Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

American Society of Regional Anesthesia and Pain Medicine

Evidence-Based Guidelines (Fourth Edition)

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Evolution 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. 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. The third consensus conference, based on limited information, recommended that parturients be managed similarly to nonpregnant patients undergoing neuraxial block. More recently, the National Partnership for Maternal Safety (NPMS) 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.

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, 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. 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 therapeutic and 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 patients receiving these medications while undergoing neuraxial and peripheral blockade, and case reports of neuraxial and peripheral 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...
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. The new recommendation is based on the work of Rosencher et al, 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 al cited the work of Bouma and Mosnier, who noted that it takes approximately 8 hours for a platelet plug to become stable. For example, the efficacy of thrombolytics following a cerebral embolic clot markedly decreases after 6 to 8 hours. 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. 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, Scandinavian, and most recent German guidelines (all of which incorporate a pharmacologic approach to newer anticoagulants where data are sparse).

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 co-morbidities 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 hematocele, 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).

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 factors (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).

**TABLE 1. Risk Factors for Venous Thromboembolism**

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

Adapted from Geerts et al 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. 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.

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. 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, 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.” 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.” Thus, with AT8, for patients undergoing major orthopedic surgery, LMWH, fondaparinux, and vitamin K antagonists were the only recommended agents of thromboprophylaxis. However, with the AT9 guidelines, clinicians may now choose from LMWH, fondaparinux, vitamin K antagonists, dabigatran, rivaroxaban, apixaban, low-dose unfractionated heparin (UFH), aspirin, or an intermittent pneumatic compressive device. 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.

### TABLE 2. Recommendations for Thromboprophylaxis in Nonorthopedic Surgical Patients

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

ES indicates elastic stockings; IPC, intermittent pneumatic compression; LDUH, low-dose UFH. Adapted from Gould et al., with permission.
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 reintiated 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 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, Tryba 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 al 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>
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<th>TABLE 3. Perioperative Management of Patients on Warfarin</th>
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<tr>
<td><strong>Preoperative</strong></td>
</tr>
<tr>
<td>• Discontinue warfarin at least 5 days before elective procedure</td>
</tr>
<tr>
<td>• Assess INR 1–2 d prior to surgery, if &gt;1.5, consider 1–2 mg oral vitamin K</td>
</tr>
<tr>
<td>• Reversal for urgent surgery/procedure, consider 2.5–5 mg oral or IV vitamin K; for immediate reversal, consider PCC’s, fresh frozen plasma</td>
</tr>
<tr>
<td>• Patients at high risk of thromboembolism</td>
</tr>
<tr>
<td>o Bridge with therapeutic SC LMWH (preferred) or IV UFH</td>
</tr>
<tr>
<td>o Last dose of preoperative LMWH administered 24 h before surgery, administer half of the daily dose</td>
</tr>
<tr>
<td>o Intravenous heparin discontinued 4–6 h before surgery</td>
</tr>
<tr>
<td>• No bridging necessary for patients at low risk of thromboembolism</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
</tr>
<tr>
<td>• Patients at low risk of thromboembolism</td>
</tr>
<tr>
<td>o Resume warfarin on POD</td>
</tr>
<tr>
<td>• Patients at high risk of thromboembolism (who received preoperative bridging therapy)</td>
</tr>
<tr>
<td>o Minor surgical procedure—resume therapeutic LMWH 24 h postoperatively</td>
</tr>
<tr>
<td>o Major surgical procedure—resume therapeutic LMWH 48–72 h postoperatively or administer low-dose LMWH</td>
</tr>
<tr>
<td>• Assess bleeding risk and adequacy of hemostasis when considering timing of the resumption of LMWH or UFH therapy</td>
</tr>
</tbody>
</table>

Recommendations from Douketis et al.36

<table>
<thead>
<tr>
<th>TABLE 4. Perioperative Management of Patients on Antiplatelet Therapy</th>
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<tbody>
<tr>
<td><strong>Patients with coronary stents</strong></td>
</tr>
<tr>
<td>• Elective surgery postponed for the following durations if aspirin and thienopyridine (eg, clopidogrel or prasugrel) therapy must be discontinued</td>
</tr>
<tr>
<td>o Bare metal stents: 6 wk</td>
</tr>
<tr>
<td>o Drug-eluting stents: 6 mo</td>
</tr>
<tr>
<td>• If surgery cannot be postponed, continue dual antiplatelet therapy throughout perioperative period</td>
</tr>
<tr>
<td><strong>Patients at high risk of cardiac events (exclusive of coronary stents)</strong></td>
</tr>
<tr>
<td>• Continue aspirin throughout the perioperative period</td>
</tr>
<tr>
<td>• Discontinue clopidogrel/prasugrel 5 d prior to surgery</td>
</tr>
<tr>
<td>• Resume thienopyridine 24 h postoperatively</td>
</tr>
<tr>
<td><strong>Patients at low risk of cardiac events</strong></td>
</tr>
<tr>
<td>• Discontinue dual antiplatelet therapy 7–10 d prior to surgery</td>
</tr>
<tr>
<td>• Resume antiplatelet therapy 24 h postoperatively</td>
</tr>
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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 dysfunction.46

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 al.48 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 al.49 involving 43,000 orthopedic patients undergoing epidural blockade reported a similar frequency, 1.38/10,000 (95% confidence interval, 0–0.002).

Overall, these studies 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 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. Importantly, original contraindications to thrombolytic therapy included surgery or puncture of noncompressible vessels within 10 days.

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. 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, and 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. 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, with permission.](http://rapm.bmj.com/content/43/3/268)
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 disproportionally 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.79

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.79 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.76 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.42,47,82,83 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. Although some investigators have recommended cancellation of the surgical procedures should these events occur, there are no clinical data to support this recommendation. 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 postoperative 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., 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, there have been continued discussions regarding the relative risk (and benefit) of neuraxial anesthesia and analgesia in the patient undergoing heparinization for cardiopulmonary bypass. 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. 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 al. 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 risk:

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. 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. 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. 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. There are only 4 case reports of neuraxial hematomas, 3 epidural and 1 spinal, 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. 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. Timing of assessment of coagulation status for residual heparin effect is based on dose and frequency of dosing. For example, the subcutaneous heparin dose of 20,000 U or less 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. 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. Hence the 4- to 6-hour delay after administration for needle placement. Finally, these recommendations are consistent with those of the ESA, as well as British and German guidelines, 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...
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.

3.3.7 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.

<table>
<thead>
<tr>
<th>TABLE 7. European Society of Anaesthesiology’s Recommended Time Intervals Before and After Neuraxial Puncture or Catheter Removal*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Before</strong> Manipulation or Removal</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>UFHs (for prophylaxis, ≤15,000 IU/d)</td>
</tr>
<tr>
<td>UFHs (for treatment)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LMWHs (for prophylaxis)</td>
</tr>
<tr>
<td>LMWHs (for treatment)</td>
</tr>
<tr>
<td>Fondaparinux (for prophylaxis, 2.5 mg/d)</td>
</tr>
<tr>
<td>Rivaroxaban (for prophylaxis, 10 mg daily)</td>
</tr>
<tr>
<td>Apixaban (for prophylaxis, 2.5 mg BID)</td>
</tr>
<tr>
<td>Dabigatran (for prophylaxis, 150–220 mg)</td>
</tr>
<tr>
<td>Coumarins</td>
</tr>
<tr>
<td>Hirudins (desirudin)</td>
</tr>
<tr>
<td>Argatroban</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Prasugrel</td>
</tr>
<tr>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Cilostazol</td>
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<tr>
<td>NSAIDs</td>
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</tbody>
</table>

*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.
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. 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. Prolonged LMWH therapy may be associated with an accumulation of anti-factor Xa activity and fibrinolysis.

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 activity is unknown. For example, while targeted levels have been established for therapeutic anticoagulation, the level of residual anti-factor Xa activity is undetermined.

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. Experience in Europe suggests that the rate of spinal hematoma is similar among LMWH preparations.

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. The risk of spinal hematoma was estimated to be approximately 1 in 3000 continuous epidural anesthetics compared with 1 in 40,000 spinal anesthetics. 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 al 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.

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. 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.

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 LMWHs (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

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

*More than 1 risk factor may have been present in a single case. Adapted from the FDA Drug Safety Communication.19

Therapeutic (Off-label) Applications

Bringing 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.74,106 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 daily for 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). 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).107

Both the FDA and ACCP recommend a reduction in the therapeutic dosing in patients who have severe renal disease (CrCl <30 mL/min).106 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 the 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, who 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. 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). Fondaparinux (Arixtra) is an injectable synthetic pentasaccharide approved by the FDA for the prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults. The recommended dosage for prophylaxis is 25 or 50 mg subcutaneously every 24 hours for 5 days, and for treatment of DVT and PE it is 50 mg subcutaneously every 24 hours for 10 days. Fondaparinux is a Factor Xa inhibitor that is administered by subcutaneous injection. It is used for the prophylaxis and treatment of DVT and PE in adults. The recommended dosage for prophylaxis is 25 or 50 mg subcutaneously every 24 hours for 5 days, and for treatment of DVT and PE it is 50 mg subcutaneously every 24 hours for 10 days. Fondaparinux is a Factor Xa inhibitor that is administered by subcutaneous injection. It is used for the prophylaxis and treatment of DVT and PE in adults.

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 antiaggregants (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.\(^{212}\) 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.\(^{212-213}\) 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 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.\(^{214}\) 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 are not suited to qualitatively and quantitatively assess the effects of rivaroxaban.\(^{214}\) 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.\(^{214}\)

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, 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 hematoma 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%. 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.\(^{212,133}\) 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.
TABLE 9. New (Direct) Oral Anti-Factor Xa Anticoagulants

<table>
<thead>
<tr>
<th>Betrixaban*</th>
<th>Rivaroxaban†</th>
<th>Apixaban‡</th>
<th>Edoxaban§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications and dosing</td>
<td>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 &gt;50 mL/min: 20 mg QD (United States)</td>
<td>Reduction of risk of stroke and systemic embolism in NVAF In patients with CrCl &lt;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 &gt;15 mL/min: 15 mg BID for the first 21 d of the initial treatment for 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 TKA: 30 mg QD (EU, United States) Prevention of athrombogenic 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)</td>
<td>Reduction of risk of stroke and systemic embolism in NVAF: 5 mg BID (EU, United States) 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 TKA: 2.5 mg BID (EU, United States)</td>
</tr>
</tbody>
</table>
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. There are very few prospective data concerning the use of these anticoagulants and the subsequent neuraxial puncture and/or catheter manipulation/withdrawal of the neuraxial catheter. 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.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>History</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>72 y, M, 150 mg BID dabigatran for AF; T2–T7 burst fracture after a fall, 3 h after last dose of dabigatran; bony retroplusion and epidural hematoma on MRI</td>
<td>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</td>
<td>Spontaneous hematoma</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>70 y, 150 mg dabigatran for AF; tetraplegia f2 h after dabigatran; C2–C4 hematoma on CT</td>
<td>PCC; urgent C2–C4 laminectomy; complete neurological recovery</td>
<td>Spontaneous hematoma</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>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</td>
<td>Rivaroxaban discontinued; spontaneous recovery, without surgery, 4 h after onset</td>
<td>Spontaneous hematoma; patient was also on ibuprofen postoperatively</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>69 y, F, THR; 40 mg/d enoxaparin started f2 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</td>
<td>Symptoms improved 4 h later, complete recovery 48 h after symptoms</td>
<td>Spontaneous hematoma</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>69 y, M, 20 mg rivaroxaban for AF; T8 paraplegia; T3-conus subdural hematoma on MRI</td>
<td>Steroids, lumbar and cervical drains placed 8 d later (surgery not recommended); no recovery</td>
<td>Spontaneous hematoma</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>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</td>
<td>IV dexamethasone, sensory/motor improvement after 1 d; C7 corpectomy done of fourth day; almost complete recovery</td>
<td>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</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>72 y, M, 20 mg daily rivaroxaban × 3 y for AF; interscapular pain flaccid paraplegia; T6–T8 subdural hematoma on MRI</td>
<td>PCC; laminectomy next day, IV steroids; no improvement at 6-mo follow-up</td>
<td>Spontaneous hematoma</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>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</td>
<td>Emergency laminectomy IVC filter, residual peroneal anesthesia and neurogenic bladder at 2-5y follow-up</td>
<td>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</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>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</td>
<td>Emergency laminectomy; complete recovery after 5 d</td>
<td>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</td>
</tr>
<tr>
<td>Apixaban</td>
<td>78 M, apixaban 2.5 mg BID and clopidogrel after coronary stent placement; back pain; hyperintense fluid level (subarachnoid hemorrhage) on MRI</td>
<td>Anticoagulants dcd; complete recovery at 3 wk</td>
<td>Spontaneous spinal subarachnoid hemorrhage</td>
</tr>
</tbody>
</table>

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.
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. 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. Edoxaban is used in the prevention of stroke and systemic embolism in patients with NVD and the treatment of VTE and of PE (Savaysa [full prescribing information], available at http://dsi.com/prescribing-information-portlet/getPIContent?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 NVD 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 NVD 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/getPIContent?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 (530 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.

Betraxaban

The latest arrival in the family of the oral anti–factor Xa agents is betrixaban (Beyvxxa; 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.114,115,116 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

Betraxaban 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 assessed using a calibrated chromogenic anti–factor Xa assay.144,115,115

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. If recombinant factor VIIa is used, the potential risk of thrombotic events must always be taken into account. 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 serves as a universal antidote for factor Xa inhibitors, LMWH, and pentasaccharide. 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.

Another compound that binds and neutralizes heparins, dabigatran, 50 IU/kg, 90 to 100 IU/kg, and 90–280% eliminated through the kidney in an unchanged form (grade 2C).

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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. Desirudin is approved for prevention of VTE/PE following hip replacement. 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.

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. Peak plasma levels will be reached within 0.5 to 2 hours after administration (Table 11). The drug is primarily (280%) 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).
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); dabigatran: Epar—product information (available at http://www.eva.europa.eu/docs/en_GB/document_library/EPAR_%20Product_Information/human/000829/WC500041059.pdf, accessed December 22, 2015). The PT and the INR lack any reliable correlation to the anticoagulant effect of dabigatran within minutes. 174 In October 2015, idarucizumab was approved by the FDA to be used in adult 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.

**Table 11. Oral Antithrombin Agents (Dabigatran)**

<table>
<thead>
<tr>
<th>Indications and dosing</th>
<th>Reduction of risk of stroke and systemic embolism in NVAF:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In patients with CrCl &gt;30 mL/min: 150 mg BID (EU, United States)</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl 30–50 mL/min and high bleeding risk: consider 110 mg BID (EU)</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl 15–30 mL/min: 75 mg BID (United States)</td>
</tr>
<tr>
<td>Treatment of VTE and PE:</td>
<td>In patients with CrCl &gt;30 mL/min: 150 mg BID after 5–10 d of parenteral anticoagulation (EU, United States)</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl 30–50 mL/min and high bleeding risk: consider 110 mg BID (EU)</td>
</tr>
<tr>
<td></td>
<td>Reduction in the risk of recurrent VTE and PE:</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl &gt;30 mL/min: 150 mg BID after previous treatment (EU, United States)</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl 30–50 mL/min and high bleeding risk: consider 110 mg BID (EU)</td>
</tr>
<tr>
<td>Prophylaxis of VTE following THA:</td>
<td>In patients with CrCl ≥30 mL/min: 110 mg QD first day, then 220 mg QD (United States)</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl &gt;30 mL/min: 110 mg QD first day, then 220 mg QD (EU)</td>
</tr>
<tr>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Prophylaxis of VTE following TKA:</td>
<td>In patients with CrCl ≥30 mL/min: 110 mg QD first day, then 220 mg QD (EU)</td>
</tr>
<tr>
<td></td>
<td>In patients with CrCl 30–50 mL/min, concomitant use of P-gp inhibitors: 75 mg QD first day, then 150 mg QD (EU)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal clearance</th>
<th>CrCl, mL/min</th>
<th>Elimination half-life tβ, h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥80</td>
<td>50–79</td>
</tr>
<tr>
<td></td>
<td>30–49</td>
<td>15–29</td>
</tr>
<tr>
<td></td>
<td>&lt;15 (Off-dialysis)</td>
<td>No data</td>
</tr>
</tbody>
</table>


Reversal of Dabigatran

In 2013, Schiele et al 186 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 with NVAF who require urgent surgery or invasive procedures, including cardiovascular and noncardiovascular surgeries requiring VTE prophylaxis or treatment and acute coronary syndromes requiring parenteral anticoagulation.
patients treated with dabigatran when rapid access to 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), 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 of 50 to 79 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. 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.

11.2 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 prior to the first (postoperative) dose (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 cloting 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. 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. 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. 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. The association of renal insufficiency and increased response to warfarin has also been noted by Benzon et al. One patient in their study evaluating the concentration of clotting factors after discontinuation of warfarin had renal insufficiency (blood urea nitrogen of 64 mg/dL, 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. 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. The ACCP recommended against the use of pharmacogenetic-based initial dosing until randomized data showed it to be beneficial. 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. However, 2 other studies did not show a difference. 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 13. Patient Characteristics Associated With Increased Sensitivity to Warfarin

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sensitivity Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>5%</td>
</tr>
<tr>
<td>Female sex</td>
<td>3%</td>
</tr>
<tr>
<td>Weight &lt;100 lb</td>
<td>4%</td>
</tr>
<tr>
<td>Liver, cardiac, or renal disease</td>
<td>6%</td>
</tr>
<tr>
<td>Asian ancestry</td>
<td>1%</td>
</tr>
<tr>
<td>Excessive surgical blood loss</td>
<td>2%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-Life, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VII</td>
<td>6–8</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24</td>
</tr>
<tr>
<td>Factor X</td>
<td>25–60</td>
</tr>
<tr>
<td>Factor II</td>
<td>50–80</td>
</tr>
</tbody>
</table>
When warfarin is stopped before a neuraxial or surgical procedure, most clinicians bridge anticoagulation with LMWH. 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. 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 assessment.

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. 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 warfarin. PCC is better than recombinant activated factor VIIa; and 4-factor PCC appears to be more effective than 3-factor PCC.

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

<table>
<thead>
<tr>
<th>Day after warfarin</th>
<th>INR of ≤1.4</th>
<th>INR &gt;1.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD1 (12–14 h)</td>
<td>99 (SD, 35)</td>
<td>60 (SD, 28)</td>
</tr>
<tr>
<td>POD2 (36–38 h)</td>
<td>74 (SD, 20)</td>
<td>32 (SD, 15)</td>
</tr>
<tr>
<td>POD3 (60–62 h)</td>
<td>87 (SD, 26)</td>
<td>44 (SD, 14)</td>
</tr>
</tbody>
</table>

Values are in percent.
Adapted from Benzon et al.

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). 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 al. 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

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 anesthetic 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 thrombophrophylaxis 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 increased 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 on warfarin therapy. To facilitate neurologic evaluation, we suggest that their INR be monitored (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 (abximab, epftibatide, 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.17,218 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 Cetelecoxib (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 effects, 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.224 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://usplilly.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.236

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_ticlid.pdf, accessed March 4, 2017). Clopidogrel should be discontinued 5 days (clopidogrel [full prescribing information], available at http://packagenserts.bms.com/pi/pi_plavix.pdf, accessed March 4, 2017), and prasugrel discontinued 7 days (prasugrel [full prescribing information], available at http://uspililly.com/effient/effient.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.223 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.aspcentral.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 (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. 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.3

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. The terminal half-life is 10 hours. There are no data to support discontinuation of dipyridamole peripheratively. 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 interscalene while receiving dipyridamole.

Spinal Hematoma in Patients Receiving Antplatelet 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 (nonchonic pain) procedures. Vandermeulen et al implicated antplatelet 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. 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. 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. 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. These results confirm those of previous studies performed in obstetric and surgical populations. An exception to this is 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. 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. 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. In general, the cardiac surgical literature recommends that elective surgery be delayed 24 to 48 hours following abciximab and 4 to 8 hours following epifibatide or tirofiban. 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.

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. For example, in the series of 40 spinal hematomas associated with LMWH reported in 1998, 10 patients received concomitant antiplatelet medications.

The addition of antiplatelet therapy to postoperative thromboprophylaxis was implicated in a similar number of cases in the survey by Moen et al. Likewise, in a case report of spinal hematoma following ESI, Benzon et al noted the patient had received multiple antiplatelet medications, including clopidogrel and aspirin.

13.0 Antithrombotic Management of the Patient Receiving Antiplatelet Medications

Antplatelet 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.
13.3 Ticagrelor
13.3.1 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.
13.3.2 Postoperative. In accordance with ACCP recommendations, ticagrelor therapy may be reinstated 24 hours postoperatively (grade 1A).
Remarks: This is a new recommendation.
13.3.3 Neuraxial catheters should not be maintained with ticagrelor because of the rapid onset (grade 2C).
Remarks: This is a new recommendation.
13.3.4 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.
13.4 Dipyridamole
13.4.1 Preoperative. The platelet GP IIb/IIa 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 epifibatide and tirofiban.
13.5.1 Preoperative. We recommend that neuraxial techniques should be avoided while platelet function—assessed 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 biloba253–256. 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...
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.1,12,259 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.17 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 15. Three Herbal Medications With the Greatest Impact on Hemostasis*

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

*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.
difficult to determine, although it is widely reported these patients have a significantly lower incidence of complications than their elderly counterparts. Moen et al 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 1:20,000, which was significantly lower than the incidence of 1:3600 elderly females undergoing total knee arthroplasty. Bateman et al confirmed the incidence of spinal hematomas among 142,287 patients undergoing epidural anesthesia/analgesia, for the differing incidence. Both Moen et al and Pöpping et al 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.

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. 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 twice as frequently as in the elderly. The peripartum management of the anticoagulated parturient represents a significant clinical challenge to both the obstetrician and the anesthesiologist. The ACCP and the NPMS recommend discontinuing anticoagulant therapy upon the onset of labor, as (1) discontinuing anticoagulant therapy upon the onset of labor, and per the NPMS, (2) using 5000 SC UFH BID for thromboprophylaxis, but she had signs and symptoms of an expanding spinal hematoma before receiving the LMWH dose.

**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 compared with alternative modes of pain management. For labor, neuraxial analgesia provides superior pain relief compared with alternative modes of pain management. For labor, neuraxial analgesia provides superior pain relief compared with alternative modes of pain management. For labor, neuraxial analgesia provides superior pain relief compared with alternative modes of pain management.

**Obstetric and Anesthetic Management**

The peripartum management of the anticoagulated parturient represents a significant clinical challenge to both the obstetrician and the anesthesiologist. The ACCP and the NPMS recommend discontinuing anticoagulant therapy upon the onset of labor, as (1) discontinuing anticoagulant therapy upon the onset of labor.

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

<table>
<thead>
<tr>
<th>ACOG</th>
<th>ACCP</th>
<th>NPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylactic UFH</strong></td>
<td>5000–10,000 U every 12 h</td>
<td>5000 U every 12 h</td>
</tr>
<tr>
<td>• 5000–7500 U every 12 h in 1st trimester</td>
<td>• 5000–7500 U every 12 h in 1st trimester</td>
<td>• 7500–10,000 U every 12 h in 2nd trimester</td>
</tr>
<tr>
<td>• 10,000 U every 12 h in the 3rd trimester unless aPTT is elevated</td>
<td>• 10,000 U every 12 h in the 3rd trimester unless aPTT is elevated</td>
<td>• 10,000 U every 12 h in the 3rd trimester unless aPTT is elevated</td>
</tr>
<tr>
<td><strong>Minidose:</strong> 5000 U every 12 h</td>
<td><strong>Hospitalized antepartum patients may receive:</strong> 5000 U every 12 h</td>
<td><strong>Hospitalized antepartum patients may receive:</strong> 5000 U every 12 h</td>
</tr>
</tbody>
</table>

| **Prophylactic LMWH** | Dalteparin 5000 U once daily | Dalteparin 5000 U once daily |
| Enoxaparin 40 mg once daily | Enoxaparin 40 mg once daily |
| At extremes of body weight, modification of dose may be required | 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 | ≥10,000 U BID adjusted to midinterval aPTT |
| **Therapeutic-dose LMWH** | Dalteparin 200 U/kg QD or dalteparin 100 U/kg every 12 h | Dalteparin 200 U/kg QD |
| Enoxaparin 1 mg/kg every 12 h | Enoxaparin 1 mg/kg every 12 h |
| **Table 16 continued** |

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

Adapted from Horlocker et al, \(^{7}\) with permission.
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 episiotomy. 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 21.236,237,303,304,310,312–325 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 perineural, 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
European societies have approved official guidelines for thromboembolism prophylaxis and regional anesthesia. Both ESA (Table 7) and ASRA published updated recommendations in 2010. 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. 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.
### TABLE 20. Hemorrhagic Complications Following Plexus and Peripheral Block in Patients Without Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Information</th>
<th>Block Type</th>
<th>Clinical Course/Outcomes</th>
</tr>
</thead>
</table>
| Wheatley et al306 (1984) | 59-y-old woman with chronic pelvic pain | Lumbar sympathetic blocks over a 5-d period (paravertebral approach 5 cm lateral to the 2nd lumbar vertebrae) | • 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 al307 (1995)   | No information                             | Axillary (transarterial)                        | • Patient developed small (<2 cm) hematoma  
  • Resolved without sequelae                                                                                                                                  |
| Kurzel et al308 (1996) | 17-y-old admitted for induction of labor  | Bilateral pudendal block                        | • 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 al309 (1998)| 62-y-old woman with sudden deafness       | Sequential (on alternate days) stellate ganglion blocks at C7, anterior paratracheal approach | • 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 Stahl310 (1999)| 38-y-old healthy man, procedure on palmar surface of wrist | Axillary (transarterial)                        | • Large axillary hematoma causing paresthesias and radial nerve weakness  
  • Electromyogram at 4 wk demonstrated signs of neuropraxia  
  • Complete recovery after 6 mo  
  • 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                                                                                     |
| Thomas et al311 (1999)| 65-y-old woman undergoing thoracotomy for recurrent esophageal hernia | Paravertebral (loss of resistance to saline technique) | • 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                                                                 |
| Vaisman312 (2001)      | 40-y-old man with left testicular pain     | Ilioinguinal                                     |                                                                                                                             |
TABLE 20. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Information</th>
<th>Block Type</th>
<th>Clinical Course/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borgeat al(^{313}) (2001)</td>
<td>No information</td>
<td>Infraclavicular (modified approach of the Raj technique)</td>
<td>• Patient developed hematoma at the puncture site</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No information about outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous interscalene catheter</td>
<td>• 3 d postoperatively, the patient complained of blurred vision and painful swelling on right side of neck</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ultrasound of neck revealed 4 × 5-cm hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous interscalene catheter</td>
<td>• Neurologic investigation confirmed Horner syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Catheter removed immediately</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 6 mo later, Horner syndrome began to improve</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Complete resolution at 1 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• POD1 patient noted visual disturbances and neck swelling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ultrasound of the neck revealed 3 × 4-cm hematoma</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Neurologic investigation confirmed Horner syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous interscalene catheter</td>
<td>• Catheter removed immediately</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 6 mo later, only slight ptosis present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Complete resolution at 1 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patient developed axillary hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Resolved spontaneously without sequelae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Large, obstructing subserosal hematoma, which presented as intestinal obstruction 5 d postoperatively</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Diagnostic laparoscopy and bowel resection with an uneventful recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hematoma (2 cm in diameter) in the wall of the terminal ileum noted upon opening peritoneum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hematoma was nonobstructing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Uneventful recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Paresthesia elicited on 3rd attempt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• At the end of procedure, complained of slight chest pain in ipsilateral infraclavicular region</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Chest x-ray negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Adequate sensory/motor block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 12 h later, worsening chest pain and palpitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Chest x-ray revealed massive fluid collection on the right side with partial collapse of right lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Chest tube placed with 1300 mL of blood drained and transfused 4 U whole blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intensive care unit for 5 d, dismissed in 10 d in satisfactory condition</td>
</tr>
</tbody>
</table>

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 antplatelet 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 antplatelet and anticoagulant medications and/or if respondents incorporated different protocols for different pain procedures.

Most of the respondents followed ASRA guidelines for anticoagulants but not for antplatelet 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Information</th>
<th>Anticoagulant/ Antiplatelet Agent(s)</th>
<th>Block Type</th>
<th>Clinical Course/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielsen319 (1989)</td>
<td>80-y-old man with severe postoperative pain</td>
<td>Preoperative</td>
<td>Lumbar plexus block</td>
<td>Small chest wall hematoma noted on POD3 at T7 before the last block was placed</td>
</tr>
<tr>
<td></td>
<td>Cholecystectomy</td>
<td>Postoperative</td>
<td>Place 20 h postoperatively</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Pain due to herniated lumbar disc</td>
<td>Warfarin preoperatively</td>
<td>Blocks repeated 4 times</td>
<td>Required transfusion of 8 U of packed red blood cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT on operative day 13 s</td>
<td>(approximately every 7 h)</td>
<td>Heparin infusion was stopped</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparin 5000 U subcutaneously every 8 h</td>
<td></td>
<td>Patient recovered uneventfully but had pain for 4 wk in the area of the hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>started 8 h postoperatively and discontinued on POD2</td>
<td></td>
<td>Low back pain became more intense 1 d after the last block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POD2 heparin bolus 4500 U intravenously followed by continuous infusion (PTT ranged from 99–29 s)</td>
<td></td>
<td>Difficulty walking for several days</td>
</tr>
<tr>
<td>Aida et al320 (1996)</td>
<td>71-y-old woman</td>
<td>Preoperative</td>
<td>Lumbar plexus block</td>
<td>Pain still present 10 d after the block</td>
</tr>
<tr>
<td></td>
<td>Pain due to herniated lumbar disc</td>
<td>None</td>
<td>Performed 4 times for 4 wk</td>
<td>CT scan and ultrasonography revealed renal subcapsular hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postoperative</td>
<td>Level of L3 using loss of resistance technique</td>
<td>Microscopic hematuria resolved after 2 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain treated with mefenamic acid (NSAID)</td>
<td></td>
<td>Back pain resolved after 3 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hematoma resolved spontaneously within 4 mo</td>
</tr>
<tr>
<td>Aida et al320 (1996)</td>
<td>68-y-old woman</td>
<td>Lumbar plexus block at the level of L3 using loss of resistance technique</td>
<td>Low back pain became more intense 1 d after the block</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain due to spinal spondylosis</td>
<td>Preoperative</td>
<td></td>
<td>Pain remained severe and patient could not ambulate for several days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>Low back pain became more intense 1 d after the last block</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postoperative</td>
<td></td>
<td>3 d after block CT scan and ultrasonography revealed renal subcapsular hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain treated with 200 mg IV diclofenac (NSAID)</td>
<td></td>
<td>Microscopic hematuria resolved after 1 wk</td>
</tr>
<tr>
<td>Klein et al321 (1997)</td>
<td>67-y-old woman</td>
<td>Lumbar plexus block at the level of L3</td>
<td>Low back pain became more intense 1 d after the block</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repair of open right calcaneal fracture</td>
<td>Preoperative</td>
<td></td>
<td>Pain markedly decreased after 2 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin 325 mg/d</td>
<td></td>
<td>Discharged after a 10-d hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postoperative</td>
<td></td>
<td>Pain resolved after 6 wk, hematoma resolved within 4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POD1 enoxaparin 30 mg BID and aspirin 325 mg/d</td>
<td></td>
<td>Hospital day 7 (1 d after below the knee amputation) patient complained of right hip pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin continued 30 mg every 12 h</td>
<td></td>
<td>Hospital day 14 severity of pain worsened</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd operative procedure was 19½ h after last dose of enoxaparin</td>
<td></td>
<td>Hospital day 15 patient was unable to move right leg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First postoperative enoxaparin dose (after 3rd procedure) 4.5 h after block placement</td>
<td></td>
<td>Abdominal CT revealed a large retroperitoneal hematoma involving the right psoas muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin discontinued on hospital day 15 after CT scan</td>
<td></td>
<td>Patient regained motor function over the next 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Night of admission</td>
<td></td>
<td>No subjective or objective evidence of sensory deficit at the 4-mo follow-up visit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incision and drainage of ankle</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sciatic block (Labat approach), saphenous nerve block posterior to the sartorius muscle</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Open reduction internal fixation of ankle</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Sciatic block (Raj approach) and lumbar plexus block (femoral approach)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital day 3 (2nd procedure)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Right below knee amputation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Lumbar plexus block (posterior approach)—unable to place despite multiple attempts</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lumbar plexus block (femoral approach) and sciatic block (Raj approach)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital day 6 (3rd procedure)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Information</th>
<th>Anticoagulant/Antiplatelet Agent(s)</th>
<th>Block Type</th>
<th>Clinical Course/Outcomes</th>
</tr>
</thead>
</table>
| Maier et al\(^{322}\) (2002) | • 79-y-old woman  
• Generalized peripheral arterial disease  
• Severe pain in lower extremities | Preoperative  
• Clopidogrel 75 mg/d  
• Discontinued 3 d prior to block  
Postoperative  
• None | • Diagnostic lumbar sympathetic block at the L3 level | • 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) |
| Maier et al\(^{322}\) (2002) | • 71-y-old man  
• Left leg claudication | Preoperative  
• Ticlopidine 500 mg/d  
Postoperative  
• Ticlopidine stopped 2 d after the first block | • 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 | • No vascular puncture during first block  
• 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) | • 85-y-old woman  
• Unicompartmental right knee arthroplasty | Preoperative  
• No anticoagulant medication  
Postoperative  
• POD2 at 0900 enoxaparin 30 mg  
• Enoxaparin continued 30 mg every 12 h  
• Enoxaparin discontinued on POD4 | • 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 | • 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 |

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<tr>
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<th>Anticoagulant/Antiplatelet Agent(s)</th>
<th>Block Type</th>
<th>Clinical Course/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weller et al323</td>
<td>65-y-old man, Left knee arthroscopy, Mechanical aortic valve</td>
<td>Preoperative</td>
<td>Block Type</td>
<td>Clinical Course/Outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin 5 mg/d, Aspirin 81 mg BID</td>
<td></td>
<td>POD3 patient complained of back pain at the site of the lumbar plexus block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient admitted with INR 5.19, coumadin stopped, and heparin started</td>
<td></td>
<td>CT scan revealed moderate-size retroperitoneal hematoma that appeared to originate in the psoas muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Next day INR measured 9.27, given 10 mg vitamin K and 1 U fresh frozen plasma</td>
<td></td>
<td>Transfused 2 U packed red blood cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morning of surgery INR 0.92</td>
<td></td>
<td>Discharged on POD10 with plan to restart anticoagulation 2 wk after discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postoperative</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Heparin infusion initiated at 1200 U/h 8 h after the lumbar plexus block</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>aPTT on POD1 was 77.7 s</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Coumadin restarted evening of POD1</td>
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<tr>
<td></td>
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<td>POD3 aPTT &gt;100 s and INR 1.4</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Heparin adjusted and POD4 aPTT 60.2 s</td>
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<tr>
<td></td>
<td></td>
<td>POD5 anticoagulation discontinued and vitamin K 1 mg subcutaneously and 2 U fresh frozen plasma given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aveline et al324</td>
<td>72-y-old woman, Total hip replacement, Heterozygous Leiden mutation</td>
<td>Preoperative</td>
<td>Block Type</td>
<td>Clinical Course/Outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenylindanedione stopped 5 d before surgery</td>
<td></td>
<td>POD17, the patient complained of progressive left leg motor deficit and left lumbar back pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin 60 mg BID started 5 d before surgery and held 24 h before surgery</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INR and aPTT normal</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postoperative</td>
<td></td>
<td>Patient received 3 U of packed red blood cells and vitamin K</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anticoagulation initiated at 14 h with enoxaparin 40 mg and then increased to 60 mg once daily on POD2</td>
<td></td>
<td>Motor function started to progressively recover on POD19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenylindanedione restarted on POD3 and enoxaparin stopped on POD7</td>
<td></td>
<td>Recovery was complete on POD45</td>
</tr>
<tr>
<td>Bickler et al325</td>
<td>49-y-old man, Right total knee replacement</td>
<td>Preoperative</td>
<td>Block Type</td>
<td>Clinical Course/Outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No anticoagulant medication</td>
<td></td>
<td>POD3 patient complained of back pain at the site of the lumbar plexus block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POD2 enoxaparin 40 mg/d subcutaneously</td>
<td></td>
<td>CT scan revealed moderate-size retroperitoneal hematoma that appeared to originate in the psoas muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>POD5 enoxaparin discontinued</td>
<td></td>
<td>Transfused 2 U packed red blood cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous sciatic nerve catheter (lateral, midfemoral region)</td>
<td></td>
<td>Discharged on POD7, which was 2 d later than expected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous femoral catheter</td>
<td></td>
<td>No specific treatment for the hematoma</td>
</tr>
<tr>
<td>Reference</td>
<td>Patient Information</td>
<td>Anticoagulant/ Antiplatelet Agent(s)</td>
<td>Block Type</td>
<td>Clinical Course/Outcomes</td>
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<tr>
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</tr>
<tr>
<td>Bickler et al (2006)</td>
<td>78-y-old woman • Total knee replacement</td>
<td>Preoperative • No anticoagulant medication Postoperative • POD1 enoxaparin 40 mg/d subcutaneously</td>
<td>Continuous sciatic nerve catheter • Continuous femoral catheter</td>
<td>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</td>
</tr>
<tr>
<td>Bickler et al (2006)</td>
<td>48-y-old woman • Total knee replacement</td>
<td>Preoperative • No anticoagulant medication Postoperative • POD1 enoxaparin 40 mg/d subcutaneously</td>
<td>Continuous sciatic nerve catheter (lateral, midfemoral region) • Continuous femoral catheter</td>
<td>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 • 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</td>
</tr>
<tr>
<td>Wiegel et al (2007)</td>
<td>No information</td>
<td>Preoperative • Aspirin 1 g/d</td>
<td>Continuous femoral catheter</td>
<td></td>
</tr>
<tr>
<td>Clendenen et al (2010)</td>
<td>66-y-old woman • Right shoulder hemiarthroplasty and rotator cuff repair</td>
<td>Preoperative • Dipyridamole • Aspirin (stopped 1 wk preoperative) Postoperative • Dipyridamole</td>
<td>Continuous interscalene block</td>
<td>Nerve stimulator guided block with puncture of external jugular vein during placement • Interscalene catheter noted to be dislodged in the arm 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 <em>Staphylococcus aureus</em> • Discharged after 30-d hospital stay to extended care facility in good condition</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Reference</th>
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<th>Anticoagulant/ Antiplatelet Agent(s)</th>
<th>Block Type</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez et al. 303 (2011)</td>
<td>59-y-old woman undergoing bullet removal from left calf</td>
<td>Preoperative</td>
<td>Single injection femoral and sciatic nerve blocks</td>
<td>• 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</td>
</tr>
<tr>
<td>Parvaiz et al. 237 (2012)</td>
<td>• 71-y-old man • Inguinal hernia</td>
<td>Preoperative</td>
<td>ilioinguinal/iliohypogastric nerve block</td>
<td>• 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</td>
</tr>
<tr>
<td>Warner et al. 304 (2016)</td>
<td>• 87-y-old man • Left total hip arthroplasty and essential thrombocytosis</td>
<td>Preoperative</td>
<td>Posterior lumbar plexus catheter</td>
<td>• 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</td>
</tr>
</tbody>
</table>

Adapted from Horlocker et al., 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 Anesthesia & 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 antithrombotic effects including NSAIDs and aspirin.

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

**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 mild, intermediate, and high bleeding risks and made recommendations (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 antithrombotic 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, antithrombotic 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. 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 etodolac; and 10 days for oxaprozin and piroxicam. Aspirin and NSAIDs can be resumed a day after the procedure. There is no significant difference between the guidelines in managing the more potent antithrombotic 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>
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<th>TABLE 22. Stratification of Risk According to Procedures</th>
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<tr>
<td><strong>Low Risk</strong></td>
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<tr>
<td>Regional Guidelines</td>
</tr>
<tr>
<td>Superficial and compressible plexus/peripheral nerve blocks</td>
</tr>
</tbody>
</table>

Narouze et al, 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.\(^\text{3,187,331}\) 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

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### Procedural Anticoagulation Management Checklist

**Evaluate baseline patient specific risk factors for perioperative bleeding:**

- History and physical examination signs suggestive of a bleeding disorder:
  - 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.

**For individuals on aspirin categorize reason for utilization:**

- Primary prophylaxis → absence of established cardiovascular disease or risk factor.
- Secondary prophylaxis → presence of cardiovascular disease.

**Process the anatomical location of procedural intervention into decision-making:**

- Intracranal vs extracranial spinal procedures
- Cervicothoracic neuraxial area or lumbosacral neuraxial area
- Surrounding vascular structures at risk for penetration.

**Review appropriate radiographic imaging to identify and understand anatomic challenges:**

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

**Identify and manage pharmacologic coagulopathies:**

- 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.

**Employ post-procedure surveillance for the detection of bleeding complications**

| SNRIs = Selective serotonin reuptake inhibitors | SSRIs = Selective serotonin reuptake inhibitors |

**FIGURE 2.** Procedural management checklist. Adapted from Narouze et al,\(^\text{18}\) 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 colleagues’43 series, all of guidelines will not completely eliminate the complication of membered that identification of risk factors and establishment of guidelines will not completely eliminate the complication of spinal hematoma. In Vandermeulen and colleagues’43 series, all of guidelines will not completely eliminate the complication of spinal hematoma.

ACKNOWLEDGMENTS

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REFERENCES


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