This dosage regimen is associated with an increased risk of spinal hematoma. We recommend the first dose of LMWH should be administered the following day and no earlier than 12 hours after needle/catheter placement, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed prior to initiation of LMWH thromboprophylaxis. Administration of LMWH should be delayed for 4 hours after catheter removal (grade 1C).

Remarks: Previously recommended was a first dose 24 hours after needle/catheter placement and a delay of LMWH dosing for only 2 hours after catheter removal. These recommendations incorporate labeling changes made by the FDA.

4.6.2 Single daily prophylactic dosing. We recommend the first postoperative LMWH dose should be administered at least 12 hours after needle/catheter placement. The second postoperative dose should occur no sooner than 24 hours after the first dose. Indwelling neuraxial catheters do not represent increased risk and may be maintained. However, no additional hemostasis altering medications should be administered

because of the additive effects. The catheter should be removed 12 hours after the last dose of LMWH. Subsequent LMWH dosing should occur at least 4 hours after catheter removal (grade 1C).

Remarks: Previously recommended was a 10- to 12-hour range for both needle/catheter placement and catheter removal. Subsequent LMWH was previously 2 hours after catheter removal. These recommendations incorporate labeling changes made by the FDA.

4.6.3 Single or BID therapeutic dosing. Therapeutic-dose LMWH may be resumed 24 hours after non-high-bleeding-risk surgery and 48 to 72 hours after high-bleeding-risk surgery. We recommend that indwelling neuraxial catheters be removed 4 hours prior to the first postoperative dose and at least 24 hours after needle/catheter placement, whichever is greater (grade 1C).

Remarks: There is no change in this recommendation.

Anti-Factor Xa Agents

Fondaparinux

Fondaparinux (Arixtra), an injectable synthetic pentasaccharide, was approved in December 2001. The FDA released fondaparinux with a black box warning similar to that of LMWHs and heparinoids. Fondaparinux produces its antithrombotic effect through factor Xa inhibition. The plasma half-life of fondaparinux is 21 hours, allowing for single-daily dosing, with the first dose administered 6 hours postoperatively.¹⁰⁹ Investigators reported a spinal hematoma among the initial dose-ranging study (at a dose that was subsequently determined to be twice that required for thromboprophylaxis).^{109,110} No additional spinal hematomas were reported in the combined series of 3600 patients who underwent spinal or epidural anesthesia in combination with fondaparinux thromboprophylaxis. However, the conditions for performance of neuraxial block were strictly controlled. Patients were included in subsequent clinical trials only if needle placement was atraumatic and accomplished on the first attempt. In addition, indwelling epidural catheters were removed 2 hours prior to fondaparinux administration. These strict parameters suggested that neuraxial blockade in patients with planned fondaparinux thromboprophylaxis may not be feasible in clinical practice. For example, in a prospective series, less than 40% of neuraxial blocks were successful with 1 pass.⁴⁴ A recent series of 1631 patients undergoing continuous neuraxial or deep peripheral block reported no serious hemorrhagic complications. However, the catheters were removed 36 hours after the last dose of fondaparinux, and subsequent dosing was delayed for 12 hours after catheter removal.¹¹¹ Although these results are reassuring, the deviation from the manufacturer's suggested dosing guidelines is of concern.

5.0 Anesthetic Management of the Patient Receiving Fondaparinux

5.1 Based on the sustained and irreversible antithrombotic effect, early postoperative dosing, and the spinal hematoma reported during initial clinical trials, we recommend that until further clinical experience is available performance of neuraxial techniques should occur under conditions used in clinical trials (single needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters). If this is not feasible, an alternate method of prophylaxis should be considered (grade 1C).

Remarks: There is no change in this recommendation.

5.2 We suggest that neuraxial catheters 6 hours be removed prior to the first (postoperative) dose (grade 2C).

Remarks: There is no change in this recommendation.

New (or Direct) Oral Anti-Factor Xa Agents

The new oral anti-factor Xa antiagents (rivaroxaban, apixaban, edoxaban, and betrixaban) are used in the primary prevention of VTE after elective total hip replacement surgery, the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAf), and the prevention and treatment of (recurrent) VTE and pulmonary embolism (PE)^{112–117} (Table 9). These drugs are at least as effective anticoagulants as the vitamin K antagonists but seem to be safer in terms of bleeding, have a rapid onset of action and a short half-life, and are devoid of the need for routine laboratory monitoring. Until recently, any specific antidotes were lacking.

Rivaroxaban

Rivaroxaban (Xarelto) is an oral inhibitor of the active site of factor Xa. It is used in the same indications as dabigatran and has an oral bioavailability and a plasma protein binding of 80% to 100% and 90%, respectively.¹²¹ Two to 4 hours after oral ingestion, maximum plasma levels will be reached. Approximately one-third of the drug is eliminated in an unchanged form through the kidney, whereas the remaining two-thirds will be metabolized by the liver and excreted in equal amounts by the kidney and the gut.^{121–123} The terminal elimination half-life is 5 to 9 hours in healthy patients but is prolonged to 11 to 13 hours in the elderly (rivaroxaban [full prescribing information], available at <https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf>, accessed March 4, 2017). In individuals with mild, moderate, and severe renal impairment, rivaroxaban exposure was increased 1.4-, 1.5-, and 1.6 fold, respectively.

Twenty milligrams BID is used in the prevention of systemic embolism in patients with NVAf and for the prevention of recurrent of VTE or PE, whereas 15 mg BID for 3 weeks followed by 20 mg once a day is advised for the treatment of VTE and PE. In the prevention of VTE, a dose of 10 mg once daily is started 6 to 10 hours after orthopedic surgery (rivaroxaban [full prescribing information], available at <https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf>, accessed March 4, 2017). The manufacturer does not recommend a dose adjustment in patients with a CrCl of greater than 30 mL/min. Rivaroxaban should be avoided when the CrCl is less than 30 mL/min, with the exception of patients with NVAf having a CrCl of 15 to 30 mL/min, where a dose reduction to 15 mg once daily applies. Rivaroxaban should also not be used in patients treated with cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors and in the presence of hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including Child-Pugh B and C cirrhotic patients.

Rivaroxaban prolongs the international normalized ratio (INR) in a dose-dependent way, but the results are not always reliable because of an important interassay variability dependent on the reagent used.¹²⁴ At best, the PT can give some qualitative information. The aPTT is even less sensitive, has a nonlinear dose-dependent prolongation and an important interassay variability, and is not suited to qualitatively and quantitatively assess the effects of rivaroxaban.¹²⁴ The best method to assess rivaroxaban is the use of chromogenic anti-factor Xa assays developed for the measurement of direct factor Xa inhibitors using specific rivaroxaban calibrators.¹²⁴

There are minimal clinical data on the use of neuraxial anesthesia in rivaroxaban-treated patients.²³ Product labeling states, “Epidural or spinal hematomas have occurred in patients treated with rivaroxaban who received neuraxial anesthesia or underwent spinal puncture” (rivaroxaban [full prescribing information], available at <https://www.xarelto-us.com/shared/product/xarelto/>

[prescribing-information.pdf](https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf), accessed March 4, 2017). However, no details regarding risk factors or frequency are reported. A review of the literature noted 7 neuraxial hematomas associated with rivaroxaban^{125–134} (Table 10). Three of the patients had undergone a neuraxial block. However, in 2 of the cases, an alternate agent of thromboprophylaxis was used immediately postoperatively, and the hematomas occurred after hospital discharge.^{126,127} In the remaining case, the epidural catheter was removed 18 hours after the first dose of rivaroxaban, a shorter time interval than the 26 hours (2 elimination half-lives as is recommended by the manufacturer in elderly patients (rivaroxaban [full prescribing information], available at <https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf>, accessed March 4, 2017).¹²⁵

If a neuraxial block is considered in patients treated with prophylactic rivaroxaban (≤ 10 mg/d), a time interval of 22 to 26 hours should be observed between the last dose of rivaroxaban and the subsequent neuraxial puncture and/or catheter manipulation/withdrawal. In the presence of a CrCl of less than 50 mL/min and/or when greater than 10 mg/d is used, this time interval should be extended to 44 to 65 hours. The absence of any remaining anticoagulant activity may be documented using a chromogenic anti-factor Xa assay calibrated for rivaroxaban. Importantly, although it appears “safe” to proceed with neuraxial block if zero anti-factor Xa activity is noted, the residual level acceptable for performance of neuraxial remains unknown. The first or next dose of rivaroxaban should be given only 6 hours after the neuraxial puncture or neuraxial catheter withdrawal.

Apixaban

Apixaban (Eliquis) is an oral highly selective reversible factor Xa inhibitor. The drug has an oral bioavailability of 51% to 85% and a plasma protein binding of approximately 87%.¹²¹ The maximum plasma concentration is reached 2 to 4 hours after oral intake. Approximately 27% of the clearance is renal; the remainder will undergo hepatic or biliary transformation prior to being eliminated via the gut.^{121,135} The terminal elimination half-life in healthy patients is 10 to 15 hours and is only marginally influenced by the renal function, with half-life increasing up to only 17.5 hours in the presence of moderate to severe renal insufficiency (apixaban [full prescribing information], available at http://packageinserts.bms.com/pi/pi_eliquis.pdf, accessed March 4, 2017).¹¹⁹ Apixaban should not be used in patients with a CrCl of less than 15 mL/min and in patients with Child-Pugh class B and C hepatic impairment. The concomitant use of strong inhibitors of CYP3A4 and P-gp should also be avoided and may be an indication for a 50% dose reduction of apixaban.

Apixaban is used in a dose of 5 mg BID in the prevention of stroke and systemic embolism in NVAf. This dose is reduced to 2.5 mg BID in patients with at least 2 of the following conditions: age 80 years or older, a serum creatinine 1.5 mg/dL or greater, or a body weight 60 kg or less. A dose reduction is not necessary in all of the other indications (apixaban [full prescribing information], available at http://packageinserts.bms.com/pi/pi_eliquis.pdf, accessed March 4, 2017). Following elective hip or knee replacement surgery, a dose of 2.5 mg BID is used and started 12 to 24 hours after surgery. In the treatment of VTE or PE, a starting dose of 10 mg BID is used for 7 days, followed by 5 mg BID. For the subsequent prevention of recurrent VTE and PE, a dose of 2.5 mg BID is recommended.

Both the PT and the aPTT are not suited to qualitatively and quantitatively assess the effects of apixaban.¹³⁶ These tests produce unreliable results because of a low sensitivity for apixaban and a large interassay variability dependent on the reagents used. The aPTT also displays a nonlinear dose-dependent prolongation.¹³⁶

TABLE 9. New (Direct) Oral Anti-Factor Xa Anticoagulants

	Betrixaban*	Rivaroxaban†	Apixaban‡	Edoxaban§
Indications and dosing	Prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk of thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE In patients with CrCl 15–30 mL/min: 80 mg QD, then 40 mg QD (United States) In patients with CrCl >30 mL/min: 160 mg every day (QD) first day, then 80 mg QD (United States)	Reduction of risk of stroke and systemic embolism in NVAE: In patients with CrCl >50 mL/min: 20 mg QD (European Union [EU], United States) In patients with CrCl 15–50 mL/min: 15 mg QD (EU, United States) Treatment of VTE, PE, and reduction in the risk of recurrent VTE and of PE: In patients with a CrCl >15 mL/min: 15 mg BID for the first 21 d of the initial treatment period, VTE or PE. After the initial treatment period, 20 mg QD for the remaining treatment and the long-term reduction in the risk of recurrence of VTE and of PE (EU, United States) In patients with a CrCl 15–50 mL/min and a high bleeding risk, consider 15 mg QD instead of 20 mg QD for the remaining treatment and the long-term reduction in the risk of recurrence of VTE and of PE (EU) Prophylaxis of VTE following THA or TKAs: 10 mg QD (EU, United States) Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (coadministered with acetylsalicylic acid [ASA]) alone or with ASA plus clopidogrel or ticlopidine): 2.5 mg BID (EU)	Reduction of risk of stroke and systemic embolism in NVAE: 5 mg BID In patients with at least 2 of the following characteristics: age ≥80 y; body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL; 2.5 mg BID (EU, United States) Treatment of VTE and PE: 10 mg BID for 7 d, followed by 5 mg BID (EU, United States) Reduction in the risk of recurrent VTE and PE following initial therapy: 2.5 mg BID (EU, United States) Prophylaxis of VTE following THA or TKAs: 2.5 mg BID (EU, United States)	Reduction of risk of stroke and systemic embolism in NVAE: In patients with CrCl 50–95 mL/min: 60 mg QD (EU, United States) Do not use in patients with CrCl >95 mL/min (United States) In patients with CrCl 15–50 mL/min: 30 mg QD (United States) In patients with ≥1 of the following clinical factors: CrCl 15–50 mL/min or body weight ≤60 kg, or the concomitant use of P-gp inhibitors: 30 mg QD (EU) Treatment of VTE and PE: 60 mg QD (EU, United States) In patients with ≥1 of the following clinical factors: CrCl 15–50 mL/min or body weight ≤60 kg, or the concomitant use of P-gp inhibitors: 30 mg QD (EU, United States) Reduction in the risk of recurrent VTE and PE following initial therapy: 60 mg QD (EU) In patients with CrCl 15–50 mL/min or body weight ≤60 kg, or the concomitant use of P-gp inhibitors: 30 mg QD (EU)
Renal clearance	59%–111% ^{12,113,118}	35%	27%	50%
CrCl, mL/min	≥90 37 h ^{114,115} No data 60–89 30–59 15–29 <15 (off-dialysis)	≥80 50–79 30–49 15–29 <15 (off-dialysis)	≥80 50–79 30–49 15–29 <15 (off-dialysis)	≥80 50–79 30–49 15–29 <15 (off-dialysis)
Elimination half-life, t _{1/2} , h	37 h ^{114,115} No data	5–9 (young), 11–13 (elderly) [†] 8.7 ^{116,117} 9.0 ^{116,117} 9.5 ^{116,117}	15.1 ¹¹⁹ 14.6 ¹¹⁹ 17.6 ¹¹⁹ 17.3 ¹¹⁹	10–14 [†] 8.4 ¹²⁰ 9.4 ¹²⁰ 16.9

*Betrixaban full prescribing information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383S0001b1.pdf, accessed November 15, 2017).

†Xarelto: Epar product information (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf, accessed December 22, 2015, 2011); rivaroxaban full prescribing information (<https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf>, accessed March 4, 2017).

‡Apixaban full prescribing information (http://packageinserts.bms.com/pi/pi_eliquis.pdf, accessed March 4, 2017); apixaban: Epar—product information (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf, accessed 22/12/2015, 2015); Savaysa

§Edoxaban: Epar—product information (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf, accessed 22/12/2015, 2015); Savaysa full prescribing information (<http://dsi.com/prescribing-information-portlet/getPIContent?productName=Savaysa&inline=true>, accessed March 4, 2017).

TABLE 10. Case Reports of Spinal Hematoma in Patients on New Oral Anticoagulants

Drug	History	Outcome	Comments
Dabigatran ¹²⁸	72 y, M, 150 mg BID dabigatran for AF; T2–T7 burst fracture after a fall, 3 h after last dose of dabigatran; bony retropulsion and epidural hematoma on MRI	Fresh frozen plasma, factor VII; decompression initially performed; PSF done 7 d later when coagulation status was normal; bowel function returned but bladder function did not and unable to walk	Spontaneous hematoma
Dabigatran ¹²⁹	70 y, 150 mg dabigatran for AF; tetraplegia 12 h after dabigatran; C2–C4 hematoma on CT	PCC; urgent C2–C4 laminectomy; complete neurological recovery	Spontaneous hematoma
Rivaroxaban ¹³⁰	61 y, F, 10 mg rivaroxaban started 8 h after tibial osteotomy (general anesthesia); T8 paraplegia 22 h after last dose; C2–C8 SEH on MRI	Rivaroxaban discontinued; spontaneous recovery, without surgery, 4 h after onset	Spontaneous hematoma; patient was also on ibuprofen postoperatively
Rivaroxaban ¹²⁶	69 y, F, THR; 40 mg/d enoxaparin started 12 h after epidural, continued for 4 d; 10 mg rivaroxaban started on POD5, 22 h after enoxaparin; neck pain and LE weakness 5 d after rivaroxaban started, 14 h after last dose; C2–C4 SEH on CT	Symptoms improved 4 h later, complete recovery 48 h after symptoms	Spontaneous hematoma
Rivaroxaban ¹³¹	69 y, M, 20 mg rivaroxaban for AF; T8 paraplegia; T3–conus subdural hematoma on MRI	Steroids, lumbar and cervical drains placed 8 d later (surgery not recommended); no recovery	Spontaneous hematoma
Rivaroxaban ¹³²	58 y, M, 20 mg rivaroxaban daily for AF; interscapular pain after 30 d on rivaroxaban; bilateral LE weakness; C7–T2 intradural hematoma on MRI	IV dexamethasone, sensory/motor improvement after 1 d; C7 corpectomy done of fourth day; almost complete recovery	Spontaneous hematoma. Patient had THR (spinal) 3 wk before episode, rivaroxaban stopped 3 d before surgery and restarted a few days later; he was asymptomatic before episode
Rivaroxaban ¹³³	72 y, M, 20 mg daily rivaroxaban × 3 y for AF; interscapular pain flaccid paraplegia; T6–T8 subdural hematoma on MRI	PCC; laminectomy next day, IV steroids; no improvement at 6-mo follow-up	Spontaneous hematoma
Rivaroxaban ¹²⁷	53 y, F, TKR (spinal); 5–7 mg warfarin on hospital day 1 and POD2–POD3, and 40 mg enoxaparin on POD1–POD3. Switched to rivaroxaban on POD4 (dose not stated); leg pain on POD6 and numbness on POD7; L4–5 SEH on MRI	Emergency laminectomy IVC filter; residual peroneal anesthesia and neurogenic bladder at 2-y follow-up	Patient had spinal stenosis; SEH may have been initiated or aggravated by the multiple anticoagulants and the intake of rivaroxaban while warfarin was still fully active
Rivaroxaban ¹²⁵	59 y, F, TKR (CSE), postoperative epidural infusion; 10 mg rivaroxaban started the night of surgery, epidural catheter removed 18 h after rivaroxaban; rivaroxaban repeated 6 h after removal; bladder incontinence and back pain 12 h after last dose of rivaroxaban; L2–L4 SEH on CT	Emergency laminectomy; complete recovery after 5 d	Short interval between rivaroxaban dose and removal of epidural catheter (18 h); 6-h interval between catheter removal and resumption of rivaroxaban (6 h) may be just a little short
Apixaban ¹³⁴	78 M, apixaban 2.5 mg BID and clopidogrel after coronary stent placement; back pain; hyperintense fluid level (subarachnoid hemorrhage) on MRI	Anticoagulants dcd; complete recovery at 3 wk	Spontaneous spinal subarachnoid hemorrhage

AF indicates atrial fibrillation; CT, computed tomography; IVC, inferior vena cava; LE, lower extremity; PCC, prothrombin complex concentrate; PSF, posterior spinal fusion; SEH, spinal-epidural hematoma; THR, total hip replacement; TKR, total knee replacement.

Chromogenic anti-factor Xa assays developed for the measurement of direct factor Xa inhibitors and using specific calibrators for apixaban are the monitoring tests of choice.¹³⁶

There are very few prospective data concerning the use of neuraxial blocks in apixaban-treated patients. A literature search up to November 2017 found no reports of epidural/spinal bleeding associated with a neuraxial anesthesia, although a single spontaneous hematoma has been reported.¹³⁴ Thus, after a cautious risk-benefit analysis, there is justification to proceed with a neuraxial block; there should be at least a 26- to 30-hour time interval

between the last dose of prophylactic dose of apixaban (2.5 mg/d) and the subsequent neuraxial puncture and/or catheter manipulation/removal. If a dose of 5 mg/d is used and/or in patients with a serum creatinine of 1.5 mg/dL or greater and aged 80 years or older or a body weight 60 kg or less, a time interval of 40 to 75 hours should be observed. The absence of any remaining apixaban activity can be documented using a chromogenic anti-factor Xa assay calibrated for apixaban. The next dose of apixaban should be administered at least 6 hours after the neuraxial puncture or withdrawal of the neuraxial catheter.

Edoxaban

Edoxaban (Savaysa; Daiichi Sankyo Inc, Parsippany, New Jersey) is also an oral highly selective reversible factor Xa inhibitor. Following oral ingestion, maximum plasma levels are reached within 1 to 2 hours. Edoxaban has an absolute bioavailability and a plasma protein binding of approximately 62% and 55%, respectively. The kidney clears approximately 50% of the administered dose, whereas metabolism and biliary/intestinal excretion account for the remainder. The elimination half-life after oral administration is 10 to 14 hours in healthy patients.^{137–141} In the presence of mild, moderate, and severe renal insufficiency, the total exposure to edoxaban is increased by 32%, 74%, and 72%, resulting in an elimination half-life of 8.4, 9.45, and 16.9 hours, respectively.^{120,142–145}

Edoxaban is used in the prevention of stroke and systemic embolism in patients with NVAF and the treatment of VTE and of PE (Savaysa [full prescribing information], available at <http://dsi.com/prescribing-information-portlet/getPICContent?productName=Savaysa&inline=true>, accessed March 4, 2017). A dose of 60 mg once daily is recommended in both indications. The dose should be reduced to 30 mg/d in NVAF patients with CrCl of 15 to 49 mL/min and in patients treated for VTE/PE with body weight of 60 kg or less and/or concomitant use of P-gp inhibitors.^{146–150} Interestingly, edoxaban should not be used in NVAF patients with a CrCl of greater than 95 mL/min because of an increased risk of ischemic stroke (Savaysa [full prescribing information], available at <http://dsi.com/prescribing-information-portlet/getPICContent?productName=Savaysa&inline=true>, accessed March 4, 2017). The 30-mg daily dose was also effective in the prevention of VTE following prosthetic surgery of the knee and hip,^{151,152} but this indication has not been registered in the United States or in Europe.

The PT and aPTT should not be used to assess the anticoagulant activity of edoxaban as the compound behaves in much the same way as apixaban.¹⁵³ Edoxaban is best assessed using tailor-made chromogenic anti-factor Xa assays.¹⁵³

There have been no reports of any neuraxial bleeding in association with neuraxial anesthesia up to November 2017, but the use of neuraxial anesthetic techniques in edoxaban-treated patients should be cautiously considered as there are no data. There should be at least a 20- to 28-hour time interval (2 half-lives) between the last dose of preventive dose of edoxaban (≤ 30 mg/d) and the subsequent neuraxial puncture and/or catheter manipulation/removal. In case of a higher dose (>30 mg/d) and/or in patients with CrCl 15 to 49 mL/min, a body weight 60 kg or less, and/or the concomitant use of P-gp inhibitors, a time interval of 40 to 70 hours (4–5 half-lives) should be observed. The presence of any residual edoxaban activity can be excluded using a chromogenic anti-factor Xa assay calibrated for edoxaban. As with the other new oral anticoagulants, an acceptable level of residual edoxaban activity to proceed with neuraxial block remains undetermined. The next dose of edoxaban should be administered at least 6 hours after the neuraxial puncture or withdrawal of the neuraxial catheter.

Betrixaban

The latest arrival in the family of the oral anti-factor Xa agents is betrixaban (Bevyxxa; Portola Pharmaceuticals, Inc, San Francisco, California). Betrixaban is also an oral reversible selective factor Xa inhibitor that recently received FDA approval. After oral intake, peak plasma levels will be reached 3 to 4 hours. The drug has an oral bioavailability of approximately 34% and an *in vitro* plasma protein binding of 60%. The excretion of betrixaban occurs mainly through the liver.^{112–115,154} Hepatic metabolism is minimal ($<1\%$), and the unchanged drug is primarily excreted via a P-gp-dependent mechanism in the hepatobiliary

route. As a result, 82% to 89% of the drug can be found in the feces, whereas the remainder (5%–11% of an orally administered dose) is eliminated through the kidney, which makes betrixaban the least kidney-dependent factor Xa inhibitor.^{112,113,118} The resulting terminal half-life is 37 hours, whereas the pharmacodynamic half-life is 19 to 27 hours.^{114,115,118} Compared with healthy subjects, renal impairment will still cause an increase of the patient exposure to the drug by 1.89-, 2.27-, and 2.63-fold in the presence of mild, moderate, and severe renal insufficiency, respectively.¹¹⁸

Betrixaban is used in prophylaxis of VTE in adult patients hospitalized for an acute medical illness (who are not undergoing surgery) and are at risk of thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.¹¹⁸ Treatment is initiated with a single dose of 160 mg, followed by 80 mg once daily. In patients with severe renal impairment or treated with P-gp inhibitors, the dose should be reduced to a single dose of 80 mg initially, followed by 40 mg once daily.¹¹⁸

As with the other factor Xa inhibitors, routine monitoring of the anticoagulant effect is not necessary. However, if necessary, any betrixaban effect should be assessed using a calibrated chromogenic anti-factor Xa assay.^{114,115,155}

As of August 2017, there have been no reports of neuraxial bleeding in patients treated with betrixaban who underwent a neuraxial anesthetic technique. Still, the use of epidural or spinal anesthesia in these patients should once again be carefully considered as clinical experience with betrixaban is lacking. The drug was released with a black box warning regarding spinal/epidural hematoma in patients who are receiving neuraxial anesthesia or undergoing spinal puncture.¹¹⁸ The FDA-approved labeling recommends that prior to neuraxial intervention the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis should be considered and that an epidural catheter should be placed/removed no earlier than 72 hours after the last administration of betrixaban, while the next dose of betrixaban should be administered no earlier than 5 hours after the removal of the catheter. If traumatic puncture occurs, administration of betrixaban should be delayed for 72 hours.¹¹⁸

Using a pharmacologic approach, if a neuraxial block is considered in patients receiving Betrixaban, a minimum time interval of 72 hours should be respected between the last prophylactic dose of betrixaban and the following neuraxial puncture and/or catheter manipulation/withdrawal. In patients with CrCl of 15 to 29 mL/min and/or the concomitant use of other P-gp inhibitors (or if in the future higher doses should be used), a time interval of 76 to 135 hours (5 half-lives) should be observed. The presence of any residual betrixaban activity can be excluded using a chromogenic anti-factor Xa assay calibrated for betrixaban. The next dose of betrixaban should be administered at least 5 hours after the neuraxial puncture or withdrawal of the neuraxial catheter.

Reversal of Oral Anti-Factor Xa Agents

Specific antidotes that reverse the anticoagulant effects of the oral anti-factor Xa agents are still lacking. Most of the limited data available on the reversal of novel oral anticoagulants are based on preclinical data, animal experiments, studies in healthy volunteers, and a limited number of case reports. Fortunately, all of these agents have, at least in healthy patients, a relatively short half-life. If there is time to await spontaneous clearance, discontinuation of the drug is a possible strategy.^{156,157}

The reversal of factor Xa inhibitors still depends on the use of prohemostatic agents such as prothrombin complex concentrates (PCCs), activated PCC or factor VIII inhibitor bypassing activity, and recombinant factor VIIa. The recommended doses are 25 to

50 IU/kg, 90 to 100 IU/kg, and 90 µg/kg IV when PCC, activated PCC, or recombinant factor VIIa is used, respectively.^{157–159} If recombinant factor VIIa is used, the potential risk of thrombotic events must always be taken into account.¹⁶⁰ Factor Xa inhibitors all have a high degree of protein binding and are therefore not suited to be eliminated via hemodialysis.

Two promising antidotes for factor Xa inhibitors are currently under investigation. The first is a recombinant protein, named PRT064445 (also known as andexanet alfa or andexanet), which that serves as a universal antidote for factor Xa inhibitors, LMWH, and pentasaccharide.^{161,162} A recent multicenter, prospective, open-label, single-group study evaluated 67 patients who had an acute major bleeding within 18 hours after the administration of a factor Xa inhibitor. Andexanet substantially reduced anti-factor Xa activity, with effective hemostasis occurring in 79% of the patients.¹⁶³ PER977 (also known as ciraparantag) is another compound that binds and neutralizes heparins, dabigatran, and all factor Xa inhibitors in preclinical models.¹⁶⁴ In healthy volunteers, it was found to completely reverse the anticoagulant effects of both enoxaparin and edoxaban.^{165,166} However, further clinical studies are needed before both of these compounds will become available.

6.0 Anesthetic Management of the Patient Receiving Rivaroxaban

6.1 We suggest that rivaroxaban be discontinued 72 hours prior to neuraxial block. Consider checking rivaroxaban or anti-factor Xa activity level if less than 72 hours. An acceptable level of residual rivaroxaban activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: This is a new recommendation.

6.2 We suggest that neuraxial catheters be removed 6 hours prior to the first (postoperative) dose (grade 2C).

Remarks: This is a new recommendation.

6.3 With unanticipated administration with indwelling catheter, we suggest that rivaroxaban dosing be held for 22 to 26 hours before or an anti-factor Xa assay calibrated to rivaroxaban be assessed before the catheter is removed (grade 2C).

Remarks: This is a new recommendation.

7.0 Anesthetic Management of the Patient Receiving Apixaban

7.1 We suggest that apixaban be discontinued 72 hours prior to neuraxial block. Consider checking apixaban or anti-factor Xa activity level if less than 72 hours. An acceptable level of residual apixaban activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: This is a new recommendation.

7.2 We suggest that neuraxial catheters be removed 6 hours prior to the first (postoperative) dose (grade 2C).

Remarks: This is a new recommendation.

7.3 With unanticipated administration with indwelling catheter, we suggest that apixaban dosing be held for 26 to 30 hours or an anti-factor Xa assay calibrated to apixaban before the catheter is removed (grade 2C).

Remarks: This is a new recommendation.

8.0 Anesthetic Management of the Patient Receiving Edoxaban

8.1 We suggest that edoxaban be discontinued 72 hours prior to neuraxial block. Consider checking edoxaban or anti-factor Xa activity level if less than 72 hours. An acceptable level of residual edoxaban activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: This is a new recommendation.

8.2 We suggest that neuraxial catheters be removed 6 hours prior to the first (postoperative) dose (grade 2C).

Remarks: This is a new recommendation.

8.3 With unanticipated administration with indwelling catheter, we suggest that edoxaban dosing be held for 20 to

28 hours or an anti-factor Xa assay calibrated to edoxaban before the catheter is removed (grade 2C).

Remarks: This is a new recommendation.

9.0 Anesthetic Management of the Patient Receiving Betrixaban

9.1 We suggest that betrixaban be discontinued a minimum of 3 days prior to neuraxial block. Consider checking betrixaban or anti-factor Xa level if less than 3 days (grade 2C).

Remarks: This is a new recommendation.

9.2 We suggest against the performance of neuraxial blocks in patients with a CrCl of less than 30 mL/min (grade 2C).

Remarks: This is a new recommendation.

9.3 We suggest that neuraxial catheters 5 hours be removed prior to next dose (grade 2C).

Remarks: This is a new recommendation.

9.4 With unanticipated administration with indwelling catheter, we suggest that betrixaban dosing be held for 72 hours, then the catheter removed (grade 2C).

Remarks: This is a new recommendation.

Direct Thrombin Inhibitors

Parenteral Thrombin Desirudin, Bivalirudin, and Argatroban

Recombinant hirudin derivatives, including desirudin (Revasc) and bivalirudin (Angiomax), inhibit both free and clot-bound thrombin. Argatroban (Acova), an L-arginine derivative, has a similar mechanism of action. These medications are indicated for the treatment and prevention of thrombosis in patients with HIT and as an adjunct to angioplasty procedures.^{167,168} Desirudin is approved for prevention of VTE/PE following hip replacement.¹⁶⁹ The anticoagulant effect of thrombin inhibitors is monitored by the aPTT and is present for 1 to 3 hours after IV administration. Hemorrhagic complications, particularly when combined with thrombolytic or antiplatelet agents, may be life threatening. There is no "antidote"; the antithrombin effect cannot be reversed pharmacologically. Although there are no case reports of spinal hematoma related to neuraxial anesthesia among patients who have received a thrombin inhibitor, spontaneous intracranial bleeding has been reported. The lack of information available and the approved applications of these agents (typically patients with HIT who will need therapeutic levels of anticoagulation) make patients who are receiving these medications poor candidates for neuraxial blockade.

10.0 Anesthetic Management of Patients Receiving Parenteral Thrombin Inhibitors (Desirudin, Bivalirudin, and Argatroban)

10.1 In patients receiving parenteral thrombin inhibitors, we recommend against the performance of neuraxial techniques (grade 2C).

Remarks: There is no change in this recommendation.

Oral Thrombin Inhibitors (Dabigatran)

Dabigatran (Pradaxa) is an oral competitive direct inhibitor of both free and clot-bound thrombin with a bioavailability and plasma protein binding of approximately 7% and 35%, respectively.^{170–172} Peak plasma levels will be reached within 0.5 to 2 hours after administration (Table 11). The drug is primarily (≥80%) eliminated through the kidney in an unchanged form and has a terminal elimination half-life of 12 to 17 hours after multiple doses in healthy patients. A mild (CrCl 50–80 mL/min) to moderate (CrCl 30–49 mL/min) renal insufficiency increases the half-life up to 18 hours and 28 hours in severe renal insufficiency (CrCl 15–29 mL/min).^{170,172,173}

TABLE 11. Oral Antithrombin Agents (Dabigatran)*

Indications and dosing	<p>Reduction of risk of stroke and systemic embolism in NVAF: In patients with CrCl >30 mL/min: 150 mg BID (EU, United States) In patients with CrCl 30–50 mL/min and high bleeding risk: consider 110 mg BID (EU) In patients with CrCl 15–30 mL/min: 75 mg BID (United States) Treatment of VTE and PE: In patients with CrCl >30 mL/min: 150 mg BID after 5–10 d of parenteral anticoagulation (EU, United States) In patients with CrCl 30–50 mL/min and high bleeding risk: consider 110 mg BID (EU) Reduction in the risk of recurrent VTE and PE: In patients with CrCl >30 mL/min: 150 mg BID after previous treatment (EU, United States) In patients with CrCl 30–50 mL/min and high bleeding risk: consider 110 mg BID (EU) Prophylaxis of VTE following THA: In patients with CrCl >30 mL/min: 110 mg QD first day, then 220 mg QD (United States) In patients with CrCl >50 mL/min: 110 mg QD first day, then 220 mg QD (EU) In patients with CrCl 30–50 mL/min, or aged ≥75 or concomitant use of P-gp inhibitors: 75 mg QD first day, then 150 mg QD (EU) Prophylaxis of VTE following TKA: In patients with CrCl >50 mL/min: 110 mg QD first day, then 220 mg QD (EU) In patients with CrCl 30–50 mL/min, concomitant use of P-gp inhibitors: 75 mg QD first day, then 150 mg QD (EU)</p>				
Renal clearance	≥80%				
CrCl, mL/min	≥80	50–79	30–49	15–29	<15 (Off-dialysis)
Elimination half-life $t_{1/2\beta}$, h	12–17 ¹⁷⁰	16.6 ¹⁷³	18.7 ¹⁷³	27.5 ¹⁷³	No data

*Pradaxa full prescribing information (available at <http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf>, accessed March 4, 2017); dabigatran: Epar—product information (available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf, accessed December 22, 2015).

EU indicates European Union; THA, total hip arthroplasty; TKA, total knee arthroplasty.

A dose of 150 mg BID is used in the treatment of VTE and PE, the prevention of recurrent VTE and PE, and in the prevention of systemic embolism in NVAF. A dose reduction to 75 mg BID is recommended for the latter indication in the presence of a CrCl of 15 to 29 mL/min and in the presence of CrCl of 30 to 49 mL/min with the concomitant use of the P-gp inhibitors.¹⁷⁴ In the prevention of VTE following orthopedic surgery, the first oral dose of dabigatran 110 mg is given 1 to 4 hours postoperatively, followed by 220 mg BID on subsequent days. Except for the NVAF patients, dabigatran should not be used in patients with a CrCl of less than 30 mL/min or on dialysis (Pradaxa [full prescribing information], available at <http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf>, accessed March 4, 2017).

The PT and the INR lack any reliable correlation to dabigatran plasma levels and should not be used for the monitoring of dabigatran.¹⁷⁵ In contrast, the aPTT is prolonged in a dose-dependent but nonlinear correlation and with considerable interindividual and interassay variability. The aPTT can only be used to provide rapid qualitative information in emergency situations.^{175–178} The thrombin time (TT) and the dilute TT (dTT) are best suited to monitor dabigatran.^{176,178,179} The latter is now routinely available as the Hemoclot thrombin inhibitor assay.¹⁸⁰ These tests, as well as the chromogenic anti-factor Xa assays used to monitor the other novel oral anticoagulants, may not be readily available in many institutions.

There is limited experience with dabigatran and neuraxial anesthesia, and none with the use of indwelling epidural catheters. Neuraxial blockade was performed in approximately 70% of all patients in the first studies with dabigatran, but the drug was started postoperatively, and neuraxial catheters were removed at least 2 hours, but mostly 4 to 6 hours before the first dose of dabigatran.^{181–184} Dabigatran was not used if an indwelling epidural catheter remained in place for postoperative pain relief.^{182,184,185}

There have been 2 neuraxial hematomas associated with patients receiving dabigatran for chronic atrial fibrillation (one spontaneous and one related to a trauma/fall).^{128,129} Although there are no reports up to November 2017 of a spinal/epidural hematoma after neuraxial anesthesia, it is still too early to make any firm endorsements on the use of neuraxial anesthetic (catheter) techniques in dabigatran-treated patients. Therefore, any recommendations on the use of neuraxial techniques in dabigatran-treated patients are based on expert opinion and on the pharmacokinetics of the drugs involved.

The use of a neuraxial block in dabigatran-treated patients should be carefully and individually considered. The 12- to 17-hour half-life of dabigatran in healthy patients suggests a time interval of 34 hours (ie, 2 half-lives) between the last prophylactic dose (≤220 mg/d) of dabigatran and the subsequent neuraxial puncture and/or catheter manipulation or withdrawal. This time interval should be extended to 48 to 85 hours (4–5 half-lives) when higher doses (>220 mg/d) are used and up to 72 to 90 hours in patients with a CrCl of 30 to 49 mL/min. In case of any doubt, the absence of any residual anticoagulant dabigatran activity can be documented using the dTT. The first or next dose of dabigatran should be given at least 6 hours after the neuraxial puncture or neuraxial catheter withdrawal.

Reversal of Dabigatran

In 2013, Schiele et al¹⁸⁶ described idarucizumab as a monoclonal antibody fragment that binds to dabigatran and reverses its anticoagulant effects both in vitro and in vivo in rats. A recent clinical trial in patients with bleeding or requiring urgent surgery demonstrated that idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.¹⁷⁴ In October 2015, idarucizumab was approved by the FDA to be used in adult

patients treated with dabigatran when rapid reversal of its anticoagulant effects is required in situations of emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding (idarucizumab [full prescribing information, <http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf>, accessed March 4, 2017). The recommended dose is 5 g via an IV infusion/injection.

11.0 Anesthetic Management of the Patient Receiving Dabigatran

Dabigatran is highly dependent (>80%) on renal excretion. Estimated CrCl tends to overestimate actual renal function. Furthermore, renal function may be further impaired perioperatively.

11.1 We suggest that dabigatran be discontinued 120 hours prior to neuraxial block. However, if renal function has been reliably determined, and there are no additional risk factors for bleeding (eg, age >65 years, hypertension, concomitant antiplatelet medications),¹⁸⁷ a more graded approach may be considered.

Remarks: This is a new recommendation.

11.1.1 We suggest that dabigatran be discontinued 72 hours in patients with a CrCl 80 mL/min or greater. Consider checking dTT or ecarin clotting time (ECT) if less than 72 hours. An acceptable level of residual dabigatran activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: This is a new recommendation.

11.1.2 We suggest that dabigatran be discontinued 96 hours in patients with a CrCl of 50 to 79 mL/min. Consider checking dTT or ECT if less than 96 hours. An acceptable level of residual dabigatran activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: This is a new recommendation.

11.1.3 We suggest that dabigatran be discontinued 120 hours in patients with a CrCl of 30 to 49 mL/min. Consider checking dTT or ECT if less than 120 hours. An acceptable level of residual dabigatran activity to proceed with neuraxial block remains undetermined (grade 2C).

Remarks: This is a new recommendation.

11.1.4 We suggest against the performance of neuraxial blocks in patients with a CrCl of less than 30 mL/min (grade 2C).

Remarks: This is a new recommendation.

11.2 We suggest that neuraxial catheters be removed 6 hours prior to the first (postoperative) dose (grade 2C).

Remarks: This is a new recommendation.

11.3 With unanticipated administration with indwelling catheter, we suggest that dabigatran dosing be held for 34 to 36 hours or the dTT or ECT assessed before the catheter is removed (grade 2C).

Remarks: This is a new recommendation.

Vitamin K Antagonists (Warfarin)

Warfarin Pharmacology

Oral anticoagulants, including warfarin, exert their anticoagulant effect by interfering with the synthesis of the vitamin K-dependent

TABLE 13. Patient Characteristics Associated With Increased Sensitivity to Warfarin

Age >65 y
Female sex
Weight <100 lb
Liver, cardiac, or renal disease
Asian ancestry
Excessive surgical blood loss

clotting factors VII, IX, X, and II (thrombin). The effects of warfarin are not apparent until there is a significant amount of biologically inactive clotting factors and are dependent on factor half-life.¹⁸⁸ Clinical experience with patients who are congenitally deficient in factor II, IX, or X suggests that a factor activity level of 40% for each factor is adequate for normal or near-normal hemostasis.¹⁸⁹ Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. During the first few days of therapy, the PT reflects primarily a reduction of factor VII, the half-life of which is approximately 6 hours (Table 12). After a single dose, marked prolongation of the INR may occur, although adequate factor levels are still present.¹⁹⁰ Discontinuation of warfarin requires normalization of the INR to ensure adequate activities of all the clotting factors.

Clinical Use of Warfarin

The measured response to anticoagulant therapy at the initiation of treatment varies significantly. Some of the variability may be attributed to age, female sex, preexisting medical conditions (low patient weight or liver, cardiac, and renal disease), race, and drug interactions that are associated with an enhanced response to warfarin and/or a lower dose requirement for maintenance anticoagulation.^{1,188,191,192} (Table 13). Women and the elderly are more susceptible to warfarin. In a study of 12,202 patients on the effect of age and sex on warfarin maintenance dosing, it was noted that warfarin dose was inversely related to age and strongly associated with sex.¹⁹³ The association of renal insufficiency and increased response to warfarin has also been noted by Benzon et al.¹⁹⁴ One patient in their study evaluating the concentration of clotting factors after discontinuation of warfarin had renal insufficiency (blood urea nitrogen of 64 mg/mL, creatinine of 5.3 mg/dL, and a glomerular filtration rate of 10 mL/min). Her INR 5 days after discontinuation of warfarin was 0.9, but her clotting factors VII, IX, X, and II were 159%, 55%, 37%, and 41% respectively.

There are many drug interactions with warfarin therapy that potentiate the anticoagulant effect, including concomitant administration of antiplatelet medications, heparin, and LMWH.^{188,195,196} Recent clinical studies have demonstrated that patients with variations in the CYP2C9 and/or VKORC1 genes are at risk of increased bleeding and require lower doses of warfarin.¹⁸⁸ The ACCP recommended against the use of pharmacogenetic-based initial dosing until randomized data showed it to be beneficial.¹⁸⁸ Recent studies did not resolve the issue. One study showed a greater mean percentage time in the therapeutic INR in the patients who had genotype-guided dosing of warfarin compared with a clinically guided group.¹⁹⁷ However, 2 other studies did not show a difference.^{198,199} As the advantage of genetic-based dosing of warfarin has not been uniformly shown, to date, adjusted-dose warfarin is the most common agent used for thromboembolism prophylaxis after hip and knee replacement surgery in the United States.

TABLE 12. Half-lives of Vitamin K-Dependent Clotting Factors

Factor	Half-Life, h
Factor VII	6–8
Factor IX	24
Factor X	25–60
Factor II	50–80

When warfarin is stopped before a neuraxial or surgical procedure, most clinicians bridge anticoagulation with LMWH.³⁹ A recent study showed that there was no benefit in this practice. A randomized, double-blind, placebo-controlled trial that compared dalteparin with placebo showed that there was no difference in the incidence of arterial thromboembolism between the 2 groups.²⁰⁰ In addition, the incidence of major bleeding was 1.3% in the no-bridging group versus 3.2% in the bridging group. It should be emphasized that the patients who were studied had atrial fibrillation associated with valvular heart disease; patients with a mechanical heart valve, stroke, or transient ischemic attack within 12 weeks of the study or those with CrCl less than 30 mL/min were excluded. Overall, the ACCP recommends patients at low risk of thromboembolism undergo no bridging therapy during interruption of warfarin therapy, whereas patients at high risk receive bridging therapy, and those at intermediate risk undergo an individualized assessment³⁶ (Table 3).

When there is elevated INR without major bleeding, the warfarin can be reversed with oral vitamin K. Intravenous vitamin K can be administered when there is serious bleeding.¹⁸⁸ When there is life-threatening bleeding, recombinant activated factor VIIa; 3-factor PCC, which contains factors II, IX, and X; or 4-factor PCC, containing factors II, VII, IX, and X, can be given. Activated recombinant activated factor VIIa and PCCs are better than fresh frozen plasma in reversing warfarin²⁰¹; PCC is better than recombinant activated factor VIIa²⁰²; and 4-factor PCC appears to be more effective than 3-factor PCC.^{188,203,204}

Neuraxial Techniques in Relation to the INR and in the Chronically Anticoagulated Patient

Spinal hematoma has been reported when a neuraxial procedure was performed or an epidural catheter removed in a patient who is fully anticoagulated with warfarin.^{191,205,206} Other cases have been reported through the MedWatch system. Odom and Sih²⁰⁷ did not observe a spinal hematoma in 950 patients who had 1000 continuous lumbar epidural anesthetics and received oral anticoagulants preoperatively. However, an obsolete test was used (thrombotest), and the coagulation status of the patients at the time of catheter removal (at 48 hours) was not known. Two other studies with more than 600 patients reported no spinal hematoma in patients who received neuraxial block in conjunction with low-dose warfarin therapy.^{208,209}

The INR is most sensitive to clotting factors VII and X.²¹⁰ The INR value is prolonged when factor VII is reduced to approximately 55% of baseline; an INR of 1.5 is associated with a factor VII activity of 40%.²¹¹ An INR less than 1.5 should therefore be associated with normal coagulation. For this reason, INRs of 1.4 or less in patients who have not been on warfarin are not at increased risk of spinal bleeding.¹ The occurrence of spinal hematoma after removal of catheter^{212,213} led to the recommendation that the same guidelines should apply to placement and removal of the epidural catheter.²¹⁴

Neuraxial injections and removal of epidural catheters appear to be safe when done within 24 hours after warfarin was initiated. This was documented by Parvizi et al,²¹⁵ who noted the absence of spinal hematoma in more than 12,000 patients in whom they removed the epidural catheters within 24 to 48 hours of initiation of warfarin therapy. The safety of removing epidural catheters was also documented by other investigators.^{190,216} No spinal hematoma occurred after removal of catheters 12 to 14 hours after warfarin therapy, even in the patients with INRs of 1.5 to 1.9. The mean (SD) factor VII levels 12 hours after warfarin were noted to be normal in the patients with INRs less than or equal to 1.4 and acceptable in the patients with INRs¹⁹⁰ of 1.5 to 1.9 (Table 14).

TABLE 14. Activities of Clotting Factor VII During Initiation of Warfarin Therapy

Day	INR of ≤ 1.4	INR > 1.4
POD1 (12–14 h after warfarin)	99 (SD, 35)	60 (SD, 28)
POD2 (36–38 h after warfarin)	74 (SD, 20)	32 (SD, 15)
POD3 (60–62 h after warfarin)	87 (SD, 26)	44 (SD, 14)

Values are in percent.

Adapted from Benzon et al.¹⁹⁰

Three patients had factor VII levels of less than 40%, but any coagulation deficiency is antagonized by a decrease in the anticoagulant protein C. In addition, the activities of the clotting factors IX, X, and II are probably in the reference range. Another group of investigators showed no spinal hematoma in 4365 patients in whom their epidural catheters were removed while they were on warfarin; the mean duration of warfarin treatment was 2.1 (SD, 0.6) days, and the INRs at the time of removal was 1.9 (SD, 0.4) (range, 1.5–7.1).²¹⁶ In this study, no other anticoagulant was given except nonsteroidal anti-inflammatory drugs (NSAIDs), and the patients were closely monitored. A closer look at this study showed that most catheters were removed on POD2 (4090 patients); 140 were removed on POD3.

Although it does not appear to increase risk to remove epidural catheters 12 to 24 hours after warfarin was given, the risk of removing epidural catheters at 48 hours is not guaranteed. This is because adequate activities of clotting factor VII is not ensured (Table 14). The activities of factors IX and X also start to decline. This scenario is fortunately not encountered today because most epidural catheters are immediately removed after total joint surgery or left for 24 hours, at most.

Warfarin is discontinued for at least 5 days before a neuraxial procedure is performed. While ASRA recommends the INR is normalized, the European and Scandinavian guidelines accept an INR of 1.4 or lower. Based on the concentration of the clotting factors, neuraxial procedure in a patient with an INR of 1.3 to 1.4 may not be safe. In a study of 23 patients, Benzon et al¹⁹⁴ noted that the average activities of clotting factors VII, IX, X, and II were normal in the patients with INR of 1.2 or less. In contrast, a patient with an INR of 1.3 had concentrations of 105%, 78%, 36%, and 46% for factors VII, IX, X, and II, respectively. A patient with an INR of 1.4 had clotting factors of 89, 66%, 20%, and 37%, respectively.

The management of patients receiving warfarin perioperatively remains controversial. Recommendations are based on warfarin pharmacology, the clinical relevance of vitamin K coagulation factor levels/deficiencies, case series, and the case reports of spinal hematoma among these patients. Web sites are available to assist clinicians with warfarin dosing (www.WarfarinDosing.org).

12.0 Regional Anesthetic Management of the Patient on Warfarin

12.1 Caution should be used when performing neuraxial techniques in patients recently discontinued from chronic warfarin therapy. In the first 1 to 3 days after discontinuation of warfarin therapy, the coagulation status (reflected primarily by factors II and X levels) may not be adequate for hemostasis despite a decrease in the INR (indicating a return of factor VII activity). Adequate levels of II, VII, IX, and X may not be present until the INR is within normal limits. We recommend that the anticoagulant therapy must be stopped (ideally 5 days prior to the planned procedure), and the INR normalized prior to initiation of neuraxial block (grade 1B).

Remarks: There is no change in this recommendation.

12.2 We recommend against the concurrent use of medications that affect other components of the clotting mechanisms and may increase the risk of bleeding complications for patients receiving oral anticoagulants and do so without influencing the INR. These medications include aspirin and other NSAIDs, thienopyridines, UFH, and LMWH (grade 1A).

Remarks: There is no change in this recommendation.

12.3 In patients who are likely to have an enhanced response to the drug, we recommend that a reduced dose be administered (grade 1B).

Remarks: There is no change in this recommendation.

12.4 In patients receiving an initial dose of warfarin prior to surgery, we suggest the INR should be checked prior to neuraxial block if the first dose was given more than 24 hours earlier or a second dose of oral anticoagulant has been administered (grade 2C).

Remarks: There is no change in this recommendation.

12.5 In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored on a daily basis (grade 2C).

Remarks: There is no change in this recommendation.

12.6 Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. To facilitate neurologic evaluation, we recommend that the type of analgesic solution be tailored to minimize the degree of sensory and motor blockade (grade 1C).

Remarks: There is no change in this recommendation.

12.7 As thromboprophylaxis with warfarin is initiated, we suggest that neuraxial catheters be removed when the INR is less than 1.5. While removal of epidural catheters 12 to 24 hours after warfarin was given does not appear to represent increase risk, the risk of removing epidural catheters at 48 hours is not guaranteed.

Remarks: This is a new recommendation based on recent laboratory studies assessing factor levels and INR as well as clinical studies in patients receiving warfarin during epidural catheterization.

12.8 In patients with INR of greater than 1.5 but less than 3, the increase in risk with progressive INR prolongation remains unknown. We suggest indwelling catheters may be maintained with caution, based on INR and duration of warfarin therapy (grade 2C).

Remarks: This is a new recommendation based on recent laboratory studies assessing factor levels and INR as well as clinical studies in patients receiving warfarin during epidural catheterization.

12.9 In patients with an INR of greater than 3, we recommend that the warfarin dose be held or reduced in patients with indwelling neuraxial catheters (grade 1A). We can make no definitive recommendation regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion (grade 2C).

Remarks: There is no change in this recommendation.

12.10 We suggest that neurologic assessment be continued for at least 24 hours following catheter removal (grade 2C).

Remarks: There is no change in this recommendation.

Antiplatelet Medications

Antiplatelet agents include NSAIDs, thienopyridine derivatives/platelet ADP antagonists (ticlopidine, clopidogrel, prasugrel), platelet glycoprotein (GP) IIb/IIIa receptor antagonists (abciximab, eptifibatide, and tirofiban), platelet P2Y₁₂ receptor antagonists

(ticagrelor), and platelet phosphodiesterase (PDE) IIIA inhibitors (cilostazol). It is important to note the pharmacologic differences among the drugs with antiplatelet effects.

Nonsteroidal Anti-inflammatory Drugs

Cyclooxygenase (COX) exists in 2 forms. Cyclooxygenase 1 regulates constitutive mechanisms, whereas COX-2 mediates pain and inflammation. Nonsteroidal anti-inflammatory drugs inhibit platelet COX and prevent the synthesis of thromboxane A₂. Platelets from patients who have been taking these medications have normal platelet adherence to subendothelium and normal primary hemostatic plug formation. Depending on the dose administered, aspirin (and other NSAIDs) may produce opposing effects on the hemostatic mechanism. For example, platelet COX is inhibited by low-dose aspirin (60–325 mg/d), whereas larger doses (1.5–2 g/d) will also inhibit the production of prostacyclin (a potent vasodilator and platelet aggregation inhibitor) by vascular endothelial cells and thus result in a paradoxical thrombogenic effect.^{217,218} As a result, low-dose aspirin (81–325 mg/d) is theoretically a greater risk factor for bleeding than higher doses. There is consensus that the optimal dose of aspirin for prevention of myocardial infarction, stroke, or vascular death lies within the narrow range of 75 to 160 mg/d.³⁴ Spontaneous²¹⁹ and postoperative (unrelated to neuraxial technique)²²⁰ spinal hematomas have been reported with low-dose aspirin therapy.

Platelet function is affected for the life of the platelet following aspirin ingestion; other nonsteroidal analgesics produce a short-term defect, which normalizes within 3 days; for short-acting NSAIDs such as ibuprofen, diclofenac, and indomethacin, the effect on platelet aggregation is normalized after 24 hours, and more than 50% is restored after 6 hours.²²¹

Celecoxib (Celebrex) is an anti-inflammatory agent that primarily inhibits COX-2, an inducible enzyme that is not expressed in platelets and thus does not cause platelet dysfunction.²²² After single dosing and multidosing, there have not been findings of significant disruption of platelet aggregation; nor is there a history of undesirable bleeding events.

Thienopyridines

The antiplatelet effect of the thienopyridine derivatives, ticlopidine (Ticlid), clopidogrel (Plavix), and prasugrel (Effient) results from inhibition of ADP-induced platelet aggregation. These antiplatelet agents, used in the prevention of cerebrovascular thromboembolic events, affect both primary and secondary platelet aggregation. Thienopyridines also interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions.²²³ All 3 are prodrugs that must undergo metabolic activation through the hepatic CYP450 system to generate the active metabolites that inhibit the platelet P2Y₁₂ receptor.³⁴ Thienopyridine derivatives demonstrate both time- and dose-dependent effects. For example, steady state is achieved within 7 days for clopidogrel with doses of 75 mg/d. However, steady-state levels of clopidogrel are reached within 2 to 15 hours with 300- to 600-mg loading doses.^{39,224} Prasugrel is typically administered with a loading dose that results in 50% of platelet aggregation within 1 hour of administration (prasugrel [full prescribing information], available at <http://uspl.lilly.com/effient/effient.html#pi>, accessed March 4, 2017). Compared with clopidogrel, prasugrel exhibits a more rapid onset of action, a higher potency, and more consistent antiplatelet effects. It is also associated with a higher frequency of major bleeding.³⁴

Although often administered in combination with aspirin, the concomitant use of thienopyridines and aspirin may be associated with increased risk of hemorrhagic events. Serious hematologic adverse reactions, including agranulocytosis, thrombotic

thrombocytopenic purpura, and aplastic anemia, have resulted in placement of a black box warning on ticlopidine. Because of these toxicities, ticlopidine has been essentially replaced with clopidogrel and prasugrel.³⁴

Labeling of the thienopyridine derivatives recommends that if a patient is to undergo an elective procedure and an antiplatelet effect is not desired, ticlopidine should be discontinued for 10 to 14 days (ticlopidine [full prescribing information], available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/19979-s019_ticlo.pdf, accessed March 4, 2017). Clopidogrel should be discontinued 5 days (clopidogrel [full prescribing information], available at http://packageinserts.bms.com/pi/pi_plavix.pdf, accessed March 4, 2017), and prasugrel discontinued 7 days (prasugrel [full prescribing information], available at <http://uspl.lilly.com/efficient/efficient.html#pi>, accessed March 4, 2017), prior to surgery. The ACCP recommends discontinuation of clopidogrel and prasugrel for 5 days (Table 4).³⁶ Although it is possible to assess residual clopidogrel effect using assays of platelet function (eg, PFA II, P2Y₁₂ assay), only a normal result would be reassuring.²²⁵ Thus, the clinical significance of assay findings is uncertain, and the assay results have not been shown to predict clinical outcomes, and the clinical applicability of these tests remains undetermined at this time.³⁶ The potency of these medications is demonstrated by recent reports of spontaneous spinal hematomas during clopidogrel therapy.^{226–228}

Ticagrelor

Ticagrelor (Brilinta) represents a new class of non-thienopyridine platelet inhibitors designed to address the limitations of current oral platelet drugs. Ticagrelor completely but reversibly inhibits ADP-induced platelet activation, unlike the thienopyridines (eg, clopidogrel, prasugrel). Ticagrelor also acts directly on the P2Y₁₂ receptor and does not require CYP biotransformation. After a loading dose, an antiplatelet effect is observed within 30 minutes, whereas maximum effect is achieved within 2 hours. Ticagrelor has been studied in acute coronary syndrome in combination with aspirin. Maintenance doses of aspirin greater than 100 mg decrease the effectiveness. In theory, the reversible antiplatelet effect may improve the perioperative safety of ticagrelor relative to the other agents. However, medication labeling recommends that when possible ticagrelor should “be discontinued at least 5 days prior to any surgery” (ticagrelor [full prescribing information], available at <http://www.azpicentral.com/brilinta/brilinta.pdf#page=1>, accessed March 4, 2017).

In Europe, labeling of clopidogrel, prasugrel, and ticagrelor recommends that they all be discontinued 7 days prior to elective surgery. Hence, a somewhat longer interval is typically advised in “European” recommendations.^{8,25,97,229}

Cangrelor

Cangrelor (Kengreal) is a direct and reversible IV P2Y₁₂ inhibitor. It is indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with another P2Y₁₂ inhibitor and are not being given a GP IIb/IIIa inhibitor.

The dosage of the drug is 30-μg/kg bolus followed by an infusion 4 μg/kg per minute. Its onset is rapid, and its offset short. Its antiplatelet effect is seen within 2 minutes of administration and inhibits platelet aggregation by 95% to 100%.²³⁰ Its plasma half-life is 3 to 6 minutes, and platelet recovery is quick; 80% and 90% of the samples recover in 60 and 90 minutes, respectively.²³¹ The adverse effects of cangrelor include bleeding, dyspnea, and decreased renal function. The dyspnea is seen with

ticagrelor and cangrelor and may be related to the drug-induced accumulation of adenosine with inhibition of the P2Y₁₂ effect on sensory neurons and stimulation of the adenosine receptors on bronchopulmonary vagal fibers. Although there is no clear evidence of acute renal toxicity, animal studies suggested that cangrelor may injure renal tubules.

Two earlier studies on the efficacy of cangrelor, the CHAMPION PLATFORM and CHAMPION PCI trials, were not supportive. However, the CHAMPION PHOENIX trial, wherein the definition of myocardial infarction was based on the universal definition, showed superiority of the drug over clopidogrel in terms of reduction of periprocedural myocardial infarction with no difference in the incidence of severe bleeding between the 2 drugs.²³² Patients given cangrelor for PCI are usually continued on one of the oral P2Y₁₂ inhibitors. Both clopidogrel and prasugrel will not work while the cangrelor is being infused because their metabolite cannot bind to the receptor while it is being occupied by cangrelor. Ticagrelor, on the other hand, has a binding site separate from cangrelor. For these reasons, clopidogrel and prasugrel should be given (immediately) after discontinuation of cangrelor, whereas ticagrelor can be given during or immediately after the infusion.²³⁰ The recommended loading doses are 600 mg for clopidogrel, 60 mg for prasugrel, and 180 mg for ticagrelor.

The oral P2Y₁₂ inhibitors need to be stopped for 5 to 10 days before surgery. Cangrelor can therefore be used as a bridge therapy in these situations. A study showed efficacy of cangrelor over placebo; the incidence of greater than 60% platelet inhibition was more than 80% of the patients on cangrelor versus 19% for placebo, and there was no significant difference in major bleeding.²³³ It is possible that perioperative anesthesiologists will encounter this scenario more often in the future. In these cases, a minimum of 3-hour interval, preferably longer, should be observed.

Platelet GP IIb/IIIa Receptor Antagonists

Platelet GP IIb/IIIa receptor antagonists, including abciximab (Reopro), eptifibatide (Integrilin), and tirofiban (Aggrastat), inhibit platelet aggregation by interfering with platelet-fibrinogen and platelet-von Willebrand factor binding. Because fibrinogen and von Willebrand factor have multiple binding sites, they can bind to multiple platelets, causing cross-linking and platelet aggregation. Conversely, inhibition of GP IIb/IIIa receptors blocks the final common pathway to platelet aggregation.²²³ The majority of clinical trials involving the GP IIb/IIIa antagonists have evaluated their use in the treatment of acute coronary syndrome (with or without PCI). Importantly, the GP IIb/IIIa antagonists are typically administered in combination with aspirin and heparin. Contraindications include a history of surgery within 4 to 6 weeks. Time to normal platelet aggregation following discontinuation of therapy ranges from 8 hours (eptifibatide, tirofiban) to 24 to 48 hours (abciximab).³⁴ Thrombocytopenia is a frequent adverse effect.³⁴ Platelet counts usually recover upon discontinuation of therapy. During therapy with GP IIb/IIIa antagonists, labeling precautions recommend that needle puncture sites should be minimized and monitored (abciximab [full prescribing information], available at <https://www.drugs.com/pro/reopro.html>, accessed March 4, 2017).

Cilostazol

Cilostazol (Pletal) produces a selective inhibition of PDE IIIA resulting in a reversible inhibition of platelet aggregation. Cilostazol is used in peripheral arterial vascular disease because of its vasodilatory properties (vascular muscle also contains PDE IIIA). It has a half-life of 11 hours, which is prolonged in patients with severe renal impairment.³⁴ The terminal half-life of

active metabolites is 21 hours. There are limited data on perioperative administration of cilostazol. However, a single case report of spinal hematoma following epidural catheter removal in the presence of cilostazol therapy has been reported.²³⁴ The ESA recommendations include maintaining a time interval of 2 elimination half-lives (42 hours) after the last dose of cilostazol prior to neuraxial blockade, and the next dose administered at least 5 hours after neuraxial catheter manipulation/removal.⁸

Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent is controversial. Historically, the efficacy of immediate-release dipyridamole (alone or in combination with aspirin) was not established. However, a new extended-release formulation appears to be more efficacious than aspirin in the prevention of stroke. However, the combination of aspirin and extended-release dipyridamole is associated with more bleeding complications than clopidogrel.^{34,235} The terminal half-life is 10 hours. There are no data to support discontinuation of dipyridamole perioperatively. However, the combination of dipyridamole and aspirin may increase the risk of bleeding. Although there are no spinal hematomas associated with neuraxial block and dipyridamole, as will be noted in the upcoming section on plexus and peripheral block, 2 serious hematomas were reported in patients who underwent continuous interscalene²³⁶ or ilioinguinal/iliohypogastric block²³⁷ while receiving dipyridamole.

Spinal Hematoma in Patients Receiving Antiplatelet Medications

At the previous ASRA Consensus Conferences on Neuraxial Anesthesia and Anticoagulation, it was concluded NSAIDs did not appear to present significant risk to patients for developing spinal-epidural hematomas for patients undergoing neuraxial techniques for surgery (nonchronic pain) procedures.^{3,6,7} Vandermeulen et al⁴³ implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia. These patients had received aspirin, indomethacin, or ticlopidine. Four additional case reports related to neuraxial techniques have been published, 2 involving ketorolac and 2 involving a thienopyridine derivative.^{238–241} The paucity of case reports is important, given the prevalence of NSAID use among the general population.

Several large studies have demonstrated the relative safety of central neural blockade in combination with NSAID therapy, although the total number of patients in this combined series is only 4714.⁶ If low-dose aspirin creates the greatest impact on platelet function, patients receiving 60 to 325 mg aspirin would theoretically represent the greatest risk of significant bleeding. However, the CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) Group included 1422 high-risk obstetric patients, approximately 700 of whom were administered 60 mg aspirin daily who underwent epidural anesthesia without any neurologic sequelae.²⁴² A recent prospective study evaluated the risk of neurologic complications following ESI. There were no spinal hematomas among the 1214 patients, including the 32% of patients who reported NSAID use prior to injection.²⁴³ These results confirm those of previous studies performed in obstetric and surgical populations. An exception to this are patients undergoing invasive pain procedures, among whom 3 spinal hematomas have been reported following spinal cord stimulator lead placement while receiving aspirin or other NSAIDs.^{16–18} The differences in the pain and surgical populations and their associated risks of significant spinal bleeding will be discussed later.

There are minimal published data purporting the safety of neuraxial blockade in the presence of thienopyridine derivatives or platelet GP IIb/IIIa receptor antagonists.²⁴⁴ Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving thienopyridines and GP IIb/IIIa antagonists has been noted.^{36,245,246} In general, the cardiac surgical²⁴⁶ and interventional radiology literature recommends that elective surgery be delayed 24 to 48 hours following abciximab and 4 to 8 hours following eptifibatide or tirofiban.²⁴⁷ Surgery performed within 12 hours of abciximab administration will most likely necessitate a platelet transfusion; After transfusion, the antibody redistributes to the transfused platelets, reducing the mean level of receptor blockade and improving platelet function. However, subsequent platelet transfusion may be necessary. There have been 3 spinal hematomas attributed to neuraxial techniques and ticlopidine or clopidogrel, including 1 patient undergoing a series of ESIs.^{238,241,248}

Combination of Antiplatelet Medications With Anticoagulants and Thrombolytics

Nonsteroidal anti-inflammatory drugs alone do not significantly increase the risk of spinal hematoma. However, combination therapy with UFH, LMWH, oral anticoagulants, and thrombolytics has been demonstrated to increase the frequency of spontaneous hemorrhagic complications, bleeding at puncture sites, and spinal hematoma.^{2,50,79} For example, in the series of 40 spinal hematomas associated with LMWH reported in 1998, 10 patients received concomitant antiplatelet medications.² The addition of antiplatelet therapy to postoperative thromboprophylaxis was implicated in a similar number of cases in the survey by Moen et al.⁴² Likewise, in a case report of spinal hematoma following ESI, Benzon et al²³⁸ noted the patient had received multiple antiplatelet medications, including clopidogrel and aspirin.

13.0 Anesthetic Management of the Patient Receiving Antiplatelet Medications

Antiplatelet medications exert diverse effects on platelet function. The pharmacologic differences make it impossible to extrapolate between the groups of drugs regarding the practice of neuraxial techniques. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. These conditions include a history of easy bruising/excessive bleeding, female sex, and increased age.

13.1 Nonsteroidal anti-inflammatory drugs

13.1.1 Nonsteroidal anti-inflammatory drugs appear to represent no added significant risk of the development of spinal hematoma in patients having epidural or spinal anesthesia. Nonsteroidal anti-inflammatory drugs (including aspirin) do not create a level of risk that will interfere with the performance of neuraxial blocks. In patients receiving these medications, we do not identify specific concerns as to the timing of single-injection or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal (grade 1A).

Remarks: There is no change in this recommendation.

13.1.2 In patients receiving NSAIDs, we suggest caution in the performance of neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as other (non-NSAID) antiplatelet agents, oral anticoagulants, UFH, and LMWH, is anticipated in the early postoperative period because of the increased risk of bleeding complications. Cyclooxygenase 2 inhibitors have minimal effect on platelet function and should be considered in patients who require anti-inflammatory therapy in the presence of anticoagulation (grade 2C).

Remarks: There is no change in this recommendation.

13.2 Thienopyridines (ticlopidine, clopidogrel, prasugrel)

13.2.1 Preoperative. Based on labeling and surgical/procedural experience, the recommended time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 10 days for ticlopidine, 5 to 7 days for clopidogrel, and 7 to 10 days for prasugrel (grade 1C).

Remarks: Previous time intervals were 14 days for ticlopidine and 7 days for clopidogrel. The new time intervals reflect ACCP recommendations. The recommendation for prasugrel is new.

13.2.2 Postoperative. In accordance with ACCP recommendations, thienopyridine therapy may be reinstituted 24 hours postoperatively (grade 1A).

Remarks: This is a new recommendation.

13.2.3 Neuraxial catheters should not be maintained with prasugrel or ticagrelor because of the rapid onset. However, because the antiplatelet effect is not immediate with ticlopidine and clopidogrel, neuraxial catheters may be maintained for 1 to 2 days, provided a loading dose of the antiplatelet agent is not administered (grade 2C).

Remarks: This is a new recommendation.

13.2.4 Thienopyridine therapy may be resumed immediately after needle placement/catheter removal, provided a loading dose of the drugs is not administered. If a loading dose is administered, we suggest a time interval of 6 hours between catheter removal and administration (grade 2C).

Remarks: This is a new recommendation.

13.4 Ticagrelor

13.4.1 Preoperative. Based on labeling and surgical/procedural experience, the recommended time interval between discontinuation of ticagrelor therapy is 5 to 7 days (grade 1C).

Remarks: This is a new recommendation.

13.4.2 Postoperative. In accordance with ACCP recommendations, ticagrelor therapy may be reinstituted 24 hours postoperatively (grade 1A).

Remarks: This is a new recommendation.

13.4.3 Neuraxial catheters should not be maintained with ticagrelor because of the rapid onset (grade 2C).

Remarks: This is a new recommendation.

13.4.4 Ticagrelor therapy may be resumed immediately after needle placement/catheter removal, provided a loading dose of the drugs is not administered. If a loading dose is administered, we suggest a time interval of 6 hours between catheter removal and administration (grade 2C).

Remarks: This is a new recommendation.

13.5 Platelet GP IIb/IIIa. The platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. Following administration, the time to normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for eptifibatide and tirofiban.

13.5.1 Preoperative. We recommend that neuraxial techniques should be avoided until platelet function—as impacted by the GP IIb/IIIa inhibitor—has recovered. (Patients are typically on dual therapy and may still have residual NSAID effect.)

Remarks: There is no change to this recommendation.

13.5.2 Postoperative. Although GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery, should one be emergently administered in the postoperative period (following a neuraxial technique), we recommend the infusion should be limited to drugs minimizing sensory and motor block to facilitate assessment of neurologic function and that the patient be carefully monitored neurologically (grade 1C). Timing of catheter removal is based on ongoing risk of thromboembolism and need for continued antithrombotic therapy and the potential for spinal bleeding during catheter maintenance and removal.

Remarks: This is a new recommendation.

13.6 Cilostazol. The risk of serious bleeding associated with neuraxial block performed or maintained in the presence of residual cilostazol effect is unknown.

13.6.1 Based on the elimination half-life, we suggest that neuraxial techniques be avoided for 2 days after discontinuation of cilostazol (grade 2C).

Remarks: This is a new recommendation.

13.6.2 We suggest that neuraxial catheters be removed prior to reinstitution of cilostazol therapy postoperatively (grade 2c).

Remarks: This is a new recommendation.

13.6.3 We suggest that the first postoperative dose of cilostazol be administered 6 hours after neuraxial catheter removal (grade 2C).

Remarks: This is a new recommendation.

13.7 Dipyridamole. The risk of dipyridamole in combination with aspirin therapy may represent an increased risk.

13.7.1 Based on the elimination half-life, we suggest discontinuing extended-release dipyridamole for 24 hours prior to neuraxial block. Aspirin may be continued perioperatively (grade 2C).

Remarks: This is a new recommendation.

13.7.2 We suggest that neuraxial catheters be removed prior to reinstitution of dipyridamole therapy postoperatively (grade 2C).

Remarks: This is a new recommendation.

13.7.3 We suggest that the first postoperative dose of dipyridamole be administered 6 hours after neuraxial catheter removal (grade 2C).

Remarks: This is a new recommendation.

13.8 Cangrelor. The risk of serious bleeding associated with neuraxial block performed or maintained in the presence of residual cangrelor effect is unknown.

13.8.1 Based on the elimination half-life, we suggest that neuraxial techniques be avoided for 3 hours after discontinuation of cangrelor (grade 2C).

Remarks: This is a new recommendation.

13.8.2 We suggest that neuraxial catheters be removed prior to reinstitution of cangrelor therapy postoperatively (grade 2C).

Remarks: This is a new recommendation.

13.8.3 We suggest that the first postoperative dose of cangrelor be administered 8 hours after neuraxial catheter removal (grade 2C).

Remarks: This is a new recommendation.

Herbal Medications

There is a widespread use of herbal medications in surgical patients. Most patients do not volunteer information regarding herbal medication use; obtaining such a history may be difficult.^{249–251} Morbidity and mortality associated with herbal use may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur. Such complications include bleeding from garlic, ginkgo and ginseng, and potential interaction between ginseng-warfarin³ (Table 15).

There have been case reports of spontaneous neuraxial bleeding following ingestion of garlic²⁵² and ginkgo biloba.^{253–256}

Despite the widespread use of herbal medications, there are few controlled clinical trials of the efficacy (or adverse effects) and few outcome studies of the effects of herbal medications on surgical patients; a prospective study including more than 600 patients found no differences in surgical outcomes, including bleeding, in patients reporting recent herbal therapy.²⁵⁷ However, although overall there does not appear to be a clinically significant increase in surgical bleeding or spinal hematoma in patients

TABLE 15. Three Herbal Medications With the Greatest Impact on Hemostasis*

Herb	Important Effects	Perioperative Concerns	Time to Normal Hemostasis After Discontinuation
Garlic	Inhibition of platelet aggregation (may be irreversible) Increased fibrinolysis Equivocal antihypertensive activity	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	7 d
Ginkgo	Inhibition of platelet-activating factor	Potential to increase bleeding, especially when combined with other medications that inhibit platelet aggregation	36 h
Ginseng	Lowers blood glucose Increased prothrombin and activated partial PTs in animals Other diverse effects	Hypoglycemia Potential to increase risk of bleeding Potential to decrease anticoagulant effect of warfarin	24 h

*At this time, it is not deemed necessary to discontinue herbal medications and allow resolution of their effects on hemostasis prior to surgery or anesthesia.

Adapted from Horlocker et al,³ with permission.

receiving herbal medications, data on the combination of herbal therapy with other forms of anticoagulation are lacking. The concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants or heparin, may increase the risk of bleeding complications in these patients. Thus, it is often recommended that these medications be discontinued in anticipation of surgery, but there is no reason for cancellation of the procedure if patients have not done so.²⁵⁸

14.0 Anesthetic Management of the Patient Receiving Herbal Therapy

14.1 The use of herbal medications does not create a level of risk that will interfere with the performance of neuraxial block. We recommend against the mandatory discontinuation of these medications or avoidance of regional anesthetic techniques in patients in whom these medications have been administered (grade 1C).

Remarks: There is no change in this recommendation.

Antithrombotic Therapy and Pregnancy

Venous thromboembolism is one of the most common causes of maternal morbidity and mortality, especially in high-resource countries.¹³ Pharmacologic thromboprophylaxis has been shown to significantly decrease morbidity, but possibly at the cost of an increased incidence of bleeding.^{12,259} Common risk factors that increase the incidence of thrombosis in pregnant women include increasing age, prolonged immobilization, obesity, thrombophilia, previous thromboembolism, and cesarean delivery.^{10,14} The puerperium, defined as the 6-week period following delivery, is associated with a higher rate of thrombosis and PE than that associated with pregnancy itself.^{260,261}

Although there is an increased risk of thrombosis during normal pregnancy, in the majority of healthy women with uncomplicated pregnancies and vaginal deliveries, the benefits of thromboprophylaxis do not outweigh the maternal and fetal risks. However, for maternal conditions such as acquired or inherited thrombophilia and for those women on extended bed rest, the benefits of thromboprophylaxis may outweigh the risks. The use of anticoagulation for prevention of thromboembolism in patients is becoming more frequent. However, the thromboprophylaxis recommendations from the ACCP,¹⁴ the American College of Obstetricians and Gynecologists (ACOG),²⁶² and the Royal

College of Obstetricians and Gynaecologists²⁵⁹ differ noticeably¹⁰ (Table 16). A recent review of post-cesarean delivery patients found that 1%, 35%, and 85% of patients would receive pharmacologic prophylaxis under the ACOG, ACCP, and Royal College of Obstetricians and Gynaecologists criteria, respectfully.^{11,263}

In an effort to reduce the frequency of obstetric thromboembolism and improve maternal outcomes, the NPMS, a multidisciplinary working group representing all major women's health care professional organizations, has recently published a Consensus Bundle on Venous Thromboembolism.¹³ The bundle advocates for more aggressive risk-based assessment of obstetric patients, which will ultimately result in not only an increased use, but also likely increased doses of antithrombotic agents. This will increase the likelihood that pregnant women will be anticoagulated when presenting in labor (requesting analgesia) or for an urgent, non-elective cesarean delivery and ultimately impact on the choice of analgesia or anesthesia that is offered. It will be critical that proactive, multidisciplinary communication occur to help determine the appropriate anticoagulant doses and stop times based on the risks and benefits of VTE and neuraxial analgesia/anesthesia.

Physiologic Changes in Obstetric Patients Affecting Thromboprophylaxis

Physiological changes during pregnancy result in changes in the volume of distribution, clearance, bioavailability, and metabolism of many drugs.²⁶⁴ Available data from studies examining the pharmacokinetics and pharmacodynamics of UFH suggest that, compared with nonpregnant patients, aPTT response and duration of action of UFH may be decreased in obstetric patients.^{265,266} Similarly, for LMWH, peak anti-factor Xa levels, duration of action, and the total exposure to the drug over time (area under the plasma activity vs time curve) are lower in obstetric patients versus nonpregnant or postpartum patients.^{265,267,268} These changes are primarily due to increased volume of distribution and clearance associated with pregnancy and may lead to both decreased peak effect and lower plasma concentrations over time after LMWH dosing.

Spinal Hematoma in the Obstetric Patient

The incidence of spinal hematoma after neuraxial blockade (with or without altered hemostasis) in the obstetric patient is very

TABLE 16. Suggested Dosing Regimens for Prophylaxis Against Pregnancy-Related VTE

	ACOG ²⁶²	ACCP ¹⁴	NPMS ¹³
Prophylactic UFH	5000–10,000 U every 12 h • 5000–7500 U every 12 h in 1st trimester • 7500–10,000 U every 12 h in 2nd trimester • 10,000 U every 12 h in the 3rd trimester unless aPTT is elevated Minidose: 5000 U every 12 h	5000 U every 12 h	• 5000–7500 U every 12 h in 1st trimester • 7500–10,000 U every 12 h in 2nd trimester • 10,000 U every 12 h in the 3rd trimester Hospitalized antepartum patients may receive 5000 U every 12 h
Prophylactic LMWH	Dalteparin 5000 U once daily Tinzaparin 4500 U once daily Enoxaparin 40 mg once daily At extremes of body weight, modification of dose may be required	Dalteparin 5000 U once daily Tinzaparin 4500 U once daily Enoxaparin 40 mg once daily At extremes of body weight, modification of dose may be required	Dalteparin 5000 U once daily Tinzaparin 4500 U once daily Enoxaparin 40 mg once daily At extremes of body weight, modification of dose may be required
Therapeutic UFH	≥10,000 U every 12 h in doses adjusted to target aPTT in the therapeutic range	Every 12-h dose adjusted to target a midinterval aPTT in the therapeutic range	≥10,000 U BID adjusted to midinterval aPTT
Therapeutic-dose LMWH*	Dalteparin 200 U/kg QD or dalteparin 100 U/kg every 12 h Tinzaparin 175 U/kg QD Enoxaparin 1 mg/kg every 12 h	Dalteparin 200 U/kg QD or 100 U/kg every 12 h Tinzaparin 175 U/kg QD Enoxaparin 1 mg/kg every 12 h	Dalteparin 200 U/kg QD Tinzaparin 175 U/kg QD Enoxaparin 1 mg/kg every 12 h

*LMWH adjusted to a peak anti-factor Xa level of 0.5 to 1.0 U/mL (measured 3–4 hours after dose) or trough levels of 0.2 to 0.4 U/mL (measured 12 hours after dose). Anti-factor Xa assay must be calibrated to specific LMWH.

difficult to determine, although it is widely reported these patients have a significantly lower incidence of complications than their elderly counterparts.^{42,269} Moen et al⁴² reported 2 spinal hematomas among 200,000 epidural blocks for pain relief in labor: 1 after a subarachnoid block and 1 following the removal of an epidural catheter. The authors reported the incidence of spinal hematoma after obstetric epidural blockade was 1:200,000, which was significantly lower than the incidence of 1:3600 elderly females undergoing total knee arthroplasty. Bateman et al²⁷⁰ confirm the findings of Moen et al⁴² that obstetric patients undergoing epidural catheterization are at significantly lower risk of spinal hematoma compared with perioperative (nonobstetric surgical) patients undergoing epidural catheterization. There were 7 epidural hematomas among 142,287 patients undergoing epidural anesthesia/analgesia, for an overall risk of 1 in 20,326 epidural catheterizations. However, none of the 79,837 obstetric patients who underwent epidural placement developed a neuraxial hematoma requiring decompressive laminectomy (upper limit of 95% confidence interval, 1:21,643), compared with 7 of 62,450 patients who received perioperative epidural catheter placement (1:9000; 95% confidence interval, 1:22,189–1:4330). This difference in incidence is even more striking when considering that bloody taps are more common in the obstetric population and have been reported to occur in approximately 3% of all obstetric epidural placements.²⁷¹

The relatively hypercoagulable state of pregnancy may be protective and offers 1 possible reason for the lower rate of neuraxial hematomas in this population. The normal anatomic changes that occur in the aging spine may provide another explanation for the differing incidence. Both Moen et al⁴² and Pöpping et al²⁷² cited osteoporotic deformities as likely contributing to the risk of symptomatic vertebral canal bleeding after epidural blockade in elderly women. The prevalence of vascular disease, osteoporosis, and degenerative changes of the spine increases with age, ultimately resulting in a decrease in the volume of the epidural space. In contrast, the younger obstetric patient has a more compliant epidural space, with the ability to accommodate a larger volume of blood before the onset of symptoms. Magnetic resonance imaging (MRI) after epidural blood patch revealed blood leaking out through the intravertebral foramina after injection in young individuals.²⁷³

Until 2011, all case reports of neuraxial hematomas in obstetric patients with altered hemostasis have occurred in parturients with a preexisting coagulopathy (eg, thrombocytopenia, hemorrhage, preeclampsia, thrombocytopenia, HELLP) at the time of either epidural placement or removal.^{42,47,269,274–284} (Table 17). There are 2 recent cases of spinal hematoma involving LMWH and neuraxial anesthesia in obstetric patients: in one, the patient received therapeutic anticoagulation (enoxaparin 1 mg/kg BID) for a postpartum pulmonary embolus 3 days after a cesarean delivery performed with a spinal catheter.²⁸⁶ In the second case, a postpartum patient developed a spinal hematoma after a combined spinal-epidural (CSE) for cesarean delivery and enoxaparin thromboprophylaxis, but she had signs and symptoms of an expanding spinal hematoma before receiving the LMWH dose.²⁸⁵

Neuraxial and General Anesthesia in the Obstetric Patient

Neuraxial block is particularly vital to the care of the obstetric patient compared with alternative modes of pain management. For labor, neuraxial analgesia provides superior pain relief to other analgesic modalities and decreases circulating catecholamine levels, which may be particularly beneficial for patients with hypertensive disorders of pregnancy or preexisting comorbidities. Likewise, for cesarean delivery, neuraxial anesthesia has many maternal^{287–299} and fetal^{298–302} benefits compared with general anesthesia, including decreased risk of pulmonary complications awareness under anesthesia and surgical infections, as well as enabling immediate postdelivery mother-infant bonding (Table 18).

Obstetric and Anesthetic Management

The peripartum management of the anticoagulated parturient represents a significant clinical challenge to both the obstetrician and the anesthesiologist. The ACCP¹⁴ and the NPMS¹³ recommendations support proactive measures in the obstetric patient such as (1) discontinuing anticoagulant therapy upon the onset of labor, and per the NPMS, (2) using 5000 SC UFH BID for thromboprophylaxis in antepartum inpatients near delivery to facilitate neuraxial analgesia and anesthesia when feasible (Table 19). In the event of unforeseen labor or urgent cesarean delivery, the

TABLE 17. Spinal Hematomas in Obstetric Patients

Author	Year	Technique	Coagulopathy	Outcome	Miscellaneous
Ballin ²⁷⁵	1981	Epidural	None	Recovered	• Spinal stenosis
Newman ²⁷⁸	1983	Epidural	None	Minimal weakness and paresthesia	• Presented 2 h after delivery
Roscoe and Barrington ²⁸⁰	1984	Epidural	None	Residual leg weakness	• Epidural ependymoma • Presented 3 d postpartum • Surgical treatment
Crawford ²⁶⁹	1985	Epidural	Unknown	Recovered	• Presented several weeks postpartum
Sibai et al ²⁸²	1986	Epidural	Thrombocytopenia	Unknown	• No information
Scott and Hibbard ²⁸¹	1990	Epidural	Not reported	Improving	• Surgical treatment
Lao et al ²⁷⁷	1993	Epidural	Preeclampsia and lupus anticoagulant	Residual urinary and bowel dysfunction	• Presented 1 d postpartum • Surgical treatment
Yarnell and D'Alton ²⁸³	1996	Epidural	Abnormal aPTT Elevated aPTT Elevated PT	Mild weakness of right leg	• Presented 12 h after epidural • Surgical treatment
Yuen et al ²⁸⁴	1999	Epidural	Severe pre-eclampsia Thrombocytopenia	Recovered	• Presented within hours • Surgical laminectomy
Esler et al ²⁷⁶	2001	Epidural	None	Recovered	• Neurofibromatosis • Presented on 2nd postpartum day
Moen et al ⁴²	2004	Subarachnoid	HELLP	Unknown	• Evidence of coagulopathy
Moen et al ⁴²	2004	Epidural	HELLP	Unknown	• Epidural catheter removed in setting of coagulopathy
Nguyen et al ²⁷⁹	2006	Epidural	Post partum hemorrhage Thrombocytopenia Elevated thrombin time	Recovered	• Epidural catheter inadvertently removed while coagulopathic
Walters et al ²⁸⁵	2012	CSE	Preoperative: none Postoperative: enoxaparin 40 mg given the evening of surgery after onset of symptoms	Wheelchair bound with neuropathic pain	• Uneventful placement for cesarean delivery • A few hours after the cesarean delivery, she reported new back pain radiating to both legs • Enoxaparin 40 mg that evening • 24 h later complete motor block, absent reflexes • CT scan: no evidence of hematoma • 48 h later MRI scan without obvious hematoma • Transferred to tertiary referral center. MRI reread as hematoma with cauda equina compression • Surgical treatment
Chiaghana et al ²⁸⁶	2016	Continuous spinal	Preoperative: UFH held for 24 h ASA Postoperative: enoxaparin 1 mg/kg	Fully recovered at 18 mo	• Enoxaparin started 12 h after catheter removal • POD3 dyspnea, PE • Enoxaparin increased to BID • POD 4 back pain and LE weakness • MRI T6 to sacrum hematoma • Decompressive laminectomy

Adapted from Horlocker et al,⁷ with permission.

TABLE 18. Advantages of Neuraxial Versus General Anesthesia for Cesarean Delivery in the Obstetric Patients**Maternal Benefits**

- Decreases anesthesia-related adverse events (eg, pulmonary or cardiac complications, cardiac arrest)²⁸⁷
- Reduces risk of gastric aspiration^{288–290}
- Avoids hypertensive response to intubation in vulnerable population (eg, preeclampsia)²⁹⁰
- Avoids awareness under general anesthesia²⁹¹
- Reduces risk of intraoperative uterine atony and hemorrhage^{292–294}
- Reduces surgical site infection²⁹⁵
- Provides superior quality with systemic opioid-sparing cesarean analgesia; reduces risk of chronic postdelivery pain^{296,297}
- Enables benefits of immediate postdelivery skin-to-skin bonding and breastfeeding^{298,299}
- Improves maternal and paternal participation in birth²⁹⁹

Fetal Benefits

- Reduces risks of respiratory depression at delivery, Apgar <7 at 5 min, and admission to neonatal intensive care unit^{300,301}
- Avoids in utero exposure to induction/inhalational agents with potential developmental neurotoxicity³⁰²
- Enables benefits of immediate postdelivery skin-to-skin bonding and breastfeeding^{298,299}

choice of analgesia and/or anesthesia should weigh the risks of general anesthesia and benefits of neuraxial anesthesia in the setting of the anticoagulant type, dose, time of administration, and pertinent laboratory values. The plan for reinitiating anticoagulation postpartum must also be considered when planning the anesthetic management. In general, early postpartum, administration of thromboprophylaxis is delayed until adequate hemostasis is achieved, and bleeding risk is decreased. For example, prophylactic LMWH may be started/restarted 6 to 12 hours after delivery and no sooner than 4 hours after epidural catheter removal (whichever is later). Therapeutic LMWH may be administered 24 hours after delivery, as long as hemostasis is ensured, and there has not been a bloody or traumatic epidural.¹⁰ These time intervals are consistent with those in the nonobstetric patient.⁷

15.0 Anesthetic Management of the Anticoagulated Parturient

15.1 Given the limited pharmacologic data on antithrombotic agents in pregnancy and in the absence of a large series of neuraxial techniques in the pregnant population receiving prophylaxis or treatment for VTE, we suggest that the ASRA guidelines be applied to parturients (grade 2C).

Remarks: There is no change to this recommendation.

15.2 However, in circumstances involving select high-risk parturients receiving VTE prophylaxis and requiring urgent interventions for maternal or fetal indications, the risk of general anesthesia may be greater than neuraxial anesthesia, and exceptions/modifications of the ASRA guidelines may be appropriate (grade 2C).

Remarks: This is a new recommendation.

Plexus and Peripheral Blockade in the Anticoagulated Patient

Although spinal hematoma is the most significant hemorrhagic complication of regional anesthesia due to the catastrophic nature of bleeding into a fixed and noncompressible space, the associated risk following plexus and peripheral techniques remains undefined. The fear of bleeding, specifically in a deep, noncompressible site, is frequently a deterrent from performing peripheral

nerve blockade, even in patients who would likely benefit. Unfortunately, there continues to be a lack of investigations examining the frequency and severity of hemorrhagic complications following plexus or peripheral blockade in anticoagulated patients. In addition, there continue to be case reports of significant morbidity related to hematomas following peripheral nerve blockade in coagulopathic patients.^{236,237,303,304} Idestrup et al³⁰⁵ performed a prospective, observational study investigating the incidence of hematoma formation and subsequent neurovascular compromise in patients with femoral catheters who were started on rivaroxaban postoperatively. Rivaroxaban was administered daily, and the femoral catheter was removed 20 hours after the first dose. No patient presented with a hematoma causing neurovascular compromise, although ecchymosis in the groin or upper thigh was relatively common, with the highest incidence on POD3.

All published cases of clinically significant bleeding/bruising after plexus or peripheral techniques in patients with normal hemostasis are reported in Table 20,^{306–318} and those receiving antithrombotic therapy are reported in Table 21.^{236,237,303,304,310,321–325} In all patients with neurodeficits, neurologic recovery was complete within 6 to 12 months. Thus, while bleeding into a neurovascular sheath may result in significant decreases in hematocrit, the expandable nature of peripheral site may decrease the chance of irreversible neural ischemia.

Of the 14 patients with bleeding complications following peripheral or plexus block in patients without anticoagulation, 6 were serious and required hospitalization, transfusion, and/or surgical intervention (including 1 emergency tracheostomy after traumatic stellate ganglion block). There were 18 cases (4 new cases since last publication) of hemorrhagic complications associated with peripheral or plexus block in patients receiving antithrombotic therapy preblock and/or postblock (Table 21). Fifteen of these complications were serious, including 1 death due to massive hemorrhage following lumbar sympathetic block in a patient receiving clopidogrel. In all but 1 patient, hospitalization was complicated and prolonged.

This series of 32 patients remains insufficient to make definitive recommendations. However, trends are evolving, which may assist with patient management. For example, these cases continue to suggest that significant blood loss, rather than neural deficits, may be the most serious complication of nonneuraxial regional techniques in the anticoagulated patient. In addition, hemorrhagic complications following the deep plexus/deep peripheral techniques (eg, lumbar sympathetic, lumbar plexus, and paravertebral), particularly in the presence of antithrombotic therapy, are often serious and a source of major patient morbidity. While needle/catheter placement may be described as difficult, there is often no evidence of vessel trauma (including the patient death from massive bleeding).

16.0 Anesthetic Management of the Patient Undergoing Plexus or Peripheral Block

16.1 For patients undergoing perineuraxial, deep plexus, or deep peripheral block, we recommend that guidelines regarding neuraxial techniques be similarly applied (grade 1C).

Remarks: There is no change in this recommendation.

16.2 For patients undergoing other plexus or peripheral techniques, we suggest management (performance, catheter maintenance, and catheter removal) based on site compressibility, vascularity, and consequences of bleeding, should it occur (grade 2C).

Remarks: This is a new recommendation.

Recommendations of the ESA for Regional Anesthesia and Antithrombotic Agents

Consensus statements tend to reflect the clinical experience and concerns of the conference participants. A number of

TABLE 19. Antepartum Management of Antithrombotic Therapy

	ACOG ²⁶²	ACCP ¹⁴	NPMS ¹³
Antepartum: general guidance	Heparin compounds are the preferred anticoagulant during pregnancy (level B)	For pregnant patients, recommend LMWH for prevention and treatment of VTE, instead of UFH (grade 1B) Women at very high risk of recurrent VTE (eg, proximal VTE or PE close to the expected date of delivery may benefit by having a planned delivery by induction or cesarean delivery as appropriate, so that the duration of time without anticoagulation can be minimized (no grade)	Daily LMWH or BID UFH for all antepartum patients hospitalized for at least 72 h who are not at high risk of bleeding or imminent child birth. For women at high risk of childbirth or bleeding, mechanical thromboprophylaxis or a prophylactic dose of UFH (5000 U every 12 h)
Antepartum: conversion to UFH	Women receiving therapeutic or prophylactic LMWH may be converted to UFH in the last month of pregnancy or sooner if delivery appears imminent (level C) or planned delivery with withholding of anticoagulants for 24 h (no grade)	Women at highest risk of recurrent VTE (eg, proximal VTE or PE within 2 wk) can be switched to IV UFH prior to planned delivery, which is then discontinued 4–6 h prior to the expected time of delivery or epidural insertion (no grade)	For women at high risk of childbirth or bleeding prophylactic dose of UFH (5000 U every 12 h) should be used
Antepartum: timing of neuraxial blockade after last dose of LMWH/UFH	It is recommended to withhold neuraxial blockade for 10–12 h after the last prophylactic dose of LMWH or 24 h after the last therapeutic dose of LMWH (level C)	For pregnant women receiving adjusted-dose LMWH and where delivery is planned, recommend discontinuation of LMWH at least 24 h prior to induction of labour or cesarean delivery (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (grade 1B) If spontaneous labor occurs in women receiving anticoagulation, neuraxial anesthesia should not be used. Where the level of anticoagulation is uncertain and where laboratory support allows for rapid assessment of heparin levels, then testing can be considered to guide anesthetic and surgical management (no grade)	Antepartum or intrapartum UFH prophylaxis ($\leq 10,000$ U/d) No contraindications to timing of heparin dose and performance of neuraxial blockade UFH therapeutic: wait 6 h after last dose before neuraxial blockade or check aPTT LMWH prophylaxis: wait 12 h after last dose before neuraxial blockade LMWH therapeutic: wait 24 h after last dose before neuraxial blockade

European societies have approved official guidelines for thromboembolism prophylaxis and regional anesthesia.^{8,81,327} Both ESA (Table 7) and ASRA published updated recommendations in 2010.^{7,8} Recently, the ESA has collaborated with ASRA to construct a single set of guidelines. As a result, there are only minimal differences. For example, the management of patients receiving thrombolytics, UFH, single-dose LMWH, and antiplatelet therapy is remarkably similar. As expected, the ASRA guidelines for BID prophylactic LMWH (a dosing regimen not approved in Europe) remain conservative because of the large number of hematomas in North America. An additional major difference is the management of the patient receiving warfarin. The ASRA guidelines, advocating for complete resolution of the warfarin effect, recommend a normal INR upon discontinuation of warfarin therapy prior to neuraxial block, whereas the ESA allows residual effect with an INR as high as 1.4. Conversely, the ESA guidelines do not allow warfarin to be administered in the presence of an indwelling neuraxial catheter. Finally, the ESA recommendations for the new oral anticoagulants appear to allow neuraxial block approximately 1 to 2 days earlier than ASRA after their discontinuation. However, ESA time intervals are for patients with normal renal function only; longer intervals are recommended in patients with renal compromise.⁸ In actuality, the time intervals are very similar. These time intervals may be revised as methods of monitoring, and reversing these agents becomes more readily available.

Unplanned Anticoagulation During Neuraxial Analgesia

Occasionally, patients require emergent antithrombotic therapy (vascular graft thrombosis, acute coronary syndrome/myocardial infarction), or a breakdown in communication results in unanticipated anticoagulation in the presence of indwelling epidural catheters. It is critical that the Acute Pain Medicine Service be aware of alterations in the degree and timing of anticoagulation. Increasing centralization and computerization make it possible for Hospital Pharmacy Services to assist with patient management. Because all medication orders are filled by pharmacists using a central computer, patients who receive an epidural infusion are identified within the pharmacy database. Any subsequent order for an antithrombotic agent is flagged as a drug “interaction” during entry, and the pharmacist receives an alert notice to contact the pain service. The pain service is then able to consult in a multidisciplinary manner with other services involved with the patient's care; timing of catheter removal will then be based on ongoing risk of thromboembolism and need for continued antithrombotic therapy and the potential for spinal bleeding during catheter maintenance and removal. This “pharmacy failsafe” allows the anesthesia acute pain service to participate proactively in the timing of catheter removal and subsequent anticoagulation, as well as closely monitor the patient's neurologic status.³²⁸

TABLE 20. Hemorrhagic Complications Following Plexus and Peripheral Block in Patients Without Antithrombotic Therapy

Reference	Patient Information	Block Type	Clinical Course/Outcomes
Wheatley et al ³⁰⁶ (1984)	59-y-old woman with chronic pelvic pain	4 Lumbar sympathetic blocks over a 5-d period (paravertebral approach 5 cm lateral to the 2nd lumbar vertebrae)	<ul style="list-style-type: none"> • 30 min after the last block patient noted right lower quadrant pain extending to her hip and flank • Treated with unknown analgesics and dismissed home • The next morning patient was readmitted with fever and nausea and vomiting • A palpable mass in the flank and right upper abdomen was noted • Abdominal CT scan revealed a large subcapsular hematoma causing considerable renal compression • Patient was transfused with packed red blood cells • Pain persisted and hypertension developed between the 9th and 12th day • Surgical intervention revealed a massive subcapsular hematoma (1000 mL of blood was evacuated)
Stan et al ³⁰⁷ (1995)	No information	Axillary (transarterial)	<ul style="list-style-type: none"> • Patient developed small (<2 cm) hematoma • Resolved without sequelae
Kurzel et al ³⁰⁸ (1996)	17-y-old admitted for induction of labor	Bilateral pudendal block	<ul style="list-style-type: none"> • Postpartum day 3 patient complained of abdominal distention, back pain, pain in right inguinal area, and fever • Patient was discharged and readmitted 2 d later with increasing abdominal pain radiating to right lower quadrant and flank • CT scan revealed an infected, right retroperitoneal hematoma • Treated with broad-spectrum antibiotics and dismissed after 3 d when fever and pain resolved
Mishio et al ³⁰⁹ (1998)	62-y-old woman with sudden deafness	4 Sequential (on alternate days) stellate ganglion blocks at C7, anterior paratracheal approach	<ul style="list-style-type: none"> • 30 min after the 4th block, patient complained of discomfort in her throat • Patient was noted to have a Horner syndrome • 2 h later, patient complained of dyspnea and difficulty swallowing • MRI scan revealed massive hemorrhage from clivus to the diaphragm • Patient required emergency tracheotomy due to glottic swelling and narrowing • Multiple complications during the hospitalization • Stoma closed on POD33 and discharged on 41st day after the block
Ben-David and Stahl ³¹⁰ (1999)	38-y-old healthy man, procedure on palmar surface of wrist	Axillary (transarterial)	<ul style="list-style-type: none"> • Large axillary hematoma causing paresthesias and radial nerve weakness • Electromyogram at 4 wk demonstrated signs of neuropraxia • Complete recovery after 6 mo
Thomas et al ³¹¹ (1999)	65-y-old woman undergoing thoracotomy for recurrent esophageal hernia	Paravertebral (loss of resistance to saline technique)	<ul style="list-style-type: none"> • Technical difficulty during block placement, with blood aspiration on 2nd pass of the needle • 150 mL of blood suctioned from the endotracheal tube • CT scan revealed small hematoma around thoracic spine and the aorta at the level of T6 and an area of pulmonary hemorrhage in the left lower lobe • Initial surgery canceled and patient discharged after 3 d • Readmitted 2 wk later for initial thoracotomy with no paravertebral block
Vaisman ³¹² (2001)	40-y-old man with left testicular pain	Ilioinguinal	<ul style="list-style-type: none"> • 3 h after block placement, patient returned to emergency room with nausea, dizziness, and worsening abdominal pain • CT scan revealed left pelvic hematoma (approximately 20 mL) • Symptoms resolved with conservative management, and patient was discharged home after 2 d

Continued next page

TABLE 20. (Continued)

Reference	Patient Information	Block Type	Clinical Course/Outcomes
Borgeat et al ³¹³ (2001)	No information	Infraclavicular (modified approach of the Raj technique)	<ul style="list-style-type: none"> • Patient developed hematoma at the puncture site • No information about outcome
Ekatodramis et al ³¹⁴ (2001)	48-y-old woman with chronic regional pain syndrome of the right hand	Continuous interscalene catheter	<ul style="list-style-type: none"> • 3 d postoperatively, the patient complained of blurred vision and painful swelling on right side of neck • Ultrasound of neck revealed 4 × 5-cm hematoma • Neurologic investigation confirmed Horner syndrome • Catheter removed immediately • 6 mo later, Horner syndrome began to improve • Complete resolution at 1 y
Ekatodramis et al ³¹⁴ (2001)	20-y-old healthy woman undergoing right shoulder Bankart repair	Continuous interscalene catheter	<ul style="list-style-type: none"> • POD1 patient noted visual disturbances and neck swelling • Ultrasound of the neck revealed 3 × 4-cm hematoma • Neurologic investigation confirmed Horner syndrome • Catheter removed immediately • 6 mo later, only slight ptosis present • Complete resolution at 1 y
Bergman et al ³¹⁵ (2003)	No information	Continuous axillary catheter	<ul style="list-style-type: none"> • Patient developed axillary hematoma • Resolved spontaneously without sequelae
Amory et al ³¹⁶ (2003)	6-y-old healthy boy, left herniorrhaphy	Ilioinguinal/iliohypogastric	<ul style="list-style-type: none"> • Large, obstructing subserosal hematoma, which presented as intestinal obstruction 5 d postoperatively • Diagnostic laparoscopy and bowel resection with an uneventful recovery
Frigon et al ³¹⁷ (2006)	6-y-old healthy girl, appendectomy	Ilioinguinal/iliohypogastric	<ul style="list-style-type: none"> • Hematoma (2 cm in diameter) in the wall of the terminal ileum noted upon opening peritoneum • Hematoma was nonobstructing • Uneventful recovery
Singh et al ³¹⁸ (2014)	35-y-old woman Giant cell tumor resection of radius	Supraclavicular block (paresthesia technique)	<ul style="list-style-type: none"> • Paresthesia elicited on 3rd attempt • At the end of procedure, complained of slight chest pain in ipsilateral infraclavicular region • Chest x-ray negative • Adequate sensory/motor block • 12 h later, worsening chest pain and palpitations • Chest x-ray revealed massive fluid collection on the right side with partial collapse of right lung • Chest tube placed with 1300 mL of blood drained and transfused 4 U whole blood • Intensive care unit for 5 d, dismissed in 10 d in satisfactory condition

Adapted from Horlocker et al,⁷ with permission.

Comparison Between the ASRA Regional Anesthesia and Pain Guidelines

In response to recent publications of cases of epidural hematoma during interventional pain procedures in patients receiving antiplatelet agents,^{16,17} attendees of the 11th Annual ASRA Pain Medicine Meeting of ASRA, held November 15 to 18, 2012, in Miami, Florida, were surveyed. The purpose was to determine practice patterns of pain physicians regarding continuance of concurrently administered anticoagulants, timing schedules for cessation and resumption of use, and any use of “bridging” therapies when planning for various interventional pain procedures. The survey items included specific practice characteristics and whether active protocols were used. In addition, the survey queried the frequency of adherence to specific elements of the current ASRA practice guidelines for regional anesthesia in patients on antiplatelet and anticoagulant medications and/or if respondents incorporated different protocols for different pain procedures.

Most of the respondents followed ASRA guidelines for anti-coagulants but not for antiplatelet agents. Two-thirds of the participants had separate protocols regarding aspirin or NSAIDs. Moreover, 55% stopped acetylsalicylic acid before spinal cord stimulation (SCS) trials and implants, and 32% stopped aspirin before ESIs. In addition, 17% admitted that they used different protocols for cervical spine injections as compared with lumbar spine injections. For example, although ESIs have been shown to be safe in patients who take NSAIDs in 1 study, 80% of the injections were done in the lumbar levels.²⁴³

These cases and survey results suggest that the risk of significant bleeding in patients undergoing interventional pain procedures may have been underestimated. Indeed, all previous ASRA guidelines (including the current fourth edition) do not recommend discontinuation of aspirin or NSAIDs prior to the placement of epidural and spinal blocks; nor do the guidelines differentiate between interventional pain procedures and perioperative regional anesthesia blocks, other than considering severity of

TABLE 21. Hemorrhagic Complications Following Plexus and Peripheral Block in Patients Receiving Antithrombotic Therapy

Reference	Patient Information	Anticoagulant/ Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Nielsen ³¹⁹ (1989)	<ul style="list-style-type: none"> 80-y-old man Cholecystectomy with severe postoperative pain 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> Warfarin preoperatively PT on operative day 13 s <p><i>Postoperative</i></p> <ul style="list-style-type: none"> Heparin 5000 U subcutaneously every 8 h (started 8 h postoperatively and discontinued on POD2) POD2 heparin bolus 4500 U intravenously followed by continuous infusion (PTT ranged from 99–29 s) 	<ul style="list-style-type: none"> Intercostal nerve blocks bilaterally T7–T11 Placed 20 h postoperatively Blocks repeated 4 times (approximately every 7 h) 	<ul style="list-style-type: none"> Small chest wall hematoma noted on POD3 at T7 before the last block was placed Over the next 2 d hematoma increased to 30 × 65 cm and covered a large area of the posterior and lateral chest wall down to flank and upper thigh Required transfusion of 8 U of packed red blood cells Heparin infusion was stopped Patient recovered uneventfully but had pain for 4 wk in the area of the hematoma
Aida et al ³²⁰ (1996)	<ul style="list-style-type: none"> 71-y-old woman Pain due to herniated lumbar disc 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> None <p><i>Postoperative</i></p> <ul style="list-style-type: none"> Pain treated with mephenamic acid (NSAID) 	<ul style="list-style-type: none"> Lumbar plexus block Performed 4 times for 4 wk Level of L3 using loss of resistance technique 	<ul style="list-style-type: none"> Low back pain became more intense 1 d after the last block Difficulty walking for several days Pain still present 10 d after the block CT scan and ultrasonography revealed renal subcapsular hematoma Microscopic hematuria resolved after 2 wk Back pain resolved after 3 wk Hematoma resorbed spontaneously within 4 mo
Aida et al ³²⁰ (1996)	<ul style="list-style-type: none"> 68-y-old woman Severe low back pain due to spinal spondylosis 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> None <p><i>Postoperative</i></p> <ul style="list-style-type: none"> Pain treated with 200 mg IV diclofenac (NSAID) 	<ul style="list-style-type: none"> Lumbar plexus block at the level of L3 using loss of resistance technique 	<ul style="list-style-type: none"> Low back pain became more intense 1 d after the block Pain remained severe and patient could not ambulate for several days 3 d after block CT scan and ultrasonography revealed a renal subcapsular hematoma Microscopic hematuria resolved after 1 wk Pain markedly decreased after 2 wk Discharged after a 10-d hospitalization Pain resolved after 6 wk, hematoma resorbed within 4 mo
Klein et al ³²¹ (1997)	<ul style="list-style-type: none"> 67-y-old woman Repair of open right calcaneal fracture Patient underwent 3 operative procedures over a 6-d period 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> Aspirin 325 mg/d <p><i>Postoperative</i></p> <ul style="list-style-type: none"> POD1 enoxaparin 30 mg BID and aspirin 325 mg/d Enoxaparin continued 30 mg every 12 h 3rd operative procedure was 19½ h after last dose of enoxaparin First postoperative enoxaparin dose (after 3rd procedure) 4.5 h after block placement Enoxaparin discontinued on hospital day 15 after CT scan 	<p><i>Night of admission</i></p> <ul style="list-style-type: none"> Incision and drainage of ankle <p><i>Sciatic block (Labat approach), saphenous nerve block posterior to the sartorius muscle</i></p> <p><i>Hospital day 3 (2nd procedure)</i></p> <ul style="list-style-type: none"> Open reduction internal fixation of ankle <p><i>Sciatic block (Raj approach) and lumbar plexus block (femoral approach)</i></p> <p><i>Hospital day 6 (3rd procedure)</i></p> <ul style="list-style-type: none"> Right below knee amputation Lumbar plexus block (posterior approach)—unable to place despite multiple attempts Lumbar plexus block (femoral approach) and sciatic block (Raj approach) 	<ul style="list-style-type: none"> Hospital day 7 (1 d after below the knee amputation) patient complained of right hip pain Hospital day 14 severity of pain worsened Hospital day 15 patient was unable to move right leg Abdominal CT revealed a large retroperitoneal hematoma involving the right psoas muscle Patient regained motor function over the next 5 d No subjective or objective evidence of sensory deficit at the 4-mo follow-up visit

Continued next page

TABLE 21. (Continued)

Reference	Patient Information	Anticoagulant/ Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Maier et al ³²² (2002)	<ul style="list-style-type: none"> • 79-y-old woman • Generalized peripheral arterial disease • Severe pain in lower extremities 	<i>Preoperative</i> <ul style="list-style-type: none"> • Clopidogrel 75 mg/d • Discontinued 3 d prior to block <i>Postoperative</i> <ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Diagnostic lumbar sympathetic block at the L3 level 	<ul style="list-style-type: none"> • No intravascular injection recognized • 9 h after the block patient complained of burning groin and medial thigh pain • Vital signs stable at the time • Low-dose opioids decreased pain, and patient walked on the ward without complaints • 1 h later patient was found pulseless • Resuscitation attempts were unsuccessful • Autopsy revealed a massive coagulated retroperitoneal hematoma (about 2.3–3 L) • No vascular puncture during first block
Maier et al ³²² (2002)	<ul style="list-style-type: none"> • 71-y-old man • Left leg claudication 	<i>Preoperative</i> <ul style="list-style-type: none"> • Ticlopidine 500 mg/d <i>Postoperative</i> <ul style="list-style-type: none"> • Ticlopidine stopped 2 d after the first block 	<ul style="list-style-type: none"> • Left-sided lumbar sympathetic block using radiographic control • 6 d after the first block, a second block was performed • Radiographic control using contrast medium confirmed intravascular needle position • Needle was repositioned 	<ul style="list-style-type: none"> • Within 12 h complained of numbness on medial side of thigh and groin pain • 2 d later, widespread skin hematoma was noted • The night after the second block, the patient complained of severe groin pain and decrease in blood pressure • CT scan revealed large retroperitoneal hematoma • Patient required a blood transfusion of an unknown amount • Discharged 5 d later without major complaints
Weller et al ³²³ (2003)	<ul style="list-style-type: none"> • 85-y-old woman • Unicompartmental right knee arthroplasty 	<i>Preoperative</i> <ul style="list-style-type: none"> • No anticoagulant medication <i>Postoperative</i> <ul style="list-style-type: none"> • POD2 at 0900 enoxaparin 30 mg • Enoxaparin continued 30 mg every 12 h • Enoxaparin discontinued on POD4 	<ul style="list-style-type: none"> • Single-injection sciatic (Labat approach) and continuous lumbar plexus block (posterior approach) • Blood was aspirated, catheter withdrawn 2 cm and flushed with saline, aspiration then negative • Supplemental sciatic block at the midpoint between the ischial tuberosity and greater trochanter, and a femoral block at the groin 	<ul style="list-style-type: none"> • Lumbar plexus infusion discontinued the evening of POD1 subcutaneously • Lumbar plexus catheter removed at 10:40 AM • 4 h later, patient complained of new, significant back pain • Treated with morphine • POD3 right paravertebral pain, no neurological deficit • POD4 CT scan revealed extensive retroperitoneal hematoma that extended from the retrohepatic space to the pelvis • Transfused 4 U of packed red blood cells • Protracted postoperative course with acute renal failure, ileus, pulmonary edema, and atrial fibrillation • Never developed a neurologic deficit • POD5 extensive ecchymosis and pain in flank and hip • Dismissed from hospital on POD20

Continued next page

TABLE 21. (Continued)

Reference	Patient Information	Anticoagulant/ Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Weller et al ³²³ (2003)	<ul style="list-style-type: none"> 65-y-old man Left knee arthroscopy Mechanical aortic valve 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> Warfarin 5 mg/d Aspirin 81 mg BID Patient admitted with INR 5.19, coumadin stopped, and heparin started Next day INR measured 9.27, given 10 mg vitamin K and 1 U fresh frozen plasma Morning of surgery INR 0.92 <p><i>Postoperative</i></p> <ul style="list-style-type: none"> Heparin infusion initiated at 1200 U/h 8 h after the lumbar plexus block aPTT on POD1 was 77.7 s Coumadin restarted evening of POD1 POD3 aPTT >100 s and INR 1.4 Heparin adjusted and POD4 aPTT 60.2 s POD5 anticoagulation discontinued and vitamin K 1 mg subcutaneously and 2 U fresh frozen plasma given 	<ul style="list-style-type: none"> Single-injection lumbar plexus block (posterior approach) and single-injection sciatic block No technical difficulty noted 	<ul style="list-style-type: none"> POD3 patient complained of back pain at the site of the lumbar plexus block CT scan revealed moderate-size retroperitoneal hematoma that appeared to originate in the psoas muscle Transfused 2 U packed red blood cells Discharged on POD10 with plan to restart anticoagulation 2 wk after discharge
Aveline et al ³²⁴ (2004)	<ul style="list-style-type: none"> 72-y-old woman Total hip replacement Heterozygous Leiden mutation 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> Phenylinanedione stopped 5 d before surgery Enoxaparin 60 mg BID started 5 d before surgery and held 24 h before surgery INR and aPTT normal <p><i>Postoperative</i></p> <ul style="list-style-type: none"> Anticoagulation initiated at 14 h with enoxaparin 40 mg and then increased to 60 mg once daily on POD2 Phenylinanedione restarted on POD3 and enoxaparin stopped on POD7 	<ul style="list-style-type: none"> Lumbar plexus block via the posterior approach Unable to be placed after 3 attempts Fascia iliaca compartment block on first attempt 	<ul style="list-style-type: none"> On POD17, the patient complained of progressive left leg motor deficit and left lumbar back pain Extensive ecchymosis on the left side of her back with sensory and motor deficit in the distribution of the femoral nerve and lateral cutaneous nerve of the thigh (INR 3.5) CT scan revealed large left retroperitoneal hematoma with anterior displacement of the left kidney and diffusion of the hematoma into the left psoas and iliac muscles Patient received 3 U of packed red blood cells and vitamin K Motor function started to progressively recover on POD19 Recovery was complete on POD45
Bickler et al ³²⁵ (2006)	<ul style="list-style-type: none"> 49-y-old man Right total knee replacement 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> No anticoagulant medication <p><i>Postoperative</i></p> <ul style="list-style-type: none"> POD2 enoxaparin 40 mg/d subcutaneously POD5 enoxaparin discontinued 	<ul style="list-style-type: none"> Continuous sciatic nerve catheter (lateral, midfemoral region) Continuous femoral catheter 	<ul style="list-style-type: none"> No difficulty noted with either catheter placement Nerve catheters removed on POD3 approximately 3 h after the enoxaparin dose At the time of catheter removal, swelling and discoloration were noted at both the femoral and sciatic insertion sites POD4 massive swelling of right thigh and extensive ecchymoses at both sites Sensation and strength were unaffected Patient discharged on POD7, which was 2 d later than expected No specific treatment for the hematoma

Continued next page

TABLE 21. (Continued)

Reference	Patient Information	Anticoagulant/ Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Bickler et al ³²⁵ (2006)	<ul style="list-style-type: none"> • 78-y-old woman • Total knee replacement 	<i>Preoperative</i> <ul style="list-style-type: none"> • No anticoagulant medication <i>Postoperative</i> <ul style="list-style-type: none"> • POD1 enoxaparin 40 mg/d subcutaneously 	<ul style="list-style-type: none"> • Continuous sciatic nerve catheter (lateral, midfemoral region) • Continuous femoral catheter 	<ul style="list-style-type: none"> • No difficulty noted with either catheter placement • On POD2, the lateral thigh at the site of the sciatic catheter was swollen and ecchymotic • The catheters were removed at this time, but the bruising increased over the next 24 h • No significant neurologic impairment at the time of discharge on POD5
Bickler et al ³²⁵ (2006)	<ul style="list-style-type: none"> • 48-y-old woman • Total knee replacement 	<i>Preoperative</i> <ul style="list-style-type: none"> • No anticoagulant medication <i>Postoperative</i> <ul style="list-style-type: none"> • POD1 enoxaparin 40 mg/d subcutaneously 	<ul style="list-style-type: none"> • Continuous sciatic nerve catheter (lateral, midfemoral region) • Continuous femoral catheter 	<ul style="list-style-type: none"> • No difficulty noted with either catheter placement • POD2 the dressings over the femoral catheter insertion site were soaked with 15–20 mL of blood, no hematoma noted • The catheters were removed on POD2, and the femoral site continued to ooze blood and soaked another dressing • No further bleeding on POD3 • No delay in discharge
Wiegel et al ³²⁶ (2007)	<ul style="list-style-type: none"> • No information 	<i>Preoperative</i> <ul style="list-style-type: none"> • Aspirin 1 g/d 	<ul style="list-style-type: none"> • Continuous femoral catheter 	<ul style="list-style-type: none"> • Patient complained of inguinal pain, numbness, weakness of the thigh on the 6th POD • CT scan revealed a retroperitoneal hematoma • Retroperitoneal hematoma required surgical intervention • No further information
Clendenen et al ³²⁶ (2010)	<ul style="list-style-type: none"> • 66-y-old woman • Right shoulder hemiarthroplasty and rotator cuff repair 	<i>Preoperative</i> <ul style="list-style-type: none"> • Dipyridamole • Aspirin (stopped 1 wk preoperative) <i>Postoperative</i> <ul style="list-style-type: none"> • Dipyridamole 	<ul style="list-style-type: none"> • Continuous interscalene block 	<ul style="list-style-type: none"> • Nerve stimulator guided block with puncture of external jugular vein during placement • Interscalene catheter noted to be dislodged in the am of POD1 • A 1-cm diameter hematoma noted at previous puncture site • A 2nd continuous interscalene catheter placed distal to previous puncture site • Catheter was removed 72 h later on POD5 at home • POD8, lethargic, pale, with labored breathing and signs of infection at surgical site • Admitted with sepsis and noted to have a hard mass at site or previous interscalene catheter placement • Cultures revealed <i>Staphylococcus aureus</i> • Discharged after 30-d hospital stay to extended care facility in good condition

Continued next page

TABLE 21. (Continued)

Reference	Patient Information	Anticoagulant/ Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Rodriguez et al ³⁰³ (2011)	59-y-old woman undergoing bullet removal from left calf	<i>Preoperative</i> • None <i>Postoperative</i> • Bemiparin 3500 IU subcutaneously every 24 h	Single injection femoral and sciatic nerve blocks	<ul style="list-style-type: none"> Preoperative laboratory values include platelet count 175,000, INR: 0.99, fibrinogen: 427 mg/dL, aPTT: 38.9 s Dismissed the same day without obvious complications 10 d postoperatively, the patient was readmitted with a large, soft hematoma at the proximal two-thirds of the thigh that extended to the knee CT scan revealed intermuscular and intramuscular hematoma of the quadriceps femoris muscle aPTT was prolonged at 44.4 s, and bemiparin was stopped Patient diagnosed with a mild factor XI deficiency (45%) 4 d after readmission, patient noted severe paresis and quadriceps femoris and anesthesia to pinprick in saphenous nerve distribution Emergent surgical exploration revealed a 10-cm intraneural hematoma of the femoral nerve extending toward pelvic cavity Discharged after 22 d with residual paresis but able to crutch walk; 4 mo later, able to walk without limping, although cutaneous anesthesia of medial side of the calf to medial malleolus persisted
Parvaiz et al ²³⁷ (2012)	<ul style="list-style-type: none"> 71-y-old man Inguinal hernia 	<i>Preoperative</i> • Dipyridamole • Aspirin (stopped 1 wk preoperatively) <i>Postoperative</i> • Dipyridamole	• Ilioinguinal/iliohypogastric nerve block	<ul style="list-style-type: none"> Placed uneventfully with landmark-based technique Admitted 9 d later with right flank pain and hemoglobin 7.0 g/dL CT scan revealed large retroperitoneal hematoma 22 × 10 × 7 cm Angiogram showed active bleeding from deep circumflex iliac artery, which was successfully coiled Discharged 2 d later after a blood transfusion
Wamer et al ³⁰⁴ (2016)	<ul style="list-style-type: none"> 87-y-old man Left total hip arthroplasty Myeloproliferative disorder and essential thrombocytosis 	<i>Preoperative</i> • Aspirin 325 mg BID <i>Postoperative</i> • Aspirin 325 mg BID	• Posterior lumbar plexus catheter	<ul style="list-style-type: none"> Baseline platelet count 700,000 on high-dose hydroxyurea Hemoglobin preoperatively 11.5 g/dL Several passes required to place psoas catheter and blood aspirated on initial placement. Catheter removed and replaced with negative aspiration Moderate hypotension intraoperatively with severe hypotension in the postanesthesia care unit Hemoglobin 5.2 g/dL in the postanesthesia care unit with a 250-mL surgical blood loss Urgent CT scan of abdomen/pelvis revealed a large retroperitoneal hematoma No surgical intervention required No neurologic sequelae

Adapted from Horlocker et al,⁷ with permission.

needle/catheter trauma, degree of anticoagulation, and ability to compress the site.

On the basis of these concerns, the ASRA Board of Directors appointed a committee to develop separate guidelines for pain interventions. The committee has an international representation and was endorsed by the European Society of Regional Anaesthesia & Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain.

Differences in Patient Populations

Patients undergoing spine and pain procedures may be treated differently from patients undergoing regional blocks for surgery, acute pain, or obstetrics for several reasons. Pain procedures vary from minimally invasive procedures with high-risk targets (eg, percutaneous SCS lead placement, vertebral augmentation, deep visceral blocks, and spine interventions) to low-risk peripheral nerve blocks (Table 22). The ASRA guidelines may be appropriate for the low- or intermediate-risk category, but the high-risk spine procedures require a more conservative approach.

For example, SCS involves the insertion of large-bore needles and cephalad advancement of the electrode up to the T10 (for lumbar radiculitis) or the upper thoracic levels (for upper-extremity radiculopathy). Several advancements and retractions of electrodes are needed to optimally place the electrodes, resulting in possible trauma to the vascular structures. Occasionally, 2 electrodes are placed to adequately cover the painful area (s). Most patients who are candidates for SCS placement had a prior laminectomy with postoperative scarring, further decreasing the epidural space. In addition, patients with neck or back pain undergoing ESIs or other spinal interventions may have significant spinal abnormalities including spinal stenosis, ligamentum flavum hypertrophy, spondylolisthesis, or spondylosis, which may compress the epidural venous plexus within a fixed and concealed space. The risk of bleeding is further increased in pain patients taking several concomitant analgesics and other medications with antiplatelet effects including NSAIDs and aspirin.

Chronic pain patients may also be on antiplatelet medications (aspirin or clopidogrel) for cardiovascular or central nervous system thrombotic/embolic prophylaxis. The risk is further increased in patients on multiple anticoagulants.²³⁸

Stratification of Bleeding Risk

The interventional spine and pain recommendations are based on both the risk of bleeding and the seriousness of hemorrhagic sequelae and are stratified as to mild, intermediate, and high bleeding risks and made recommendations¹⁸ (Table 22).

Patients who undergo procedures in the minor risk category, including superficial peripheral nerve blocks and joint injections, may continue their anticoagulants. For those undergoing procedures that entail intermediate or major bleeding risks, the anticoagulants are discontinued. Intermediate-risk procedures include neuraxial injections, visceral sympathetic blocks, and revisions of the pocket where the pump or generator is placed, whereas high-risk procedures include SCS and intrathecal pump placements, epiduroscopy, and vertebroplasty/kyphoplasty. Recommendations for anticoagulants, including heparin, LMWH, warfarin, and the new oral anticoagulants, are very similar to previous and current ASRA consensus statements (and validate the survey results for what is considered an acceptable practice). However, there are major differences in management of patients receiving antiplatelet therapy, particularly those receiving aspirin or NSAIDs scheduled to undergo intermediate- and high-risk pain procedures.

Aspirin, NSAIDs, and the P2Y12 Inhibitors

Similar to the regional anesthesia guidelines, aspirin and NSAIDs may be continued when the procedure is low-risk pain procedures. However, antiplatelet therapy is discontinued when medium- and high-risk procedures are planned. The length of discontinuation depends on the indication for aspirin administration, 6 days for primary prevention (patients with no overt cardiovascular disease) and 4 days for secondary prophylaxis, and is based on a study that showed platelet aggregation normalized with 4 to 6 days in the patients treated with aspirin.³²⁹ For NSAIDs, an interval of 5 half-lives of the NSAID is recommended before the procedure: 1 to 2 days for ibuprofen, diclofenac, ketorolac, indomethacin; 4 days for naproxen and meloxicam; 6 days for nabumetone; and 10 days for oxaprozin and piroxicam. Aspirin and NSAIDs can be resumed a day after the procedure.³³⁰ There is no significant difference between the guidelines in managing the more potent antiplatelet agents, including clopidogrel, ticlopidine, ticagrelor, and prasugrel.

Older Anticoagulants: Warfarin, Heparin, LMWH, Fibrinolytic Agents, and Fondaparinux

The ASRA interventional pain recommendations for patients receiving IV or SC UFH are somewhat more conservative than the regional guidelines. The pain guidelines recommend against neuraxial procedures in patients on TID heparin. While the regional guidelines allow neuraxial injections in patients receiving SC BID heparin, the pain guidelines prefer that moderate- and high-risk procedures not be performed. However, if an interventional procedure is indicated, then an interval of 6 hours (rather than 4–6 hours) should be followed. For IV heparin, the regional guidelines

TABLE 22. Stratification of Risk According to Procedures

Low Risk		Intermediate Risk		High Risk	
Regional Guidelines	Pain Guidelines	Regional Guidelines	Pain Guidelines	Regional Guidelines	Pain Guidelines
Superficial and compressible plexus/peripheral nerve blocks	Peripheral nerve blocks Joint injections Sacroiliac joint and sacral lateral branch blocks	Other procedures based on compressibility, patient body habitus, comorbidities, and the degree and duration of anticoagulation	Neuraxial injections Facet procedures Visceral sympathetic blocks Pocket revision	Neuraxial blocks Deep and noncompressible plexus/peripheral nerve blocks	Spinal cord stimulator trial and implant Intrathecal pump trial and implant Vertebroplasty and kyphoplasty Epiduroscopy

Narouze et al,¹⁸ with permission.

recommend a 4- to 6-hour interval between administration of the drug and neuraxial injection. In contrast, the pain guidelines recommended an interval of 6 hours.

The guidelines on LMWH, warfarin, thrombolytic therapy, and fondaparinux are the same for both regional anesthesia/acute pain and interventional pain patients.

New Direct Oral Anticoagulants: Dabigatran, Rivaroxaban Apixaban, and Edoxaban

For the new direct oral anticoagulants, the ASRA guidelines for both regional anesthesia and pain recommended an interval of 5 half-lives of the drug before a regional or a pain intervention. There are minor differences between the 2 guidelines. For resumption of the drug after a neuraxial procedure, the ASRA regional guidelines recommended 6 hours, whereas the pain guidelines recommended 24 hours. The longer interval in the pain guidelines is to provide a longer observation period after procedures that involve surgical dissection (ie, intrathecal pump placements, permanent spinal cord stimulator implantations). However, it is important to note that, for patients undergoing a surgical

procedure, initiation of thromboprophylaxis with the new oral anticoagulants is recommended a minimum of 24 hours, and perhaps as long as 72 hours, depending on bleeding risk.^{36,187,331} Hence, ASRA regional and pain guidelines are functionally the same.

SUMMARY

Practice guidelines or recommendations summarize evidence-based reviews. However, the rarity of spinal hematoma defies a prospective randomized study, and there is no current laboratory model. As a result, these consensus statements represent the collective experience of recognized experts in the field of neuraxial anesthesia and anticoagulation. They are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding with appropriate grading of the level of evidence and strength of the recommendations. An understanding of the complexity of this issue is essential to patient management; a “cookbook” approach is not appropriate. Rather, the decision to perform spinal or epidural anesthesia/analgesia and the timing of catheter removal in a patient receiving antithrombotic therapy

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

SNRIs = Selective serotonin norepinephrine reuptake inhibitors

SSRIs = Selective serotonin reuptake inhibitors

FIGURE 2. Procedural management checklist. Adapted from Narouze et al,¹⁸ with permission.

should be made on an individual basis, weighing the small, though definite risk of spinal hematoma with the benefits of regional anesthesia for a specific patient (and the risks of withholding these benefits) (Fig. 2). Alternative anesthetic and analgesic techniques exist for patients to a patient whose risk of regional anesthesia exceeds the expected benefit. The patient's coagulation status should be optimized at the time of spinal or epidural needle/catheter placement, and the level of anticoagulation must be carefully monitored during the period of epidural catheterization. Indwelling catheters should not be removed in the presence of therapeutic anticoagulation because this appears to significantly increase the risk of spinal hematoma. It must also be remembered that identification of risk factors and establishment of guidelines will not completely eliminate the complication of spinal hematoma. In Vandermeulen and colleagues⁴³ series, although 87% of patients had a hemostatic abnormality or difficulty with needle puncture, 13% had no identifiable risk factor. Vigilance in monitoring is critical to allow early evaluation of neurologic dysfunction and prompt intervention. Protocols must be in place for urgent MRI and hematoma evacuation if there is a change in neurologic status. We must focus not only on the prevention of spinal hematoma, but also on rapid diagnosis and treatment in order to optimize neurologic outcome.

ACKNOWLEDGMENTS

The authors thank the leadership of SOAP, specifically Lisa Leffert, Ruth Landau, Alex Butwick, and Brendan Carvalho, for their expert and gracious collaboration with the section on management of the obstetric patient receiving antithrombotic therapy.

REFERENCES

- Enneking FK, Benzon H. Oral anticoagulants and regional anesthesia: a perspective. *Reg Anesth Pain Med.* 1998;23:140–145.
- Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing perioperative analgesia and thromboprophylaxis. *Reg Anesth Pain Med.* 1998;23:164–177.
- Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA consensus conference on neuraxial anesthesia and anticoagulation). *Reg Anesth Pain Med.* 2003;28:172–197.
- Liu SS, Mulroy MF. Neuraxial anesthesia and analgesia in the presence of standard heparin. *Reg Anesth Pain Med.* 1998;23:157–163.
- Rosenquist RW, Brown DL. Neuraxial bleeding: fibrinolytics/thrombolytics. *Reg Anesth Pain Med.* 1998;23:152–156.
- Urney WF, Rowlingson J. Do antiplatelet agents contribute to the development of perioperative spinal hematoma? *Reg Anesth Pain Med.* 1998;23:146–151.
- Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition). *Reg Anesth Pain Med.* 2010;35:64–101.
- Gogarten W, Vandermeulen E, van Aken H, Kozek S, Llaou JV, Samama CM. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol.* 2010;27:999–1015.
- Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.* 2004;126:627S–644S.
- Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis.* 2016;41:92–128.
- Friedman AM, Smiley RM. Expanding venous thromboembolism prophylaxis for at-risk obstetric patients: recommendations from the national partnership bundle. *Anesth Analg.* 2016;123:806–808.
- Leffert L, Landau R. Integrating the new thromboprophylaxis guidelines into obstetric anesthesia practice. *Anesth Analg.* 2016;123:809–811.
- D'Alton ME, Friedman AM, Smiley RM, et al. National partnership for maternal safety: consensus bundle on venous thromboembolism. *Anesth Analg.* 2016;123:942–949.
- Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141:e691S–e736S.
- 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 [published online ahead of print November 21, 2017]. *Anesth Analg.* 2017.
- Giberson CE, Barbosa J, Brooks ES, et al. Epidural hematomas after removal of percutaneous spinal cord stimulator trial leads: two case reports. *Reg Anesth Pain Med.* 2014;39:73–77.
- Buvanendran A, Young AC. Spinal epidural hematoma after spinal cord stimulator trial lead placement in a patient taking aspirin. *Reg Anesth Pain Med.* 2014;39:70–72.
- Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med.* 2015;40:182–212.
- FDA Drug Safety Communication. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on low molecular weight heparins. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM373735pdf>. 2013. Accessed March 4, 2017.
- Rosencher N, Bonnet MP, Sessler DI. Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia.* 2007;62:1154–1160.
- Bouma BN, Mosnier LO. Thrombin activatable fibrinolysis inhibitor (TAFI)—how does thrombin regulate fibrinolysis? *Ann Med.* 2006;38:378–388.
- IST-3 Collaborative Group, Sandercock P, Wardlaw JM, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet.* 2012;379:2352–2363.
- Benzon HT, Avram MJ, Green D, Bonow RO. New oral anticoagulants and regional anaesthesia. *Br J Anaesth.* 2013;111(suppl 1):i96–i113.
- Breivik H, Bang U, Jalonen J, Vigfússon G, Alahuhta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand.* 2010;54:16–41.
- Waurick K, Riess H, van Aken H, Kessler P, Gogarten W, Volk T. Rückenmarksnahe regionalanästhesien und thrombembolieprophylaxe/antithrombotische medikation. *Anasth Intensivmed.* 2014;55:464–492.
- Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schünemann HJ. Grades of recommendation for antithrombotic agents: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest.* 2008;133:123S–131S.
- Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians

- evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:381S–453S.
28. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e227S–e277S.
 29. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e278S–e325S.
 30. ACCP-NHLBI national conference on antithrombotic therapy. American College of Chest Physicians and the National Heart, Lung and Blood Institute. *Chest*. 1986;89:1S–106S.
 31. Guyatt GH, Akl EA, Crowther M, et al. Introduction to the ninth edition: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:48S–52S.
 32. Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines: go gently into that good night. *JAMA*. 2009;301:868–869.
 33. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA*. 2009;301:831–841.
 34. 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–e119S.
 35. American Society of Anesthesiologists Committee on Standards and Practice Parameters Practice alert for the perioperative management of patients with coronary artery stents: a report by the American Society of Anesthesiologists committee on standards and practice parameters. *Anesthesiology*. 2009;110:22–23.
 36. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e326S–e350S.
 37. Dowling NF, Beckman MG, Manco-Johnson M, et al. The U.S. Thrombosis and Hemostasis Centers pilot sites program. *J Thromb Thrombolysis*. 2007;23:1–7.
 38. Liew A, Douketis J. Perioperative management of patients who are receiving a novel oral anticoagulant. *Intern Emerg Med*. 2013;8:477–484.
 39. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:299S–339S.
 40. Tryba M. Epidural regional anesthesia and low molecular heparin: pro. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 1993;28:179–181.
 41. Horlocker TT, Wedel DJ. Anticoagulation and neuraxial block: historical perspective, anesthetic implications, and risk management. *Reg Anesth Pain Med*. 1998;23:129–134.
 42. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. *Anesthesiology*. 2004;101:950–959.
 43. Vandermeulen EP, van Aken H, Vermeylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg*. 1994;79:1165–1177.
 44. Horlocker TT, Wedel DJ, Schroeder DR, et al. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg*. 1995;80:303–309.
 45. Stafford-Smith M. Impaired haemostasis and regional anaesthesia. *Can J Anaesth*. 1996;43:R129–R141.
 46. Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia: a closed claims analysis. *Anesthesiology*. 1999;90:1062–1069.
 47. Lee LA, Posner KL, Domino KB, Caplan RA, Cheney FW. Injuries associated with regional anesthesia in the 1980s and 1990s: a closed claims analysis. *Anesthesiology*. 2004;101:143–152.
 48. Ehrenfeld JM, Agarwal AK, Henneman JP, Sandberg WS. Estimating the incidence of suspected epidural hematoma and the hidden imaging cost of epidural catheterization: a retrospective review of 43,200 cases. *Reg Anesth Pain Med*. 2013;38:409–414.
 49. Gallus AS, Hirsh J, Tuttle RJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. *N Engl J Med*. 1973;288:545–551.
 50. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:257S–298S.
 51. Brunton LL, Lazo JS, Parker KL. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw-Hill; 2006.
 52. Chan KC, Wu DJ, Ueng KC, et al. Spinal epidural hematoma following tissue plasminogen activator and heparinization for acute myocardial infarction. *Jpn Heart J*. 2002;43:417–421.
 53. Clark MA, Paradis NA. Spinal epidural hematoma complicating thrombolytic therapy with tissue plasminogen activator—a case report. *J Emerg Med*. 2002;23:247–251.
 54. Connolly ES Jr, Winfree CJ, McCormick PC. Management of spinal epidural hematoma after tissue plasminogen activator. A case report. *Spine (Phila Pa 1976)*. 1996;21:1694–1698.
 55. Cultrera F, Passanisi M, Giliberto O, Giuffrida M, Mancuso P, Ventura F. Spinal epidural hematoma following coronary thrombolysis. A case report. *J Neurosurg Sci*. 2004;48:43–47.
 56. DePorto R, Ahn JH, Gianutsos JG. Paraplegia subsequent to administration of tissue plasminogen activator and intravenous heparin following myocardial infarction—a case report. *J Spinal Cord Med*. 2000;23:150–152.
 57. Ferrante A, Pedi C, Centamore G, et al. A rare complication of thrombolytic therapy: spinal epidural hematoma. A case report [in Italian]. *Ital Heart J Suppl*. 2003;4:688–690.
 58. Garcia Lopez A, Perez Lara JM, Herrainz Hidalgo R, Puente Gonzalo E. Spinal epidural hematoma following thrombolytic therapy for acute myocardial infarction. *Orthopedics*. 1999;22:987–988.
 59. Groen RJ, van Alphen HA. Operative treatment of spontaneous spinal epidural hematomas: a study of the factors determining postoperative outcome. *Neurosurgery*. 1996;39:494–508; discussion 508–509.
 60. Haldar S, Hudsmith L, Munir S. Cervical extradural haematoma following thrombolysis. *Heart*. 2005;91:422.
 61. Han YM, Kwak HS, Jin GY, Chung GH, Song KJ. Spinal epidural hematoma after thrombolysis for deep vein thrombosis with subsequent pulmonary thromboembolism: a case report. *Cardiovasc Intervent Radiol*. 2006;29:450–453.
 62. Kim WJ, Hong YK, Yoo WH. Epidural hematoma mimicking transverse myelitis in a patient with primary antiphospholipid syndrome. *Rheumatol Int*. 2008;28:709–712.
 63. Ozgocmen S, Yoldas T, Kocakoc E, Ozkurt-Zengin F, Ardicoglu O. Spinal epidural hematoma associated with streptokinase treatment for myocardial infarction. *Spinal Cord*. 2004;42:374–377.
 64. Sawin PD, Traynelis VC, Follett KA. Spinal epidural hematoma following coronary thrombolysis with tissue plasminogen activator. Report of two cases. *J Neurosurg*. 1995;83:350–353.
 65. Song KJ, Lee KB. The poor outcome of the delayed diagnosis of acute spontaneous spinal epidural hematoma: two cases report. *J Korean Med Sci*. 2005;20:331–334.

66. Toyonaga M, Hagiwara N, Irie F, et al. Acute cervical spinal epidural hematoma during antithrombotic therapy: dual warnings against antithrombotic therapy [in Japanese]. *Rinsho Shinkeigaku*. 2003;43:287–290.
67. Wulf H. Epidural anaesthesia and spinal haematoma. *Can J Anaesth*. 1996;43:1260–1271.
68. Gupta K, Sharma R, Agrawal N, Puttegowda B, Basappa R, Manjunath CN. Spinal epidural hematoma—a rare and debilitating complication of thrombolytic therapy. *J Cardiovasc Dis Res*. 2013;4:236–238.
69. Baron EM, Burke JA, Akhtar N, Young WF. Spinal epidural hematoma associated with tissue plasminogen activator treatment of acute myocardial infarction. *Catheter Cardiovasc Interv*. 1999;48:390–396.
70. Dickman CA, Shedd SA, Spetzler RF, Shetter AG, Sonntag VK. Spinal epidural hematoma associated with epidural anesthesia: complications of systemic heparinization in patients receiving peripheral vascular thrombolytic therapy. *Anesthesiology*. 1990;72:947–950.
71. Nava S, Rossignoli L, Tagariello V, Bertini L. Technical difficulties in epidural blocks and spinal bleeding complications [in Italian]. *Minerva Anesthesiol*. 2001;67:881–886.
72. Onishchuk JL, Carlsson C. Epidural hematoma associated with epidural anesthesia: complications of anticoagulant therapy. *Anesthesiology*. 1992;77:1221–1223.
73. Rabito SF, Ahmed S, Feinstein L, Winnie AP. Intrathecal bleeding after the intraoperative use of heparin and urokinase during continuous spinal anesthesia. *Anesth Analg*. 1996;82:409–411.
74. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JJ. Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:141S–159S.
75. Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest*. 1995;108:258S–275S.
76. Garcia DA, Baglin TP, Weitz JJ, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e24S–e43S.
77. Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy*. 2012;32:546–558.
78. Murray DJ, Brosnahan WJ, Pennell B, Kapalski D, Weiler JM, Olson J. Heparin detection by the activated coagulation time: a comparison of the sensitivity of coagulation tests and heparin assays. *J Cardiothorac Vasc Anesth*. 1997;11:24–28.
79. Ruff RL, Dougherty JH Jr. Complications of lumbar puncture followed by anticoagulation. *Stroke*. 1981;12:879–881.
80. Rao TL, El-Etr AA. Anticoagulation following placement of epidural and subarachnoid catheters: an evaluation of neurologic sequelae. *Anesthesiology*. 1981;55:618–620.
81. Vandermeulen E, Singelyn F, Vercauteren M, Brichant JF, Ickx BE, Gautier P. Belgian guidelines concerning central neural blockade in patients with drug-induced alteration of coagulation: an update. *Acta Anaesthesiol Belg*. 2005;56:139–146.
82. Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. *Anesth Analg*. 1997;84:1211–1221.
83. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non–ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. *Circulation*. 2004;110:1202–1208.
84. Wildsmith JA, McClure JH. Anticoagulant drugs and central nerve blockade. *Anaesthesia*. 1991;46:613–614.
85. Hammer GB, Ngo K, Macario A. A retrospective examination of regional plus general anesthesia in children undergoing open heart surgery. *Anesth Analg*. 2000;90:1020–1024.
86. Peterson KL, DeCampi WM, Pike NA, Robbins RC, Reitz BA. A report of two hundred twenty cases of regional anesthesia in pediatric cardiac surgery. *Anesth Analg*. 2000;90:1014–1019.
87. Sanchez R, Nygard E. Epidural anesthesia in cardiac surgery: is there an increased risk? *J Cardiothorac Vasc Anesth*. 1998;12:170–173.
88. Ralley FE. Neuraxial anesthesia is contraindicated in patients undergoing heparinization for surgery. Pro: neuraxial anesthesia should not be used in patients undergoing heparinization for surgery. *J Cardiothorac Vasc Anesth*. 1996;10:957–960.
89. Turnbull KW. Neuraxial anesthesia is contraindicated in patients undergoing heparinization for surgery. Con: neuraxial block is useful in patients undergoing heparinization for surgery. *J Cardiothorac Vasc Anesth*. 1996;10:961–962.
90. Rosen DA, Hawkinberry DW2nd, Rosen KR, Gustafson RA, Hogg JP, Broadman LM. An epidural hematoma in an adolescent patient after cardiac surgery. *Anesth Analg*. 2004;98:966–969.
91. Ho AM, Chung DC, Joynt GM. Neuraxial blockade and hematoma in cardiac surgery: estimating the risk of a rare adverse event that has not (yet) occurred. *Chest*. 2000;117:551–555.
92. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318:1162–1173.
93. Davis JJ, Bankhead BR, Eckman EJ, Wallace A, Strunk J. Three-times-daily subcutaneous unfractionated heparin and neuraxial anesthesia: a retrospective review of 928 cases. *Reg Anesth Pain Med*. 2012;37:623–626.
94. Pace M, Koury K, Gulur P. Epidurals in patients receiving thromboprophylaxis with unfractionated heparin three times a day: the value of activated partial thromboplastin time testing. *Anesth Analg*. 2014;119:1215–1218.
95. Greaves JD. Serious spinal cord injury due to haematomyelia caused by spinal anaesthesia in a patient treated with low-dose heparin. *Anaesthesia*. 1997;52:150–154.
96. Cooke ED, Lloyd MJ, Bowcock SA, Pilcher MF. Letter: monitoring during low-dose heparin prophylaxis. *N Engl J Med*. 1976;294:1066–1067.
97. Working Party, Association of Anaesthetists of Great Britain & Ireland, Obstetric Anaesthetists' Association, Regional Anaesthesia UK. Regional anaesthesia and patients with abnormalities of coagulation: the Association of Anaesthetists of Great Britain & Ireland The Obstetric Anaesthetists' Association Regional Anaesthesia UK. *Anaesthesia*. 2013;68:966–972.
98. Cosmi B, Hirsh J. Low molecular weight heparins. *Curr Opin Cardiol*. 1994;9:612–618.
99. Holst J, Lindblad B, Bergqvist D, et al. Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, logiparin). An experimental investigation in healthy volunteers. *Blood Coagul Fibrinolysis*. 1994;5:795–803.
100. Kessler CM, Esparraguera IM, Jacobs HM, et al. Monitoring the anticoagulant effects of a low molecular weight heparin preparation. Correlation of assays in orthopedic surgery patients receiving ardeparin sodium for prophylaxis of deep venous thrombosis. *Am J Clin Pathol*. 1995;103:642–648.
101. Levine MN, Planes A, Hirsh J, Goodyear M, Vochelle N, Gent M. The relationship between anti-factor Xa level and clinical outcome in patients receiving enoxaparin low molecular weight heparin to prevent deep vein thrombosis after hip replacement. *Thromb Haemost*. 1989;62:940–944.
102. Lojewski B, Bacher P, Iqbal O, et al. Evaluation of hemostatic and fibrinolytic alterations associated with daily administration of

- low-molecular-weight heparin for a 12-week period. *Semin Thromb Hemost.* 1995;21:228–239.
103. Tryba M. European practice guidelines: thromboembolism prophylaxis and regional anesthesia. *Reg Anesth Pain Med.* 1998;23:178–182.
 104. Schroeder DR. Statistics: detecting a rare adverse drug reaction using spontaneous reports. *Reg Anesth Pain Med.* 1998;23:183–189.
 105. Heit JA. Perioperative management of the chronically anticoagulated patient. *J Thromb Thrombolysis.* 2001;12:81–87.
 106. Henshaw DS, Turner JD, Forest DJ, Thompson GR, Weller RS. Residual enoxaparin activity, anti-Xa levels, and concerns about the American Society of Regional Anesthesia and Pain Medicine anticoagulation guidelines. *Reg Anesth Pain Med.* 2017;42:432–436.
 107. Shaikh SA, Regal RE. Dosing of enoxaparin in renal impairment. *P T.* 2017;42:245–249.
 108. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141:e576S–e600S.
 109. Turpie AG, Gallus AS, Hoek JA. Pentasaccharide Investigators. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med.* 2001;344:619–625.
 110. Landow L. A synthetic pentasaccharide for the prevention of deep-vein thrombosis. *N Engl J Med.* 2001;345:291–292.
 111. Singelyn FJ, Verheyen CC, Piovella F, van Aken HK, Rosensch N. EXPERT Study Investigators. The safety and efficacy of extended thromboprophylaxis with fondaparinux after major orthopedic surgery of the lower limb with or without a neuraxial or deep peripheral nerve catheter: the expert study. *Anesth Analg.* 2007;105:1540–1547.
 112. Cohen AT, Harrington R, Goldhaber SZ, et al. The design and rationale for the acute medically ill venous thromboembolism prevention with extended duration betrixaban (APEX) study. *Am Heart J.* 2014;167:335–341.
 113. Turpie AG, Bauer KA, Davidson BL, et al. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (expert). *Thromb Haemost.* 2009;101:68–76.
 114. Chan NC, Hirsh J, Ginsberg JS, Eikelboom JW. Betrixaban (prt054021): pharmacology, dose selection and clinical studies. *Future Cardiol.* 2014;10:43–52.
 115. Chan NC, Bhagirath V, Eikelboom JW. Profile of betrixaban and its potential in the prevention and treatment of venous thromboembolism. *Vasc Health Risk Manag.* 2015;11:343–351.
 116. Dias C, Moore KT, Murphy J, et al. Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. *Am J Nephrol.* 2016;43:229–236.
 117. Kubitz D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol.* 2010;70:703–712.
 118. Highlights of Prescribing Information BEVYXXA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383s000lbl.pdf. Accessed March 4, 2017.
 119. Chang M, Yu Z, Shenker A, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. *J Clin Pharmacol.* 2016;56:637–645.
 120. Ridout G, de la Motte S, Niemezyk S, et al. Effect of renal function on edoxaban pharmacokinetics (PK) and on population PK/PD model. *J Clin Pharmacol.* 2009;49:1124–1124.
 121. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet.* 2009;48:1–22.
 122. Laux V, Perzborn E, Kubitz D, Misselwitz F. Preclinical and clinical characteristics of rivaroxaban: a novel, oral, direct factor Xa inhibitor. *Semin Thromb Hemost.* 2007;33:515–523.
 123. Weitz JI, Eikelboom JW, Samama MM. New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141:e120S–e151S.
 124. Douxfils J, Mullier F, Loosen C, Chatelain C, Chatelain B, Dogne JM. Assessment of the impact of rivaroxaban on coagulation assays: laboratory recommendations for the monitoring of rivaroxaban and review of the literature. *Thromb Res.* 2012;130:956–966.
 125. Madhiseti KR, Mathew M, George M, Pillai SS. Spinal epidural haematoma following rivaroxaban administration after total knee replacement. *Indian J Anaesth.* 2015;59:519–521.
 126. Ozel O, Demircay E, Kircelli A, Cansever T. Atypical presentation of an epidural hematoma in a patient receiving rivaroxaban after total hip arthroplasty. *Orthopedics.* 2016;39:e558–e560.
 127. Radcliff KE, Ong A, Parvizi J, Post Z, Orozco F. Rivaroxaban-induced epidural hematoma and cauda equina syndrome after total knee arthroplasty: a case report. *Orthop Surg.* 2014;6:69–71.
 128. Truumees E, Gaudu T, Dieterichs C, Geck M, Stokes J. Epidural hematoma and intraoperative hemorrhage in a spine trauma patient on pradaxa (dabigatran). *Spine (Phila Pa 1976).* 2012;37:E863–E865.
 129. Bamps S, Decramer T, Vandenbussche N, et al. Dabigatran-associated spontaneous acute cervical epidural hematoma. *World Neurosurg.* 2015;83:257–258.
 130. Jaeger M, Jeanneret B, Schaeren S. Spontaneous spinal epidural haematoma during factor Xa inhibitor treatment (rivaroxaban). *Eur Spine J.* 2012;21(suppl 4):S433–S435.
 131. Castillo JM, Afanador HF, Manjarrez E, Morales XA. Non-traumatic spontaneous spinal subdural hematoma in a patient with non-valvular atrial fibrillation during treatment with rivaroxaban. *Am J Case Rep.* 2015;16:377–381.
 132. Zaarour M, Hassan S, Thumallapally N, Dai Q. Rivaaxroxaban-induced nontraumatic spinal subdural hematoma: an uncommon yet life-threatening complication. *Case Rep Hematol.* 2015;2015:275380.
 133. Dargazanli C, Lonjon N, Gras-Combe G. Nontraumatic spinal subdural hematoma complicating direct factor Xa inhibitor treatment (rivaroxaban): a challenging management. *Eur Spine J.* 2016;25(suppl 1):100–103.
 134. Heckmann JG. Spinal subarachnoid hemorrhage in cortical superficial siderosis after apixaban and clopidogrel therapy. *J Thromb Thrombolysis.* 2016;41:654–655.
 135. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos.* 2009;37:74–81.
 136. Douxfils J, Chatelain C, Chatelain B, Dogne JM, Mullier F. Impact of apixaban on routine and specific coagulation assays: a practical laboratory guide. *Thromb Haemost.* 2013;110:283–294.
 137. Lip GY, Agnelli G. Edoxaban: a focused review of its clinical pharmacology. *Eur Heart J.* 2014;35:1844–1855.
 138. Matsushima N, Lee F, Sato T, Weiss D, Mendell J. Bioavailability and safety of the factor Xa inhibitor edoxaban and the effects of quinidine in healthy subjects. *Clin Pharmacol Drug Dev.* 2013;2:358–366.
 139. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol.* 2010;50:743–753.
 140. Plitt A, Giugliano RP. Edoxaban: review of pharmacology and key phase I to III clinical trials. *J Cardiovasc Pharmacol Ther.* 2014;19:409–416.
 141. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective Anticoagulation With

- Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48). *Am Heart J*. 2010;160:635–641.
142. Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-term safety and plasma concentrations of edoxaban in Japanese patients with non-valvular atrial fibrillation and severe renal impairment. *Circ J*. 2015;79:1486–1495.
 143. Parasarmpuria DA, Marbury T, Matsushima N, et al. Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis. *Thromb Haemost*. 2015;113:719–727.
 144. Yamashita T, Koretsune Y, Yasaka M, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J*. 2012;76:1840–1847.
 145. Fuji T, Fujita S, Kawai Y, et al. A randomized, open-label trial of edoxaban in Japanese patients with severe renal impairment undergoing lower-limb orthopedic surgery. *Thromb J*. 2015;13:6.
 146. Mendell J, Chen S, He L, Desai M, Parasarmpuria DA. The effect of rifampin on the pharmacokinetics of edoxaban in healthy adults. *Clin Drug Investig*. 2015;35:447–453.
 147. Mendell J, Johnson L, Chen S. An open-label, phase I study to evaluate the effects of hepatic impairment on edoxaban pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2015;55:1395–1405.
 148. Mendell J, Noveck RJ, Shi M. Pharmacokinetics of the direct factor Xa inhibitor edoxaban and digoxin administered alone and in combination. *J Cardiovasc Pharmacol*. 2012;60:335–341.
 149. Mendell J, Noveck RJ, Shi M. A randomized trial of the safety, pharmacokinetics and pharmacodynamics of edoxaban, an oral factor Xa inhibitor, following a switch from warfarin. *Br J Clin Pharmacol*. 2013;75:966–978.
 150. Mendell J, Zahir H, Matsushima N, et al. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. *Am J Cardiovasc Drugs*. 2013;13:331–342.
 151. Fuji T, Fujita S, Kawai Y, et al. Safety and efficacy of edoxaban in patients undergoing hip fracture surgery. *Thromb Res*. 2014;133:1016–1022.
 152. Fuji T, Fujita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. *J Thromb Haemost*. 2010;8:2458–2468.
 153. Douxfils J, Chatelain B, Chatelain C, Dogne JM, Mullier F. Edoxaban: impact on routine and specific coagulation assays. A practical laboratory guide. *Thromb Haemost*. 2015;115:368–381.
 154. Zhang D, He K, Raghavan N, et al. Comparative metabolism of ¹⁴C-labeled apixaban in mice, rats, rabbits, dogs, and humans. *Drug Metab Dispos*. 2009;37:1738–1748.
 155. Samama MM, Meddahi S, Samama CM. Pharmacology and laboratory testing of the oral Xa inhibitors. *Clin Lab Med*. 2014;34:503–517.
 156. Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J Thromb Haemost*. 2011;9:1705–1712.
 157. Pernod G, Albaladejo P, Godier A, et al. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP)—March 2013. *Arch Cardiovasc Dis*. 2013;106:382–393.
 158. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J*. 2013;34:2094–2106.
 159. Vanden Daelen S, Peetermans M, Vanassche T, Verhamme P, Vandermeulen E. Monitoring and reversal strategies for new oral anticoagulants. *Expert Rev Cardiovasc Ther*. 2015;13:95–103.
 160. Jackson LR2nd, Becker RC. Novel oral anticoagulants: pharmacology, coagulation measures, and considerations for reversal. *J Thromb Thrombolysis*. 2014;37:380–391.
 161. Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med*. 2013;19:446–451.
 162. Gonsalves WI, Gupta V, Patnaik MM. Management of bleeding complications in patients on new oral anticoagulants. *J Hematol Transf*. 2014;2:1015–1020.
 163. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375:1131–1141.
 164. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med*. 2014;371:2141–2142.
 165. Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost*. 2017;117:238–245.
 166. Ansell JE, Laulicht BE, Bakhru SH, Hoffman M, Steiner SS, Costin JC. Ciraparantag safely and completely reverses the anticoagulant effects of low molecular weight heparin. *Thromb Res*. 2016;146:113–118.
 167. Carswell CI, Plosker GL. Bivalirudin: a review of its potential place in the management of acute coronary syndromes. *Drugs*. 2002;62:841–870.
 168. Greinacher A, Lubenow N. Recombinant hirudin in clinical practice: focus on lepirudin. *Circulation*. 2001;103:1479–1484.
 169. Eriksson BI, Wille-Jorgensen P, Kaleb P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med*. 1997;337:1329–1335.
 170. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet*. 2008;47:285–295.
 171. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost*. 2009;15(suppl 1):9S–16S.
 172. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol*. 2007;64:292–303.
 173. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49:259–268.
 174. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–520.
 175. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogne JM. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. *Thromb Haemost*. 2012;107:985–997.
 176. Lind SE, Boyle ME, Fisher S, Ishimoto J, Trujillo TC, Kiser TH. Comparison of the aptt with alternative tests for monitoring direct thrombin inhibitors in patient samples. *Am J Clin Pathol*. 2014;141:665–674.
 177. Lippi G, Ardissino D, Quintavalla R, Cervellin G. Urgent monitoring of direct oral anticoagulants in patients with atrial fibrillation: a tentative approach based on routine laboratory tests. *J Thromb Thrombolysis*. 2014;38:269–274.
 178. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. *Blood Coagul Fibrinolysis*. 2012;23:138–143.
 179. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation

- assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103:1116–1127.
180. van Ryn J, Grottke O, Spronk H. Measurement of dabigatran in standardly used clinical assays, whole blood viscoelastic coagulation, and thrombin generation assays. *Clin Lab Med.* 2014;34:479–501.
 181. Eriksson BI, Dahl OE, Büller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost.* 2005;3:103–111.
 182. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the re-model randomized trial. *J Thromb Haemost.* 2007;5:2178–2185.
 183. Fuji T, Fujita S, Ujihira T, Sato T. Dabigatran etexilate prevents venous thromboembolism after total knee arthroplasty in Japanese patients with a safety profile comparable to placebo. *J Arthroplasty.* 2010;25:1267–1274.
 184. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty.* 2009;24:1–9.
 185. Rosencher N, Noack H, Feuring M, Clemens A, Friedman RJ, Eriksson BI. Type of anaesthesia and the safety and efficacy of thromboprophylaxis with enoxaparin or dabigatran etexilate in major orthopaedic surgery: pooled analysis of three randomized controlled trials. *Thromb J.* 2012;10:9.
 186. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood.* 2013;121:3554–3562.
 187. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology clinical expert consensus document task force. *J Am Coll Cardiol.* 2017;69:871–898.
 188. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest.* 2008;133:160S–198S.
 189. Xi M, Beguin S, Hemker HC. The relative importance of the factors II, VII, IX and X for the prothrombinase activity in plasma of orally anticoagulated patients. *Thromb Haemost.* 1989;62:788–791.
 190. Benzon HT, Avram MJ, Benzon HA, Kirby-Nolan M, Nader A. Factor VII levels and international normalized ratios in the early phase of warfarin therapy. *Anesthesiology.* 2010;112:298–304.
 191. Wille-Jørgensen P, Jørgensen LN, Rasmussen LS. Lumbar regional anaesthesia and prophylactic anticoagulant therapy. Is the combination safe? *Anaesthesia.* 1991;46:623–627.
 192. Chan TY. Adverse interactions between warfarin and nonsteroidal antiinflammatory drugs: mechanisms, clinical significance, and avoidance. *Ann Pharmacother.* 1995;29:1274–1283.
 193. Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest.* 2005;127:2049–2056.
 194. Benzon HT, Asher Y, Kendall MC, Vida L, McCarthy RJ, Green D. Clotting factor concentrations five days after discontinuation of warfarin. *Reg Anesth Pain Med.* 2018;43 [in press].
 195. Hirsh J. Oral anticoagulant drugs. *N Engl J Med.* 1991;324:1865–1875.
 196. Harder S, Thürmann P. Clinically important drug interactions with anticoagulants. An update. *Clin Pharmacokinet.* 1996;30:416–444.
 197. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* 2013;369:2294–2303.
 198. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N Engl J Med.* 2013;369:2304–2312.
 199. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013;369:2283–2293.
 200. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med.* 2015;373:823–833.
 201. Woo CH, Patel N, Conell C, et al. Rapid warfarin reversal in the setting of intracranial hemorrhage: a comparison of plasma, recombinant activated factor VII, and prothrombin complex concentrate. *World Neurosurg.* 2014;81:110–115.
 202. Taketomi T, Szlam F, Levy JH, Tanaka KA. Warfarin reversal with prothrombin complex concentrate confers better antifibrinolytic activity compared with recombinant activated factor VII. *Blood Coagul Fibrinolysis.* 2008;19:106–108.
 203. Voils SA, Holder MC, Premraj S, Catlin JR, Allen BR. Comparative effectiveness of 3- versus 4-factor prothrombin complex concentrate for emergent warfarin reversal. *Thromb Res.* 2015;136:595–598.
 204. Al-Majzoub O, Rybak E, Reardon DP, Krause P, Connors JM. Evaluation of warfarin reversal with 4-factor prothrombin complex concentrate compared to 3-factor prothrombin complex concentrate at a tertiary academic medical center. *J Emerg Med.* 2016;50:7–13.
 205. Woolson ST, Robinson RK, Khan NQ, Rogers BS, Maloney WJ. Deep venous thrombosis prophylaxis for knee replacement: warfarin and pneumatic compression. *Am J Orthop (Belle Mead NJ).* 1998;27:299–304.
 206. Badenhorst CH. Epidural hematoma after epidural pain control and concomitant postoperative anticoagulation. *Reg Anesth.* 1996;21:272–273.
 207. Odoom JA, Sih IL. Epidural analgesia and anticoagulant therapy. Experience with one thousand cases of continuous epidurals. *Anaesthesia.* 1983;38:254–259.
 208. Wu CL, Perkins FM. Oral anticoagulant prophylaxis and epidural catheter removal. *Reg Anesth.* 1996;21:517–524.
 209. Horlocker TT, Wedel DJ, Schlichting JL. Postoperative epidural analgesia and oral anticoagulant therapy. *Anesth Analg.* 1994;79:89–93.
 210. Shields RC, McBane RD, Kuiper JD, Li H, Heit JA. Efficacy and safety of intravenous phytonadione (vitamin K₁) in patients on long-term oral anticoagulant therapy. *Mayo Clin Proc.* 2001;76:260–266.
 211. Majerus PW, Broze GJ Jr, Miletich JP, Tollefsen DM. Anticoagulant, Antiplatelet, and Thrombolytic Drugs. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AJ, eds. *The Pharmacologic Basis of Therapeutics*. 9th ed. New York, NY: MacMillan; 1990.
 212. Janis KM. Epidural hematoma following postoperative epidural analgesia: a case report. *Anesth Analg.* 1972;51:689–692.
 213. Helperin SW, Cohen DD. Hematoma following epidural anesthesia: report of a case. *Anesthesiology.* 1971;35:641–644.
 214. Horlocker TT. When to remove a spinal or epidural catheter in an anticoagulated patient. *Reg Anesth.* 1993;18:264–265.
 215. Parvizi J, Viscusi ER, Frank HG, Sharkey PF, Hozack WJ, Rothman RR. Can epidural anesthesia and warfarin be coadministered? *Clin Orthop Relat Res.* 2007;456:133–137.
 216. Liu SS, Buvanendran A, Viscusi ER, et al. Uncomplicated removal of epidural catheters in 4365 patients with international normalized ratio greater than 1.4 during initiation of warfarin therapy. *Reg Anesth Pain Med.* 2011;36:231–235.
 217. Amezcua JL, O'Grady J, Salmon JA, Moncada S. Prolonged paradoxical effect of aspirin on platelet behaviour and bleeding time in man. *Thromb Res.* 1979;16:69–79.

218. Godal HC, Eika C, Dybdahl JH, Daae L, Larsen S. Aspirin and bleeding-time. *Lancet*. 1979;1:1236.
219. Finsterer J, Seywald S, Stollberger C, et al. Recovery from acute paraplegia due to spontaneous spinal, epidural hematoma under minimal-dose acetyl-salicylic acid. *Neurol Sci*. 2008;29:271–273.
220. Hyderally HA. Epidural hematoma unrelated to combined spinal-epidural anesthesia in a patient with ankylosing spondylitis receiving aspirin after total hip replacement. *Anesth Analg*. 2005;100:882–883.
221. Cronberg S, Wallmark E, Soderberg I. Effect on platelet aggregation of oral administration of 10 non-steroidal analgesics to humans. *Scand J Haematol*. 1984;33:155–159.
222. Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. *J Clin Pharmacol*. 2000;40:124–132.
223. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:199S–233S.
224. Lange RA, Hillis LD. Antiplatelet therapy for ischemic heart disease. *N Engl J Med*. 2004;350:277–280.
225. Benzon HT, McCarthy RJ, Benzon HA, et al. Determination of residual antiplatelet activity of clopidogrel before neuraxial injections. *Br J Anaesth*. 2011;107:966–971.
226. Karabatsou K, Sinha A, Das K, Rainov NG. Nontraumatic spinal epidural hematoma associated with clopidogrel. *Zentralbl Neurochir*. 2006;67:210–212.
227. Morales Ciano RA, Drain O, Rillardon L, Guigui P. Acute spontaneous spinal epidural hematoma: an important differential diagnosis in patients under clopidogrel therapy. *Spine J*. 2008;8:544–547.
228. Sung JH, Hong JT, Son BC, Lee SW. Clopidogrel-induced spontaneous spinal epidural hematoma. *J Korean Med Sci*. 2007;22:577–579.
229. Vandermeulen E, Decoster J, Dewandre PY, et al. Central neural blockade in patients with a drug-induced alteration of coagulation. Third edition of the Belgian Association for Regional Anaesthesia (BARA) guidelines. *Acta Anaesthesiol Belg*. 2011;62:175–191.
230. Sible AM, Nawarskas JJ. Cangrelor: a new route for p2y12 inhibition. *Cardiol Rev*. 2017;25:133–139.
231. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhilbl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: a direct, parenteral p2y12 receptor antagonist. *J Clin Pharmacol*. 2010;50:27–35.
232. Bhatt DL, Stone GW, Mahaffey KW, et al. Effect of platelet inhibition with cangrelor during pci on ischemic events. *N Engl J Med*. 2013;368:1303–1313.
233. 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.
234. Kaneda T, Urimoto G, Suzuki T. Spinal epidural hematoma following epidural catheter removal during antiplatelet therapy with cilostazol. *J Anesth*. 2008;22:290–293.
235. 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.
236. 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.
237. 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.
238. Benzon HT, Wong HY, Siddiqui T, Ondra S. Caution in performing epidural injections in patients on several antiplatelet drugs. *Anesthesiology*. 1999;91:1558–1559.
239. Gerancher JC, Waterer R, Middleton J. Transient paraparesis after postdural puncture spinal hematoma in a patient receiving ketorolac. *Anesthesiology*. 1997;86:490–494.
240. Gilbert A, Owens BD, Mulroy MF. Epidural hematoma after outpatient epidural anesthesia. *Anesth Analg*. 2002;94:77–78.
241. Kawaguchi S, Tokutomi S. A case of epidural hematoma associated with epidural catheterization which occurred on 12th days after the last medication of ticlopidine hydrochloride [in Japanese]. *Masui*. 2002;51:526–528.
242. Clasp: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) collaborative group. *Lancet*. 1994;343:619–629.
243. Horlocker TT, Bajwa ZH, Ashraf Z, et al. Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg*. 2002;95:1691–1697, table of contents.
244. Osta WA, Akbary H, Fuleihan SF. Epidural analgesia in vascular surgery patients actively taking clopidogrel. *Br J Anaesth*. 2010;104:429–432.
245. Coukell AJ, Markham A. Clopidogrel. *Drugs*. 1997;54:745–750.
246. Dyke CM. Safety of glycoprotein iib-iiia inhibitors: a heart surgeon's perspective. *Am Heart J*. 1999;138:307–316.
247. Shlansky-Goldberg R. Platelet aggregation inhibitors for use in peripheral vascular interventions: what can we learn from the experience in the coronary arteries? *J Vasc Interv Radiol*. 2002;13:229–246.
248. Mayumi T, Dohi S. Spinal subarachnoid hematoma after lumbar puncture in a patient receiving antiplatelet therapy. *Anesth Analg*. 1983;62:777–779.
249. Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med*. 1997;127:61–69.
250. Elder NC, Gillcrist A, Minz R. Use of alternative health care by family practice patients. *Arch Fam Med*. 1997;6:181–184.
251. Hensrud DD, Engle DD, Scheitel SM. Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination. *Mayo Clin Proc*. 1999;74:443–447.
252. Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery*. 1990;26:880–882.
253. Gilbert GJ. Ginkgo biloba. *Neurology*. 1997;48:1137.
254. Matthews MK Jr. Association of ginkgo biloba with intracerebral hemorrhage. *Neurology*. 1998;50:1933–1934.
255. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic ginkgo biloba ingestion. *Neurology*. 1996;46:1775–1776.
256. Vale S. Subarachnoid haemorrhage associated with ginkgo biloba. *Lancet*. 1998;352:36.
257. Lee A, Chui PT, Aun CS, Lau AS, Gin T. Incidence and risk of adverse perioperative events among surgical patients taking traditional Chinese herbal medicines. *Anesthesiology*. 2006;105:454–461.
258. Moss J, Yuan CS. Herbal medicines and perioperative care. *Anesthesiology*. 2006;105:441–442.
259. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG*. 2011;118 suppl 1:1–203.
260. Greer IA. Prevention of venous thromboembolism in pregnancy. *Best Pract Res Clin Haematol*. 2003;16:261–278.
261. Kujovich JL. Hormones and pregnancy: thromboembolic risks for women. *Br J Haematol*. 2004;126:443–454.
262. James A. Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 123: thromboembolism in pregnancy. *Obstet Gynecol*. 2011;118:718–729.

263. Palmerola KL, D'Alton ME, Brock CO, Friedman AM. A comparison of recommendations for pharmacologic thromboembolism prophylaxis after caesarean delivery from three major guidelines. *BJOG*. 2016;123:2157–2162.
264. Ansari J, Carvalho B, Shafer SL, Flood P. Pharmacokinetics and pharmacodynamics of drugs commonly used in pregnancy and parturition. *Anesth Analg*. 2016;122:786–804.
265. Brancazio LR, Roperti KA, Stierer R, Laifer SA. Pharmacokinetics and pharmacodynamics of subcutaneous heparin during the early third trimester of pregnancy. *Am J Obstet Gynecol*. 1995;173:1240–1245.
266. Chunilal SD, Young E, Johnston MA, et al. The aPTT response of pregnant plasma to unfractionated heparin. *Thromb Haemost*. 2002;87:92–97.
267. Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. *Am J Obstet Gynecol*. 1999;181:1113–1117.
268. Lebaudy C, Hulot JS, Amoura Z, et al. Changes in enoxaparin pharmacokinetics during pregnancy and implications for antithrombotic therapeutic strategy. *Clin Pharmacol Ther*. 2008;84:370–377.
269. Crawford JS. Some maternal complications of epidural analgesia for labour. *Anaesthesia*. 1985;40:1219–1225.
270. Bateman BT, Mhyre JM, Ehrenfeld J, et al. The risk and outcomes of epidural hematomas after perioperative and obstetric epidural catheterization: a report from the multicenter perioperative outcomes group research consortium. *Anesth Analg*. 2012;116:1380–1385.
271. Paech MJ, Godkin R, Webster S. Complications of obstetric epidural analgesia and anaesthesia: a prospective analysis of 10,995 cases. *Int J Obstet Anesth*. 1998;7:5–11.
272. Pöpping DM, Zahn PK, van Aken HK, Dasch B, Boche R, Pogatzki-Zahn EM. Effectiveness and safety of postoperative pain management: a survey of 18 925 consecutive patients between 1998 and 2006 (2nd revision): a database analysis of prospectively raised data. *Br J Anaesth*. 2008;101:832–840.
273. Beards SC, Jackson A, Griffiths AG, Horsman EL. Magnetic resonance imaging of extradural blood patches: appearances from 30 min to 18 h. *Br J Anaesth*. 1993;71:182–188.
274. Horlocker TT, Birmbach DJ, Connis RT, et al. Practice advisory for the prevention, diagnosis, and management of infectious complications associated with neuraxial techniques: a report by the American Society of Anesthesiologists task force on infectious complications associated with neuraxial techniques. *Anesthesiology*. 2010;112:530–545.
275. Ballin NC. Paraplegia following epidural analgesia. *Anaesthesia*. 1981;36:952–953.
276. Esler MD, Durrbridge J, Kirby S. Epidural haematoma after dural puncture in a parturient with neurofibromatosis. *Br J Anaesth*. 2001;87:932–934.
277. Lao TT, Halpern SH, MacDonald D, Huh C. Spinal subdural haematoma in a parturient after attempted epidural anaesthesia. *Can J Anaesth*. 1993;40:340–345.
278. Newman B. Postnatal paraparesis following epidural analgesia and forceps delivery. *Anaesthesia*. 1983;38:350–351.
279. Nguyen L, Riu B, Minville V, Chassery C, Catalaa I, Samii K. Epidural hematoma after hemorrhagic shock in a parturient [in French]. *Can J Anaesth*. 2006;53:252–257.
280. Roscoe MW, Barrington TW. Acute spinal subdural hematoma. A case report and review of literature. *Spine (Phila Pa 1976)*. 1984;9:672–675.
281. Scott DB, Hibbard BM. Serious non-fatal complications associated with extradural block in obstetric practice. *Br J Anaesth*. 1990;64:537–541.
282. Sibai BM, Taslimi MM, el-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. *Am J Obstet Gynecol*. 1986;155:501–509.
283. Yarnell RW, D'Alton ME. Epidural hematoma complicating cholestasis of pregnancy. *Curr Opin Obstet Gynecol*. 1996;8:239–242.
284. Yuen TS, Kua JS, Tan IK. Spinal haematoma following epidural anaesthesia in a patient with eclampsia. *Anaesthesia*. 1999;54:350–354.
285. Walters MA, van de Velde M, Wilms G. Acute intrathecal haematoma following neuraxial anaesthesia: diagnostic delay after apparently normal radiological imaging. *Int J Obstet Anesth*. 2012;21:181–185.
286. Chiaghana CO, Bremer JM, Sappenfield JW, Wendling AL. Delayed neuraxial hematoma in parturient with fontan circulation following neuraxial anesthesia for cesarean section. *Reg Anesth Pain Med*. 2016;41:773–775.
287. Guglielminotti J, Wong CA, Landau R, Li G. Temporal trends in anesthesia-related adverse events in cesarean deliveries, New York state, 2003–2012. *Anesthesiology*. 2015;123:1013–1023.
288. D'Angelo R, Smiley RM, Riley ET, Segal S. Serious complications related to obstetric anesthesia: the serious complication repository project of the society for obstetric anesthesia and perinatology. *Anesthesiology*. 2014;120:1505–1512.
289. Kinsella SM, Winton AL, Mushambi MC, et al. Failed tracheal intubation during obstetric general anaesthesia: a literature review. *Int J Obstet Anesth*. 2015;24:356–374.
290. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk J. *MBRRACE-UK Saving Lives, Improving Mothers' Care: Lessons Learned to Inform Future Maternity Care From the UK and Ireland Confidential Enquiries Into Maternal Deaths and Morbidity 2009–2012*. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014.
291. Pandit JJ, Andrade J, Bogod DG, et al. The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. *Anaesthesia*. 2014;69:1089–1101.
292. Chang CC, Wang IT, Chen YH, Lin HC. Anesthetic management as a risk factor for postpartum hemorrhage after cesarean deliveries. *Am J Obstet Gynecol*. 2011;205:462.e1–462.e7.
293. Dyer RA, Els I, Farbas J, Torr GJ, Schoeman LK, James MF. Prospective, randomized trial comparing general with spinal anesthesia for cesarean delivery in preeclamptic patients with a nonreassuring fetal heart trace. *Anesthesiology*. 2003;99:561–569; discussion 5A–6A.
294. Lertakyananee J, Chinachoti T, Tritrakam T, Muangkasem J, Somboonnanonda A, Kolatat T. Comparison of general and regional anesthesia for cesarean section: success rate, blood loss and satisfaction from a randomized trial. *J Med Assoc Thai*. 1999;82:672–680.
295. Tsai PS, Hsu CS, Fan YC, Huang CJ. General anaesthesia is associated with increased risk of surgical site infection after caesarean delivery compared with neuraxial anaesthesia: a population-based study. *Br J Anaesth*. 2011;107:757–761.
296. Landau R, Bollag L, Ortner C. Chronic pain after childbirth. *Int J Obstet Anesth*. 2013;22:133–145.
297. Nikolajsen L, Sorensen HC, Jensen TS, Kehlet H. Chronic pain following caesarean section. *Acta Anaesthesiol Scand*. 2004;48:111–116.
298. Moore ER, Anderson GC, Bergman N, Dowswell T. Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database Syst Rev*. 2012;CD003519.
299. Smith J, Plaat F, Fisk NM. The natural caesarean: a woman-centred technique. *BJOG*. 2008;115:1037–1042; discussion 1042.
300. Algert CS, Bowen JR, Giles WB, Knoblanche GE, Lain SJ, Roberts CL. Regional block versus general anaesthesia for caesarean section and neonatal outcomes: a population-based study. *BMC Med*. 2009;7:20.
301. Beckmann M, Calderbank S. Mode of anaesthetic for category 1 caesarean sections and neonatal outcomes. *Aust N Z J Obstet Gynaecol*. 2012;52:316–320.
302. Palanisamy A. Maternal anesthesia and fetal neurodevelopment. *Int J Obstet Anesth*. 2012;21:152–162.

303. Rodriguez J, Taboada M, Garcia F, Bermudez M, Amor M, Alvarez J. Intraneural hematoma after nerve stimulation-guided femoral block in a patient with factor XI deficiency: case report. *J Clin Anesth*. 2011;23:234–237.
304. Warner NS, Duncan CM, Kopp SL. Acute retroperitoneal hematoma after psoas catheter placement in a patient with myeloproliferative thrombocytosis and aspirin therapy. *A A Case Rep*. 2016;6:28–30.
305. Idestrup C, Sawhney M, Nix C, Kiss A. The incidence of hematoma formation in patients with continuous femoral catheters following total knee arthroplasty while receiving rivaroxaban as thromboprophylaxis: an observational study. *Reg Anesth Pain Med*. 2014;39:414–417.
306. Wheatley JK, Motamedi F, Hammonds WD. Page kidney resulting from massive subcapsular hematoma. Complication of lumbar sympathetic nerve block. *Urology*. 1984;24:361–363.
307. Stan TC, Krantz MA, Solomon DL, Poulos JG, Chaouki K. The incidence of neurovascular complications following axillary brachial plexus block using a transarterial approach. A prospective study of 1,000 consecutive patients. *Reg Anesth*. 1995;20:486–492.
308. Kurz RB, Au AH, Rooholamini SA. Retroperitoneal hematoma as a complication of pudendal block. Diagnosis made by computed tomography. *West J Med*. 1996;164:523–525.
309. Mishio M, Matsumoto T, Okuda Y, Kitajima T. Delayed severe airway obstruction due to hematoma following stellate ganglion block. *Reg Anesth Pain Med*. 1998;23:516–519.
310. Ben-David B, Stahl S. Axillary block complicated by hematoma and radial nerve injury. *Reg Anesth Pain Med*. 1999;24:264–266.
311. Thomas PW, Sanders DJ, Berrisford RG. Pulmonary haemorrhage after percutaneous paravertebral block. *Br J Anaesth*. 1999;83:668–669.
312. Vaisman J. Pelvic hematoma after an ilioinguinal nerve block for orchialgia. *Anesth Analg*. 2001;92:1048–1049.
313. Borgeat A, Ekatodramis G, Dumont C. An evaluation of the infraclavicular block via a modified approach of the Raj technique. *Anesth Analg*. 2001;93:436–441.
314. Ekatodramis G, Macaire P, Borgeat A. Prolonged horner syndrome due to neck hematoma after continuous interscalene block. *Anesthesiology*. 2001;95:801–803.
315. Bergman BD, Hebl JR, Kent J, Horlocker TT. Neurologic complications of 405 consecutive continuous axillary catheters. *Anesth Analg*. 2003;96:247–252; table of contents.
316. Amory C, Mariscal A, Guyot E, Chauvet P, Leon A, Poli-Merol ML. Is ilioinguinal/iliohypogastric nerve block always totally safe in children? *Paediatr Anaesth*. 2003;13:164–166.
317. Frigon C, Mai R, Valois-Gomez T, Desparmet J. Bowel hematoma following an iliohypogastric-ilioinguinal nerve block. *Paediatr Anaesth*. 2006;16:993–996.
318. Singh SK, Katyal S, Kumar A, Kumar P. Massive hemothorax: a rare complication after supraclavicular brachial plexus block. *Anesth Essays Res*. 2014;8:410–412.
319. Nielsen CH. Bleeding after intercostal nerve block in a patient anticoagulated with heparin. *Anesthesiology*. 1989;71:162–164.
320. Aida S, Takahashi H, Shimoji K. Renal subcapsular hematoma after lumbar plexus block. *Anesthesiology*. 1996;84:452–455.
321. Klein SM, D'Ercole F, Greengrass RA, Warner DS. Enoxaparin associated with psoas hematoma and lumbar plexopathy after lumbar plexus block. *Anesthesiology*. 1997;87:1576–1579.
322. Maier C, Gleim M, Weiss T, Stachetzki U, Nicolas V, Zenz M. Severe bleeding following lumbar sympathetic blockade in two patients under medication with irreversible platelet aggregation inhibitors. *Anesthesiology*. 2002;97:740–743.
323. Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. *Anesthesiology*. 2003;98:581–585.
324. Aveline C, Bonnet F. Delayed retroperitoneal haematoma after failed lumbar plexus block. *Br J Anaesth*. 2004;93:589–591.
325. Bickler P, Brandes J, Lee M, Bozic K, Chesbro B, Claassen J. Bleeding complications from femoral and sciatic nerve catheters in patients receiving low molecular weight heparin. *Anesth Analg*. 2006;103:1036–1037.
326. Wiegel M, Gottschaldt U, Hennebach R, Hirschberg T, Reske A. Complicati/ Presented within hours and adverse effects associated with continuous peripheral nerve blocks in orthopedic patients. *Anesth Analg*. 2007;104:1578–1582.
327. Gogarten W, van Aken H, Buttner J, Riess H, Wulf H, Burkle H. Regional anaesthesia and thromboembolism prophylaxis/ anticoagulation—revised recommendations of the german society of anaesthesiology and intensive care medicine. *Anasth Intensivmed*. 2007;48:S109–S124.
328. Keegan MT, Horlocker TT. Epidural catheter removal before unanticipated anticoagulation: the pharmacy fail-safe. *Anesthesiology*. 1999;91:328.
329. Zisman E, Erport A, Kohanovsky E, et al. Platelet function recovery after cessation of aspirin: preliminary study of volunteers and surgical patients. *Eur J Anaesthesiol*. 2010;27:617–623.
330. Greenblatt DJ. Elimination half-life of drugs: value and limitations. *Annu Rev Med*. 1985;36:421–427.
331. Douketis JD, Syed S, Schulman S. Perioperative management of direct oral anticoagulants: comment on the 2015 American Society of Regional Anesthesia and Pain Medicine guidelines. *Reg Anesth Pain Med*. 2016;41:127–129.