

Executive Summary: Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

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

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Numerous studies have documented the safety of neuraxial anesthesia and analgesia in the anticoagulated patient. Patient management is based on appropriate timing of needle placement and catheter removal relative to the timing of anticoagulant drug administration. Familiarity with the pharmacology of hemostasis-altering drugs, the clinical studies involving patients undergoing neuraxial blockade while receiving these medications, as well as the case reports of spinal hematoma will guide the clinician in management decisions.

New challenges in the management of the anticoagulated patient undergoing neuraxial blockade have arisen as medical standards for the prevention of perioperative venous thromboembolism were established. Likewise, as more efficacious anticoagulants and antiplatelet agents have been introduced, patient management has become more complex. In response to these patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Third Consensus Conference on Regional Anesthesia and Anticoagulation. Portions of the material presented here were published as the proceedings of the 1997 and 2002 ASRA Consensus Conferences.^{1–6} The information has been updated to incorporate additional data available since the time of its publication. Variances from recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. The consensus statements are designed to encourage safe and quality patient care but cannot guarantee a specific outcome. They are also subject to timely revision as justified by evolution of information and practice.

These recommendations focus on patients receiving neuraxial and peripheral techniques. The practice settings include inpatient (eg, operating rooms, intensive care units, postoperative surgical floors, labor and delivery settings, or hospital wards) and ambulatory facilities such as pain clinics. The recommendations are intended for use by anesthesiologists and other physicians and health care providers performing

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

The original article developed from the Consensus Conference held during the 32nd Annual Regional Anesthesia Meeting and Workshops held on April 19–22, 2007, in Vancouver, British Columbia, Canada, is published in this issue of *Regional Anesthesia and Pain Medicine* (*Reg Anesth Pain Med* 35: 64–101). The full-length document provides the necessary background to a more complete understanding of the clinical issues discussed at the Consensus Conference.

1.0 Administration of Antithrombotic Agents for the Prevention and Treatment of Venous Thromboembolism

- 1.1 In accordance with American College of Chest Physicians guidelines, for each of the antithrombotic agents, we recommend that clinicians follow the manufacturer-suggested dosing guidelines (Grade 1C).

2.0 Anesthetic Management of the Patient Receiving Thrombolytic Therapy

Patients receiving fibrinolytic/thrombolytic medications are at risk for 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 epidural steroid injection to allow appropriate monitoring. Guidelines detailing original contraindications for thrombolytic drugs suggest avoidance of these drugs for 10 days after puncture of noncompressible vessels (Grade 1A).
- 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). Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.
- 2.3 In those patients who have received neuraxial blocks at or near the time of fibrinolytic and thrombolytic therapy, we recommend that neurologic monitoring

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should be continued for an appropriate interval. It may be that the interval of monitoring should not be more than 2 hrs 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).

- 2.4 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).

3.0 Anesthetic Management of the Patient Receiving Unfractionated Heparin (UFH)

Anesthetic management of the heparinized patient was established during 2 decades ago. Initial recommendations have been supported by in-depth reviews of case series, case reports of spinal hematoma, and the American Society of Anesthesiologists Closed Claims Project. Recent thromboprophylaxis guidelines identifying more patients as candidates for thrice-daily subcutaneous heparin and the potential for increased bleeding with this therapy have prompted a modification of the previous ASRA guidelines.

- 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, low-molecular weight heparin (LMWH) and oral anticoagulants (Grade 1B).
- 3.2 In patients receiving prophylaxis with subcutaneous UFH with dosing regimens of 5000 U twice daily, 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 (Grade 1C).
- 3.3 The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice-daily dosing of UFH has not been established. Although the use of thrice-daily UFH may lead to an increased risk of surgical-related bleeding, it is unclear whether there is an increased risk of spinal hematoma. We suggest that the risk and benefits of thrice-daily UFH 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).
- 3.4 Because heparin-induced thrombocytopenia may occur during heparin administration, we recommend that patients receiving heparin for greater than 4 days have a platelet count assessed before neuraxial block and catheter removal (Grade 1C).
- 3.5 Combining neuraxial techniques with intraoperative anticoagulation with heparin during vascular surgery is acceptable with the following recommendations (Grade 1A):
- 3.5.1 Avoid the technique in patients with other coagulopathies.

- 3.5.2 Delay heparin administration for 1 hr after needle placement.

- 3.5.3 Remove indwelling neuraxial catheters 2 to 4 hrs after the last heparin dose and assess the patient's coagulation status; re-heparin 1 hr after catheter removal.

- 3.5.4 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.

- 3.5.5 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 is warranted.

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

4.0 Anesthetic Management of the Patient Receiving LMWH

Anesthesiologists in North America can draw on the extensive European experience to develop practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. All consensus statements contained herein respect the labeled dosing regimens of LMWH as established by the Food and Drug Administration. Although it is impossible to devise recommendations that will completely eliminate the risk of spinal hematoma, previous consensus recommendations have seemed to improve outcome. Concern remains for higher-dose applications, where sustained therapeutic levels of anticoagulation are present.

- 4.1 The anti-Xa level is not predictive of the risk of bleeding. We recommend against the routine use of monitoring of the anti-Xa level (Grade 1A).

- 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 (Grade 1A).

- 4.3 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 hrs postoperatively and that this consideration be discussed with the surgeon (Grade 2C).

4.4 Preoperative LMWH

- 4.4.1 Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, we recommend that needle placement should occur at least 10 to 12 hrs after the LMWH dose (Grade 1C).

- 4.4.2 In patients receiving higher (treatment) dosages of LMWH, such as enoxaparin 1 mg/kg every 12 hrs, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hrs, dalteparin 200 U/kg

daily, or tinzaparin 175 U/kg daily, we recommend delay of at least 24 hrs to ensure normal hemostasis at the time of needle insertion (Grade 1C).

- 4.4.3 In patients administered a dose of LMWH 2 hrs preoperatively (general surgery patients), we recommend against a neuraxial techniques because needle placement would occur during peak anticoagulant activity (Grade 1A).

4.5 Postoperative LMWH

Patients with postoperative LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule (Grade 1C).

- 4.5.1 Twice-daily dosing. This dosage regimen is associated with an increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hrs postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed before initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight but must be removed before the first dose of LMWH. Administration of LMWH should be delayed for 2 hrs after catheter removal.
- 4.5.2 Single-daily dosing. The first postoperative LMWH dose should be administered 6 to 8 hrs postoperatively. The second postoperative dose should occur no sooner than 24 hrs after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10 to 12 hrs after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hrs after catheter removal. No additional hemostasis-altering medications should be administered owing to the additive effects.

5.0 Regional Anesthetic Management of the Patient on Oral Anticoagulants

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).

- 5.1 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 factor II and X levels) may not be adequate for hemostasis despite a decrease in the international normalized ratio (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 reference limits. We recommend that the anticoagulant therapy must be stopped (ideally 4–5 days before the planned procedure), and the INR measured before initiation of neuraxial block (Grade 1B).
- 5.2 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 nonsteroidal anti-inflammatory drugs (NSAIDs), ticlopidine and clopidogrel, UFH, and LMWH (Grade 1A).

- 5.3 In patients who are likely to have an enhanced response to the drug, we recommend that a reduced dose be administered. Algorithms have been developed to guide physicians in the appropriate dosing of warfarin based on desired indication, patient factors, and surgical factors. These algorithms may be extremely useful in patients at risk for an enhanced response to warfarin (Grade 1B).
- 5.4 In patients receiving an initial dose of warfarin before surgery, we suggest the INR should be checked before neuraxial block if the first dose was administered more than 24 hrs earlier if or a second dose of oral anticoagulant has been administered (Grade 2C).
- 5.5 In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored on a daily basis (Grade 2C).
- 5.6 Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. To facilitate neurologic evaluation, we recommend that the type of analgesic solution be tailored to minimize the degree of sensory and motor blockade (Grade 1C).
- 5.7 As thromboprophylaxis with warfarin is initiated, we suggest that neuraxial catheters should be removed when the INR is less than 1.5. This value was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%. We suggest that neurologic checks be continued for at least 24 hrs after catheter removal for these patients (Grade 2C).
- 5.8 In patients with INR greater than 1.5 but less than 3, we recommend that removal of indwelling catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not effect the INR (eg, NSAIDs, clopidogrel, ticlopidine, UFH, LMWH) (Grade 2C). We also recommend that neurologic status be assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level. (Grade 1C).
- 5.9 In patients with an INR greater than 3, we recommend that the warfarin dose be held or reduced in patients with indwelling neuraxial catheters (Grade 1A). We can make no definitive recommendation regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion (Grade 2C).

6.0 Anesthetic Management of the Patient Receiving Antiplatelet Medications

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel) and platelet glycoprotein (GP) IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) 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. There is no wholly accepted test, including the bleeding time, which will guide antiplatelet therapy. 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.

- 6.1 Nonsteroidal anti-inflammatory drugs seem to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. NSAIDs (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-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal (Grade 1A).
- 6.2 In patients receiving NSAIDs, we recommend against the performance of neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as 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).
- 6.3 The actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown. Management is based on labeling precautions and the surgical, interventional cardiology/radiology experience (Grade 1C).
 - 6.3.1 On the basis of labeling and surgical reviews, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. If a neuraxial block is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented.
 - 6.3.2 Platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. After administration, the time to normal platelet aggregation is 24 to 48 hrs for abciximab and 4 to 8 hrs for eptifibatid and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. Although GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery, should one be administered in the postoperative period (after a neuraxial technique), we recommend that the patient be carefully monitored neurologically.

7.0 Anesthetic Management of the Patient Receiving Herbal Therapy

Herbal drugs, by themselves, seem to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. This is an important observation because it is likely that a significant number of our surgical patients use alternative medications preoperatively and perhaps during their postoperative course.

- 7.1 The use of herbal medications does not create a level of risk that will interfere with the performance of neuraxial block. We recommend against mandatory discontinuation of these medications or avoidance of regional

anesthetic techniques in patients in whom these medications have been administered (Grade 1C).

8.0 Anesthetic Management of Patients Receiving Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)

- 8.1 In patients receiving thrombin inhibitors, we recommend against the performance of neuraxial techniques (Grade 2C).

9.0 Anesthetic Management of the Patient Receiving Fondaparinux

The actual risk of spinal hematoma with fondaparinux is unknown. Consensus statements are based on the sustained and irreversible antithrombotic effect, early postoperative dosing, and the spinal hematoma reported during initial clinical trials. Close monitoring of the surgical literature for risk factors associated with surgical bleeding may be helpful in risk assessment and patient management.

- 9.1 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.

10.0 Anesthetic management of the Anticoagulated Parturient

- 10.1 In the absence of a large series of neuraxial techniques in the pregnant population receiving prophylaxis or treatment of venous thromboembolism, we suggest that the ASRA guidelines (derived from mainly from surgical patients) be applied to parturients (Grade 2C).

11.0 Anesthetic Management of the Patient Undergoing Plexus or Peripheral Block

- 11.1 For patients undergoing deep plexus or peripheral block, we recommend that recommendations regarding neuraxial techniques be similarly applied (Grade 1C).

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Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

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Abstract: The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is unknown. Although the incidence cited in the literature is estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics, recent epidemiologic surveys suggest that the frequency is increasing and may be as high as 1 in 3000 in some patient populations. Overall, the risk of clinically significant bleeding increase 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 low-molecular weight heparin). The need for prompt diagnosis and intervention to optimize neurologic outcome is also consistently reported.

In response to these patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Third Consensus Conference on Regional Anesthesia and Anticoagulation. 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, the ASRA consensus statements represent the collective experience of recognized experts in the field of neuraxial anesthesia and anticoagulation. These are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding. An understanding of the complexity of this issue is essential to patient management.

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Improvement in patient outcomes, including mortality, major morbidity, and patient-oriented outcomes, has been demonstrated with neuraxial techniques, particularly with epidural anesthesia and continued epidural analgesia.^{1–5} A major component of the decreased morbidity and mortality is due to the attenuation of the hypercoagulable response and the associated reduction in the frequency of thromboembolism after neuraxial

blockade. Although this beneficial effect of neuraxial techniques continues to be recognized, the effect is insufficient as the sole method of thromboprophylaxis. Consequently, anticoagulant, antiplatelet, and thrombolytic medications have been increasingly used in the prevention and treatment of thromboembolism. For example, the initial recommendations in 1986 by the American College of Chest Physicians (ACCP) stated that patients undergoing hip arthroplasty receive dextran, adjusted-dose standard heparin (approximately 3500 U every 8 hrs), warfarin (started 48 hrs postoperatively to achieve a prothrombin time [PT] 1.25–1.5 times baseline), or dextran plus intermittent pneumatic compression (IPC).⁶ Two decades later, these patients are still identified as among the highest risk for thromboembolism and receive prophylaxis with low-molecular weight heparin (LMWH), fondaparinux (2.5 mg started 6–24 hrs postoperatively) or warfarin (started before or after operation with a mean target international normalized ratio [INR] of 2.5).⁷ However, adjusted-dose heparin, dextran, and venous foot pumps are no longer recommended as sole methods of thromboprophylaxis, although IPC is considered appropriate for patients at a high risk for bleeding. Importantly, the duration of thromboprophylaxis is continued after hospital discharge for a total of 10 to 35 days.

The development (and evolving status) of standards for the prevention of perioperative venous thromboembolism (VTE), as well as the introduction of increasingly more potent antithrombotic medications, resulted in concerns regarding the heightened risk of neuraxial bleeding. Trends in patient management included not only in the avoidance of neuraxial techniques but also in the search for alternative therapies and likely played a prominent role in the resurgence of peripheral blockade. Although meta-analyses have reported improved surgical outcomes (without a reduction in mortality or morbidity) associated with single-injection and continuous plexus and peripheral analgesic techniques,^{1,8} serious hemorrhagic complications have also occurred.^{9,10}

In response to these patient safety issues, the American Society of Regional Anesthesia and Pain Medicine (ASRA) convened its Third Consensus Conference on Regional Anesthesia and Anticoagulation. Portions of the material presented here were published as the proceedings of the 1997 and 2002 ASRA Consensus Conferences.^{11–16} The information has been updated to incorporate additional data available since the time of its publication. Variances from recommendations contained in this document may be acceptable based on the judgment of the responsible anesthesiologist. The consensus statements are designed to encourage safe and quality patient care, but they cannot guarantee a specific outcome. They are also subject to timely revision as justified by evolution of information and practice.

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The past 2 Consensus Conferences focused on *neuraxial* blocks and anticoagulants in *surgical* patients, with limited information on the management of thromboprophylaxis in the parturient or patients undergoing plexus or peripheral blockade. However, the hypercoagulability associated with pregnancy and the puerperium has resulted in more parturients receiving anti-thrombotic therapy for the treatment and prevention of thromboembolism.¹⁷ The lack of a comparable “alternative” analgesic technique has further raised concern regarding the timing of epidural catheter placement/removal and initiation of postpartum thromboprophylaxis and is addressed in this update. In addition, recent publication of large series of patients undergoing uneventful peripheral blockade in combination with antithrombotic therapy as well as case reports of hemorrhagic complications after peripheral techniques provide sufficient information to allow for evidence-based recommendations.

These recommendations focus on patients receiving neuraxial and peripheral techniques. The practice settings include inpatient (eg, operating rooms, intensive care units, postoperative surgical floors, labor and delivery settings, or hospital wards) and ambulatory facilities such as pain clinics. The recommendations are intended for use by anesthesiologists and other physicians and health care providers performing neuraxial and peripheral regional anesthetic/analgesic blockade. However, these recommendations may also serve as a resource for other health care providers involved in the management of patients who have undergone similar procedures (eg, myelography, lumbar puncture).

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 class of recommendation. The level of evidence classification combines an objective description of the types of studies/expert consensus supporting the recommendation. Unfortunately, with a complication as rare as spinal hematoma, randomized clinical trials and meta-analyses, the highest (A) level of evidence, are not available. Numerous observational and epidemiologic series (typically, level of evidence B) have documented the conditions for safe performance of neuraxial anesthesia and analgesia in the anticoagulated patient. However, high-quality evidence may come from well-done observational series yielding very large risk reduction.¹⁸ Hence, depending on the risk reduction, recommendations from these sources may be categorized as level of evidence A or B. Recommendations derived from case reports or expert opinion is based on a C level of evidence. Often, recommendations involving the anesthetic management of new anti-thrombotic agents (where data involving safety and/or risk are sparse) are based on the pharmacology of hemostasis-altering drugs, risk of surgical bleeding, and expert opinion—C level of evidence.

The grade of recommendation also 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 (but possibly harmful). In the case of regional anesthesia and anticoagulation, a Grade 1 recommendation would allow safe performance in patients who benefit from the technique, whereas Grade 3 may represent performance of the technique in a patient at unacceptably high risk for bleeding (eg, epidural analgesia in the patient receiving twice-daily LMWH) or withholding the technique from a patient who would likely benefit from its performance (eg, thoracic epidural analgesia after thoracotomy with throm-

boprophylaxis using twice-daily unfractionated heparin [UFH]). 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). When appropriate, underlying preferences and values are discussed. For example, the “safe” INR for an indwelling epidural catheter remains undetermined. The authors highly valued patient safety (considering the high patient variability in response to warfarin and the associated likelihood that the INR may become excessively prolonged) with a lower value on prolonged analgesia (>48 hrs) and recommended with a more conservative timing of catheter removal.

A recent review of the evolution of practice guidelines and the strength/grade of recommendations noted that (1) there are progressively more recommendations with each update; (2) most guidelines are based on lower levels of evidence or expert opinion—level A recommendations (derived from randomized clinical trials) are rare; and (3) bias may exist owing to funding of industry trials (in restricted patient populations) as well as conflict of interest by the guideline-writing groups.^{19,20} This update attempts to address these concerns in that *fewer* recommendations are presented to allow for flexibility and individuality in patient management, and author disclosure is prominently reported; notably none of the senior authors receive industry funding in this area.

CURRENT RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF VTE

Venous thromboembolism is an important health care problem and a significant source of morbidity and mortality. Nearly all hospitalized patients have at least one risk factor for thromboembolism; approximately 40% have 3 or more risk factors⁷ (Table 1). Consequently, most hospitalized patients are candidates for thromboprophylaxis.

TABLE 1. Risk Factors for VTE

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

From Geerts et al,⁷ with permission.

TABLE 2. Levels of Thromboembolism Risk and Recommended Thromboprophylaxis in Hospital Patients (Section 1.3)

Levels of Risk	Approximate DVT Risk Without Thromboprophylaxis, %*	Suggested Thromboprophylaxis Options
Low risk	<10	
Minor surgery in mobile patients		No specific thromboprophylaxis
Medical patients who are fully mobile		Early and “aggressive” ambulation
Moderate risk	10–40	
Most general, open gynecologic or urologic surgery patients		LMWH (at recommended doses), LDUH 2 times/d or 3 times/d, fondaparinux
Medical patients, bed rest or sick		
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§
High risk	40–80	
Hip or knee arthroplasty, hip fracture surgery		LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2–3)
Major trauma, spinal cord injury		
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis†

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*Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.

†Mechanical thromboprophylaxis includes IPC, venous foot pump and/or graduated compression stocking; consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.

LDUH indicates low-dose UFH.

The agent, dosing regimen, and duration of thromboprophylaxis are based on the identification of risk factors, both individual (eg, age, sex, previous history of thromboembolism) and group-specific (eg, primary reason for hospitalization, surgery, medical illness; Tables 1 and 2). Because an individualized approach to thromboprophylaxis is complex and has not been rigorously applied, 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.^{6,7} Recommendations from the Eighth ACCP Guidelines on Antithrombotic and Thrombolytic Therapy in 2008 are based extensively on clinical trials that assessed the efficacy of therapy using contrast venography or duplex sonography to diagnose asymptomatic thrombi. Clinical outcomes, such as fatal pulmonary embolism (PE) and symptomatic deep venous thrombosis (DVT) were rarely the primary end points.⁷ This is critical, in that despite the successful reduction of asymptomatic thromboembolic events with routine use of antithrombotic therapy, an actual reduction of clinically relevant events has been more difficult to demonstrate.^{21,22} This may be in part due to low adherence to the prescribed balance of thromboembolic complication and bleeding, a difference in patient population (controlled study patients with few comorbidities versus actual clinical practice) and the use of a surrogate end point.^{7,21} In addition, because previous studies have not included patients at risk for increased bleeding, the balance between hemostasis and thromboembolism in these patients is even less clear. In general, establishment of overall risks and benefits of antithrombotic therapy in the patient undergoing surgery (or neuraxial block) is difficult.

Health care organizations are increasingly required to comply with outcome and process measures to receive reimbursement for patient care. Quality measures established by both the Centers for Medicare and Medicaid Services (<http://www.cms.hhs.gov>) and the Joint Commission (<http://www.jointcommission.org>) require standardized processes for accessing the risk of thromboembolism, ordering appropriate therapy, and reducing the likelihood of harm in patients receiving

antithrombotic therapy. Acceptable alternatives to the ACCP guidelines are those developed by the Surgical Care Improvement Project (www.qualitynet.org).

In response to ongoing concerns regarding surgical bleeding associated with thromboprophylaxis, the American Academy of Orthopaedic Surgeons (AAOS) published guidelines in 2007 for the prevention of symptomatic PE in patients undergoing total joint replacement (www.aaos.org/guidelines.pdf). These evidence-based guidelines allowed assignment of the patient to 1 of 4 categories (based on risk of PE and bleeding) and differed from those of the ACCP. The major deviations from ACCP guidelines are as follows: (1) mechanical prophylaxis should be used in all patients, (2) warfarin is a suitable alternative in all categories, and (3) in patients in whom there is an increased risk for bleeding, regardless of the risk of PE, prophylactic options include warfarin, aspirin, or mechanical prophylaxis only (Table 3).²³ These recommendations are compatible with those of the Surgical Care Improvement Project guidelines, which state that if the patient is at high risk for bleeding, the use of mechanical prophylaxis *only* is acceptable. Bern et al²⁴ administered low-dose warfarin (1 mg for 7 days preceding surgery) to 1003 patients undergoing total hip replacement. Lower leg pneumatic compression was also used postoperatively. The frequency of symptomatic thromboembolism was 0.3% (confidence interval, 0.0%–0.6%). After 7 days of warfarin, the INR was still within the reference range in 72% of patients. This low frequency of thromboembolism, despite minimal measurable changes in coagulation, is promising and may represent a different approach to thromboprophylaxis for this group of patients at high risk for both thromboembolism and surgical bleeding. Even more controversial are the preliminary findings of Bozic et al²⁵ in a multicenter study involving 93,840 patients who underwent knee replacement between 2003 and 2005. The investigators reported patients who received aspirin for thromboprophylaxis had a decreased risk of thromboembolism compared with those who received warfarin and a similar risk to those who received LMWH. The success of aspirin for chemoprophylaxis was speculated to be due to changing trends in patient characteristics and surgical techniques. Although additional research is needed to

TABLE 3. Chemoprophylaxis of Patients Undergoing Hip or Knee Replacement*

<p>Patients at standard risk of both PE and major bleeding</p> <ul style="list-style-type: none"> • Aspirin, 325 mg 2×/d (reduce to 81 mg 1×/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 wk. • LMWH, dose per package insert, starting 12–4 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d. • Synthetic pentasaccharides, dose per package insert, starting 12–24 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d. • Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk. <p>Patients at elevated (above standard) risk of PE and at standard risk of major bleeding</p> <ul style="list-style-type: none"> • LMWH, dose per package insert, starting 12–24 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d. • Synthetic pentasaccharides, dose per package insert, starting 12–24 hrs postoperatively (or after an indwelling epidural catheter has been removed), for 7–12 d. • Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk. <p>Patients at standard risk of PE and at elevated (above standard) risk of major bleeding</p> <ul style="list-style-type: none"> • Aspirin, 325 mg 2×/d (reduce to 81 mg 1×/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 wk. • Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk. • No chemoprophylaxis <p>Patients at elevated (above standard) risk of both PE and major bleeding</p> <ul style="list-style-type: none"> • Aspirin, 325 mg 2×/d (reduce to 81 mg 1×/d if gastrointestinal symptoms develop), starting the day of surgery, for 6 wk. • Warfarin, with an INR goal of ≤2.0, starting either the night before or the night after surgery, for 2–6 wk. • No chemoprophylaxis

From the AAOS Clinical Guideline on Prevention of Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty. Adapted May 2007.²³

*All patients should be considered for intraoperative and postoperative mechanical prophylaxis in addition to appropriate chemoprophylaxis.

confirm these results, the authors contend that aspirin may be a safe and effective alternative for thromboprophylaxis among these patients.

1.0 Administration of Thromboprophylaxis

1.1 In accordance with ACCP guidelines, for each of the antithrombotic agents, we recommend that clinicians follow the manufacturer-suggested dosing guidelines (Grade 1C).

RISK OF BLEEDING ASSOCIATED WITH THERAPEUTIC ANTICOAGULATION AND THROMBOLYTIC THERAPY

Bleeding is the major complication of anticoagulant and thrombolytic therapy. Bleeding is typically classified as major if it is intracranial, intraspinal, intraocular, mediastinal, or retroperitoneal, leads directly to death, or results in hospitalization or transfusion. Risk factors for major bleeding during anticoagulation with either warfarin or UFH include the in-

tensity of the anticoagulant effect, increased age, female sex, history of gastrointestinal bleeding, concomitant aspirin use, and length of therapy.^{26,27} Large fluctuation in anticoagulant effect also increases the likelihood of a serious bleed. During warfarin therapy, an INR of 2.0 to 3.0 is associated with a low risk of bleeding: less than 3% during a 3-month treatment period. Higher-intensity regimens (INR >4) are associated with a significantly greater risk of bleeding (7%). In a case-control study, the risk of intracranial hemorrhage doubled for each increase of approximately 1 in the INR.²⁷ The incidence of hemorrhagic complications during therapeutic anticoagulation with intravenous or subcutaneous heparin is less than 3%; the risk associated with LMWH is slightly lower.²⁷ Thrombolytic therapy represents the greatest risk of bleeding; with a major hemorrhage occurring in 6% to 30% of patients treated with thrombolytic therapy for DVT, ischemic stroke, or ST elevation myocardial infarction. There is no significant difference in the risk of hemorrhage between thrombolytic agents. The addition of potent anticoagulants (LMWH, hirudin) or antiplatelet (glycoprotein IIb/IIIa [GP IIb/IIIa] agents) therapy further increases the risk of major bleeding.²⁷ Therefore, although thromboembolism remains a source of significant perioperative morbidity and mortality, its prevention and treatment are also associated with risk.

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

TABLE 4. Perioperative Management of Patients on Warfarin

<p>Preoperative</p> <ul style="list-style-type: none"> • Discontinue warfarin at least 5 d before elective procedure* • Assess INR 1 to 2 d before surgery, if >1.5, consider 1–2 mg of oral vitamin K • Reversal for urgent surgery/procedure, consider 2.5–5 mg of oral or intravenous vitamin K; for immediate reversal, consider fresh-frozen plasma • Patients at high risk for thromboembolism <ul style="list-style-type: none"> ◦ Bridge with therapeutic subcutaneous LMWH (preferred) or intravenous UFH ◦ Last dose of preoperative LMWH administered 24 hrs before surgery, administer half of the daily dose ◦ Intravenous heparin discontinued 4 hrs before surgery • No bridging necessary for patients at low risk for thromboembolism <p>Postoperative</p> <ul style="list-style-type: none"> • Patients at low risk for thromboembolism <ul style="list-style-type: none"> ◦ Resume warfarin on postoperative day • Patients at high risk for thromboembolism (who received preoperative bridging therapy) <ul style="list-style-type: none"> ◦ Minor surgical procedure—resume therapeutic LMWH 24 hrs postoperatively ◦ Major surgical procedure—resume therapeutic LMWH 48–72 hrs postoperatively or administer low-dose LMWH • Assess bleeding risk and adequacy of hemostasis when considering timing of the resumption of LMWH or UFH therapy

Recommendations from Douketis et al.²⁹

*Not all invasive procedures/surgeries require normalization of the INR.

TABLE 5. Perioperative Management of Patients on Antiplatelet Therapy

<p>Patients with coronary stents</p> <ul style="list-style-type: none"> • Elective surgery postponed for the following durations if aspirin and thienopyridine (eg, clopidogrel) therapy must be discontinued <ul style="list-style-type: none"> ◦ Bare metal stents: 4–6 wk ◦ Drug-eluting stents: 12 mo • If surgery cannot be postponed, continue aspirin throughout perioperative period <p>Patients at high risk for cardiac events (exclusive of coronary stents)</p> <ul style="list-style-type: none"> • Continue aspirin throughout the perioperative period • Discontinue clopidogrel at least 5 d (and preferably 10 d) before surgery • Resume clopidogrel 24 hrs postoperatively <p>Patients at low risk of cardiac events</p> <ul style="list-style-type: none"> • Discontinue antiplatelet therapy 7–10 d before surgery • Resume antiplatelet therapy 24 hrs postoperatively
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Recommendations from Douketis et al.²⁹

The American Society of Anesthesiologists Committee on Standards and Practice Parameters.²⁸

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 unfractionated or LMWH is required until the time of surgery (and reinitiated in the immediate postoperative period). It may also be necessary to postpone elective surgeries in patients where a suitable “bridge” has not been identified and antithrombotic therapy is critical; premature discontinuation of dual antiplatelet therapy in patients with coronary stents has been associated with stent thrombosis, myocardial infarction and death^{28,29} (Tables 4 and 5).

Evidence-based guidelines for the perioperative management of antithrombotic therapy have been recently established by the ACCP.²⁹ In general, in patients at moderate to high risk of thromboembolism, bridging therapy is recommended (and the prevention of thromboembolism is valued over the potential for increased surgical bleeding). Conversely, no bridging therapy is recommended for patients at low risk for thromboembolism. Although the recommendations for management are relatively simple, complexity arises in the determination of who is at “high risk.” This evaluation is perhaps best performed within an integrated multidisciplinary clinic by thrombophilia experts.³⁰

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, Tryba³¹ identified 13 cases of spinal hematoma after 850,000 epidural anesthetics and 7 cases among 650,000 spinal techniques. On the basis of 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.³² Because these estimates represent the upper limit of the 95% confidence interval, the actual frequency should be much less. However, the series involved in these calculations were conducted before the implementation of routine perioperative thromboprophylaxis. Recent case series and epidemiologic surveys suggest that the risk has increased.^{12,33,34}

Hemorrhage into the spinal canal most commonly occurs in the epidural space, most 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.^{35,36} In a review of the literature between 1906 and 1994, Vandermeulen et al³⁴ 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 blockade occurred in patients with evidence of hemostatic abnormality. Twenty-five of the patients had received intravenous or subcutaneous (unfractionated or low molecular weight) heparin, whereas additional 5 patients were presumably administered heparin because 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 patients (25%). Overall, in 53 (87%) of the 61 cases, either a clotting abnormality or needle placement difficulty was present. A spinal anesthetic was administered 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

TABLE 6. Neurologic Outcome in Patients With Spinal Hematoma After Neuraxial Blockade*

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

Adapted from Vandermeulen et al,³⁴ with permission.

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

laminectomy within 8 hrs of onset of neurologic dysfunction³⁴ (Table 6).

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.^{37,38} Cheney et al³⁷ 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 owing to delay in the diagnosis and resultant poor outcome. Consequently, the median payment was very high.³⁷ A more recent in-depth analysis of the claims related to nerve injury after 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.³⁸ More than half the patients received intravenous heparin during a vascular surgical or diagnostic procedure, often in combination with other medications that impair coagulation. Consistent with Vandermeulen et al,³⁴ 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 the first postoperative day, often 24 hrs or more elapsed before diagnosis.³⁸ There were permanent deficits in 90% of patients.

It is impossible to conclusively determine 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 al³³ investigated serious neurologic complications among 1,260,000 spinal and 450,000 epidural blocks performed in Sweden during 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 hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Pathologic lesion of the spine was present in 6 patients. The presenting complaint was typically lower extremity weakness. Only 5 of 33 patients recovered neurologically (owing to 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 (1/200,000) than that in elderly women undergoing knee arthroplasty (1/3600, $P < 0.0001$). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (1/22,000) compared with all patients undergoing spinal anesthesia (1/480,000).

Overall, these series suggest that the risk of clinically significant bleeding varies with age (and 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 a 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 as well. Endogenous tissue plasminogen activator formulations (Alteplase, Tenecteplase) are more fibrin-selective and have less effect on circulating plasminogen. Clot lysis leads to elevation of fibrin degradation products, which themselves have an anticoagulant effect by inhibiting platelet aggregation. In addition to the fibrinolytic agent, these patients frequently receive intravenous 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. Although the plasma half-life of thrombolytic drugs is only hours, it may take days for the thrombolytic effect to resolve; fibrinogen and plasminogen are maximally depressed at 5 hrs after thrombolytic therapy and remain significantly depressed at 27 hrs. The decrease in coagulation factor levels is greater with streptokinase compared with tissue plasminogen activator therapy. However, the frequency of hemorrhagic events is similar.²⁷ Importantly, original contraindications to thrombolytic therapy included surgery or puncture of noncompressible vessels within 10 days.³⁹

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. Harke and Rahman⁴⁰ described 4 patients who received a combined local thrombolysis with streptokinase or urokinase (dose range, 40,000–200,000 U/hr) with local anesthetic-induced sympathectomy (stellate or epidural block). There were no hemorrhagic complications. Unfortunately, there is a growing number of case reports of spinal hematoma. Most published reports involve *spontaneous* spinal or epidural hematomas after thrombolytic therapy.^{41–56} 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^{57–61}; 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 Food and Drug Administration [FDA]-approved pharmaceuticals have mandatory reporting requirements. The FDA estimates that less than 1% of serious adverse drug reactions are reported).³⁹ An epidural technique had been performed in 4 patients, a continuous spinal anesthetic in 1 patient, and an epidural steroid injection in the remaining patient. In 4 of the cases, the patients presented with lower

extremity ischemia, and a neuraxial anesthetic was intentionally performed to facilitate surgical revascularization. However, 2 of the recent spinal hematomas (including the MedWatch case) occurred in patients who underwent a neuraxial technique (epidural anesthesia for lithotripsy, epidural steroid injection [An 84-year-old man received an uncomplicated epidural steroid injection in the morning. He developed chest pain later that day, was admitted to the hospital, diagnosed with an acute myocardial infarction, and treated with tissue plasminogen activator and heparin. He subsequently developed back pain and paraplegia. Magnetic resonance imaging demonstrated an epidural hematoma extending from T10 to the sacrum. Treatment and outcome were not reported.]) and subsequently complained of myocardial ischemia and were treated with a thrombolytic.⁵⁷ 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 for 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 epidural steroid injection to allow appropriate monitoring. Guidelines detailing original contraindications for thrombolytic drugs suggest avoidance of these drugs for 10 days after puncture of noncompressible vessels (Grade 1A).
- 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). Data are not available to clearly outline the length of time neuraxial puncture should be avoided after discontinuation of these drugs.
- 2.3 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 hrs 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).
- 2.4 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).

UNFRACTIONATED INTRAVENOUS AND SUBCUTANEOUS HEPARIN

Pharmacology of UFH

The major anticoagulant effect of heparin is due to a unique pentasaccharide that binds to antithrombin (AT) with high

affinity and is present in approximately one-third of heparin molecules. Binding of this heparin pentasaccharide to AT 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 factor IIa and Xa. Smaller-molecular weight heparins will catalyze inhibition of only factor Xa.^{62,63} Intravenous injection results in immediate anticoagulant activity, whereas subcutaneous injection results in a 1 to 2 hrs' delay. The anticoagulant effect of heparin is both dose- and molecular size-dependent and is not linear but increases disproportionately with increasing doses. For example, the biologic half-life of heparin increases from 30 mins after 25 U/kg intravenous to 60 mins with 100 U/kg intravenous and to 150 mins with a bolus of 400 U/kg.⁶³ When the subcutaneous route is selected for delivery of therapeutic anticoagulation, the dose of heparin is higher than the intravenous route to compensate for the reduced bioavailability associated with subcutaneous administration.

When given in therapeutic doses, the anticoagulant effect of heparin is typically monitored with the aPTT. The activated clotting time 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,⁶² heparin level between 0.2 and 0.4 U/mL, or anti-Xa level between 0.3 and 0.7 U/mL.⁶⁴ Administration of small-dose (5000 U) subcutaneous heparin for prophylaxis of DVT generally does not prolong the aPTT 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 hrs after administration.⁶⁵

One of the advantages of heparin anticoagulation is that its effect may be rapidly reversed with protamine. Each mg of protamine can neutralize 100 U of heparin. For example, a patient who bleeds immediately after receiving a 5000-U bolus of heparin requires 50 mg of protamine. Because the half-life of intravenous heparin is 60 to 90 mins, only heparin given in the immediate preceding hours needs to be considered when calculating the protamine dose; a patient receiving a continuous infusion of 1200 U/hr requires approximately 25 mg of protamine. Neutralization of subcutaneously administered heparin may require a prolonged infusion of protamine owing to the continued absorption.⁶²

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

The combination of spinal or epidural needle insertion in the presence of anticoagulation with heparin may be 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.⁶⁶ Until the routine use of computed tomography (CT) in the 1980s, diagnostic subarachnoid puncture was routinely used to select patients for heparin therapy for acute cerebral ischemia. Ruff and Dougherty reported that 7 of 342 patients treated in this manner developed spinal hematomas. Three factors associated with increased risk were identified: less than 60-min 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^{36,67,68} (Table 7). In addition, the

TABLE 7. Risk Factors and Estimated Incidence for Spinal Hematoma and Central 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 after neuraxial procedure			
Atraumatic	3.16	1:70,000	1:100,000
Traumatic	112	1:2000	1:2900
Heparin >1 hr after puncture	2.18	1:100,000	1:150,000
Heparin <1 hr after puncture	25.2	1:8700	1:13,000
With aspirin	26	1:8500	1:12,000

Data from Stafford-Smith,³⁶ with permission.

results have been used to define safe practice protocols for patients undergoing neuraxial blockade during systemic heparinization, particularly during vascular surgery.³⁴

Intravenous UFH

Intraoperative heparinization typically involves injection of 5 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.⁶³ Neuraxial anesthetic techniques are often attractive for these patients because these techniques may provide reduced morbidity and improved postoperative analgesia.^{2,4} However, the use of neuraxial procedures in the presence of UFH may be associated with an increased risk of epidural hematoma, as demonstrated by case series, epidemiologic surveys, and the continued claims in the ASA Closed Claims database.^{33,34,38,69}

Most published case series used similar guidelines for patient management, including exclusion of high-risk patients (preexisting coagulopathy) and performance of neuraxial procedure at least 1 hr before administration of heparin.¹⁴ The question of how to manage the situation of a bloody or traumatic neuraxial procedure has been raised. 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.³⁴ Although some investigators have recommended cancellation of the surgical procedures should these events occur,⁶⁷ there are no clinical data to support this recommendation.^{56,70} Direct communication with the surgeon and a specific risk-benefit decision about proceeding in each case is warranted.

Overall, large published series and extensive clinical experience suggest that the use of regional techniques in the setting of intraoperative systemic heparinization does not seem to represent systemic heparinization and does not seem to represent a significant risk.¹⁴ However, the recent reports of paralysis relating to spinal hematoma in the ASA Closed Claims database imply a higher incidence of neuraxial hematoma with intraoperative anticoagulation than was previously suspected

and that vigilance is necessary to diagnose and intervene as early as possible should spinal hematoma be suspected.^{38,69}

Heparinization may be continued into the postoperative period. Prolonged intravenous heparin administration is usually performed with a constant intravenous infusion of heparin, usually with a goal of aPTT prolongation to 1.5 to 2 times the baseline level. The risk of any (spontaneous, surgical, or anesthesia-related) bleeding due to heparin in such an anticoagulated patient may be increased, particularly if there is marked variation in the aPTT (regardless of the mean aPTT).^{26,62} Most importantly, the initiation of systemic therapeutic heparin therapy for medical or surgical indications in the presence of a neuraxial catheter potentially increases the risk of hematoma formation during catheter removal. In the series by Vandermeulen et al,³⁴ half of the spinal hematomas associated with systemic heparinization occurred 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, the heparin should be discontinued for 2 to 4 hrs before neuraxial catheter removal, coagulation status assessed before manipulation of the catheter, and careful assessment of the presence of sensory and motor function in the lower extremities for at least 12 hrs after the catheter removal.

Heparinization During Cardiopulmonary Bypass

Since the publication of the initial ASRA guidelines in 1998,¹⁴ there have been continued discussions regarding the relative risk (and benefit) of neuraxial anesthesia and analgesia in the patient undergoing heparinization for cardiopulmonary bypass. Further reports of small series have appeared, again with no reported complications. Two of these series are retrospective reviews of pediatric cardiac surgery including a total of 250 patients that report no spinal hematomas.^{71,72} In these pediatric patients, the blocks were performed after induction of general anesthesia before surgery 1 hr before full systemic heparinization. In contrast, the adult experience with coronary bypass surgery has continued to follow the practice of placement of the epidural catheters on the evening before surgery. Sanchez and Nygard⁷³ report a large prospective series of 558 patients without complications. Despite the absence of serious sequelae, the debate continues as to the risk-benefit advantages of this technique.^{74,75} Recently, the efficacy has been examined in the newer "off-pump" approach to cardiac surgery.^{76,77} In a series of 50 patients, Priestley et al⁷⁸ reported improved postoperative analgesia and earlier extubation. However, there was no difference in time to hospital discharge. Although there were no spinal hematomas, the authors observe that "the use of thoracic epidural analgesia during coronary artery bypass grafting is controversial because the anticoagulation required during surgery raises the concern of increasing the rare but serious risk of permanent spinal cord damage from an epidural hematoma. Such a risk must be balanced by important clinical advantages if the technique is to be justified." Despite improved analgesia, they note that "convincing respiratory, cardiac, or other organ outcome data are lacking."

To date, there is a single case of spinal hematoma after the full heparinization associated with cardiopulmonary bypass.⁷⁹ However, there are confounding variables in that the patient was initially neurologically intact but developed paraplegia after anticoagulation/thrombolysis on the second day. Specifically, the patient was an 18-year-old man who underwent uneventful aortic valve replacement with thoracic epidural analgesia. On the second postoperative day, he was again anticoagulated (prosthetic valve thrombolysis) and also received a thrombolytic agent. He experienced back pain while ambulating, and when

his blood-tinged catheter was removed, he acutely developed sensory and motor loss. Emergent decompression successfully restored his neurologic function.

Thus, this analgesic technique remains controversial in that the risk seems too great for the perceived benefits. A review has recommended certain precautions to be taken to minimize the risk⁶⁹:

- (1) Neuraxial blocks should be avoided in a patient with known coagulopathy from any cause,
- (2) Surgery should be delayed 24 hrs in the event of a traumatic tap,
- (3) Time from instrumentation to systemic heparinization should exceed 60 mins,
- (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.

These recommendations, as well as the practice of inserting epidural catheters 24 hrs in advance of surgery, have been used by most of the published case series. Validity of these and future recommendations will need to be determined.

Another approach to this dilemma is presented by Ho et al⁸⁰ who calculated the risk of hematoma. In a complex mathematical analysis of the probability of predicting a rare event that has not occurred yet, they estimate the probability of a spinal hematoma (based on the total 4583 epidural and 10,840 spinal anesthetics reported without complications) to be in the neighborhood of 1:1528 for epidural and 1:3610 for spinal technique. Overall, the future of neuraxial anesthesia and analgesia for coronary bypass surgery remains somewhat unclear.

Subcutaneous UFH

Low-dose heparin is commonly used for prophylaxis against development of VTE in general and urologic surgery.⁸¹ Administration of 5000 U of heparin subcutaneously every 12 hrs has been used extensively and effectively for prophylaxis against DVT. There is often no detectable change in the clotting parameters, as measured by the aPTT. 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.⁶⁵ There is a smaller subset (2%–4%) of patients who may become therapeutically anticoagulated during subcutaneous heparin therapy. With therapy longer than 5 days, there is a subset of patients who will develop a decrease in the platelet count.⁶²

The widespread use of subcutaneous 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,¹⁴ as well as extensive experience in both Europe and United States without a significant frequency of complications. Three surveys of opinions among anesthesiologists in Denmark,⁸² Great Britain, and Scotland⁸³ and New Zealand⁸⁴ report that most anesthesiologists seem to feel that the presence of subcutaneous heparin prophylaxis is not a strong contraindication to the performance of neuraxial anesthesia. There are only 4 case reports of neuraxial hematomas, 3 epidural³⁴ and 1 subarachnoid,⁸⁵ during neuraxial block with the use of subcutaneous heparin.

Performance of neuraxial block before the injection of subcutaneous heparin may be preferable, but there does not seem

to be an increased risk with neuraxial block in the presence of subcutaneous heparin. Previous authors have recommended delaying performance of neuraxial blocks for 2 hrs after administration of subcutaneous heparin.⁷⁰ However, this may actually coincide with peak effect, and clinical experience questions the need for this delay.

Since the time of our first consensus conference, one additional spinal hematoma has been reported after epidural catheter placement in a patient receiving subcutaneous heparin. Sandhu et al⁸⁶ placed an epidural (on the third attempt and 2 hrs after a dose of 5000 U of subcutaneous UFH) in a 79-year-old woman who was to undergo abdominal perineal resection for rectal cancer. The patient also had a general anesthetic and the case report documents that there was some evidence of an intraoperative coagulopathy. She had “apparently normal coagulation” and received no antiplatelet agents while continuing to receive 5000 U of UFH twice a day postoperatively. She manifested no change in platelet count or aPTT, and the epidural catheter was removed on the third postoperative day, 6 hrs after a dose of 5000 U of subcutaneous UFH. The text of the case report reveals that there had been 2 previously noted episodes of “blood in the catheter” during her postoperative course. The patient developed a spinal epidural hematoma on postoperative day 4 requiring surgical evacuation. It is also likely that the patient’s history of spinal stenosis (and associated reduction in the capacity of the spinal canal) contributed to her deficits.³³

Subcutaneous Heparin With Thrice-Daily Dosing

It has become conventional treatment for patients to receive subcutaneous UFH 3 times per day rather than 2 times per day based on the 2008 ACCP conference guidelines.⁷ There are scarce data that aid the practitioner in determining the risk and benefit ratio for patients who would otherwise benefit from single-shot regional anesthesia/analgesia or request epidural analgesia or peripheral nerve block analgesia maintained postoperatively while receiving such therapy. To approximate the risks, one can turn to the analytical study by Leonardi et al⁸⁷ that detailed the rate of bleeding complications in general surgery patients receiving DVT prophylaxis. The authors reviewed 33 randomized controlled trials that included 33,813 patients who were to undergo general surgery and received either twice or daily dosing of LMWH, 5000 U 2 times a day or 3 times a day of UFH or placebo. The median duration of prophylaxis was 7 days. The reported incidence of major gastrointestinal tract or retroperitoneal bleeding was 0.2% and less than 0.1%, respectively. Minor bleeding occurred as follows: at the injection site in 6.9% of patients, wound hematoma in 5.7% of patients, drain site bleeding in 2% of patients, and hematuria in 1.6% of patients. The authors emphatically stated that bleeding complications that required a change in treatment occurred less than 3% of the time and was further reduced by therapy with the lower doses of LMWH or UFH. Furthermore, patients in the low UFH group had fewer instances in which the anticoagulant therapy required cessation or a surgical intervention was performed for bleeding as compared with those in the comparative high-dose group. Mild amazement was expressed by the authors in stating that there was not uniform application of ACCP guidelines, as they noted 25% of high-risk patients who were to undergo abdominal surgery received no prophylactic therapy and 50% of the patients who did receive therapy were given inadequate dosing, per the published guidelines.⁸⁷

Another study that provides insight into the possible risk of bleeding assessed the use of 2 times per day versus 3 times per day subcutaneous UFH for *prevention* of VTE in the general

medical population during the period of 1966 to 2004.⁸⁸ The authors identified 12 studies relevant to the primary question, which included 1664 patients who received 3 times a day of therapy and 6314 patients who received 2 times a day of therapy. As to a decrease in the incidence of VTE, 3 times a day of therapy proved to be more beneficial; *however*, there was an increased risk of major bleeding. Thus, the authors concluded that the clinician must pick the anticoagulant regimen in correlation to the patient's risk (in this case for prevention of the VTE).

The clinician is left to conclude that thrice-daily UFH therapy raises legitimate concerns for anesthesiologists, considering the concurrent placement of regional peripheral blocks for anesthesia/analgesia and/or the use of continuous infusion modes of therapy that have become so popular in contemporary patient care. There are no guidelines for the clinician for this practice as there are for neuraxial applications. Further concern is raised given the evidence that thrice-daily subcutaneous UFH therapy may in fact be associated with an increase in the aPTT, although the exact clinical significance of this observed, occasional laboratory finding is not known.⁸⁹⁻⁹¹

In the University of Virginia School of Medicine Department of Anesthesiology, postoperative epidural analgesia therapy has been continued in patients receiving thrice-daily UFH therapy. The hospital database was queried to derive a list of patients who had an epidural catheter placed with the primary purpose of postoperative analgesia in a recent 2-year epoch of time (2005–2007). One thousand nine hundred twenty new epidural placements were identified, and this list was crossmatched with a list of patients receiving 3 times a day of heparin therapy, revealing 768 (40%) of 1920 patients. Sixteen patients from this group had a positive match for hemorrhage codes on their discharge records, with none of the episodes being identified within a major hemorrhage category. Laboratory value analysis failed to reveal changes in the aPTT values of significance (personal communication/unpublished data from J. C. R.'s institution).

Is Administration of UFH Thrice Daily More Efficacious (and More Risky) Than Twice-Daily Dosing?

There are no data that contradict the 2 previous guideline recommendations as to the risk of bleeding with neuraxial block techniques in patients on twice-daily subcutaneous UFH.^{13,14,92} As such, patients can have epidurals placed before the next dose of UFH when it is administered twice a day. Epidural analgesia can be maintained while such thromboprophylactic therapy is continued, and the epidural can be removed ideally an hour before the next scheduled dose.

There are yet no published data to uphold a recommendation in patients receiving thrice-daily subcutaneous UFH. The clinician is currently faced with a decision to proceed with epidural analgesia because there are no data of concern or to take a more anticipatory approach of caution, awaiting adverse reports such as may appear in the ASA Closed Claims database. A review of relevant literature shows that there are reports that document an increased risk of minor and major bleeding in surgical and in nonsurgical patients receiving thrice-daily subcutaneous UFH.^{87,88} Because this is the case, given the fact that a randomized controlled trial with patients undergoing neuraxial or peripheral nerve blocks for postoperative analgesia while receiving 3 times a day of UFH has not been published, and because there is no apparent difference between twice-daily subcutaneous UFH with concurrent use of compression devices and thrice-daily subcutaneous UFH, it is advised that patients *not* receive 3 times a day of subcutaneous UFH while epidural analgesia is maintained. Rather, such patients can continue to be treated with twice-

daily subcutaneous UFH and the use of compression devices.⁷ Furthermore, it is not necessary to routinely check the aPTT or platelet count, *unless* the clinician is concerned about changes in these values after "prolonged administration" or in patients with many comorbidities that might influence the pharmacologic expression of subcutaneous UFH.

3.0 Anesthetic Management of the Patient Receiving UFH

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. Recent thromboprophylaxis guidelines identifying more patients as candidates for thrice-daily subcutaneous heparin and the potential for increased bleeding with this therapy have prompted a modification of the previous ASRA guidelines.

- 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).
- 3.2 In patients receiving prophylaxis with subcutaneous UFH with dosing regimens of 5000 U twice daily, 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 (Grade 1C).
- 3.3 The safety of neuraxial blockade in patients receiving doses greater than 10,000 U of UFH daily or more than twice-daily dosing of UFH has not been established. Although the use of thrice-daily UFH may lead to an increased risk of surgical-related bleeding, it is unclear whether there is an increased risk of spinal hematoma. We suggest that the risk and benefits of thrice-daily UFH 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).
- 3.4 Because heparin-induced thrombocytopenia may occur during heparin administration, we recommend that patients receiving heparin for more than 4 days have a platelet count assessed before neuraxial block and catheter removal (Grade 1C).
- 3.5 Combining neuraxial techniques with intraoperative anticoagulation with heparin during vascular surgery is acceptable with the following recommendations (Grade 1A):
 - 3.5.1. Avoid the technique in patients with other coagulopathies.
 - 3.5.2. Delay heparin administration for 1 hr after needle placement.
 - 3.5.3. Remove indwelling neuraxial catheters 2 to 4 hrs after the last heparin dose and assess the patient's coagulation status; re-heparin 1 hr after catheter removal.
 - 3.5.4. 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.
 - 3.5.5. 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 is warranted.

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

LOW-MOLECULAR WEIGHT HEPARIN

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

The biochemical and pharmacologic properties of LMWH differ from those of UFH.^{62,93–96} Most relevant are the lack of monitoring of the anticoagulant response (anti-Xa level), prolonged half-life, and irreversibility with protamine. For example, the elimination half-life of LMWH, which is 3–6 hrs after subcutaneous injection, is dose-independent. Anti-Xa levels peak 3 to 5 hrs after administration. However, because the half-life is 3 to 4 times that of UFH, significant anti-Xa activity is still present 12 hrs after injection. A recent clinical investigation has reported a significant anticoagulant effect present at the time of epidural catheter removal in patients receiving twice-daily LMWH compared with once-daily LMWH administration.⁹⁷

Prolonged LMWH therapy may be associated with an accumulation of anti-Xa activity and fibrinolysis.⁹⁸ The plasma half-life of LMWH also increases in patients with renal failure.⁹³ 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-IIa activity of LMWH is completely reversed, whereas anti-Xa activity is not fully neutralized. Both anti-IIa and anti-Xa activity may return up to 3 hrs after protamine reversal, possibly due to release of additional LMWH from the subcutaneous depot. The clinical significance of the residual anti-Xa effect is unknown.⁹³

L-molecular weight heparins vary both biochemically and pharmacologically, including molecular weight, anti-IIa and anti-Xa activities, and plasma half-life. However, because there are no adequate trials comparing the efficacy and safety of one LMWH to another, it is impossible to recommend one specific LMWH over another.⁶² Experience in Europe suggests that the rate of spinal hematoma is similar among LMWH preparations.⁹⁹

Spinal and Epidural Anesthesia in the Patient Receiving LMWH

The relative rarity of spinal hematoma, as well as the publication of several large studies reported during the last 2 decades, increased the clinician's confidence in management of the anticoagulated patient undergoing neuraxial blockade. The administration of LMWH in patients undergoing spinal or epidural anesthesia was examined by Bergqvist et al in 2 reviews published in 1992 and 1993.^{100,101} These studies represent the European experience with LMWH thromboprophylaxis because no LMWH preparation had been approved for general use in the United States at that time. Bergqvist et al¹⁰² identified 19 articles involving 9013 patients who safely received the combination of LMWH and spinal or epidural anesthesia. Importantly, only *one* case of spinal hematoma had been reported. To further document the safety of LMWH in combination with neuraxial block, the authors noted that although only 9013 patients were identified in their review, pharmaceutical companies had estimated that several million patients had received LMWH while undergoing neuraxial techniques. On the basis of these data, Bergqvist et al¹⁰¹ concluded that neurologic complications after spinal or epidural

anesthesia in patients receiving LMWH thromboprophylaxis are extremely rare, and the combination seemed safe. It should be noted that European dosing of LMWH is once daily, with the first dose administered 10 to 12 hrs preoperatively. In general, LMWH thromboprophylaxis is still not considered a contraindication to epidural anesthesia/analgesia in Europe.^{68,103} However, recommendations against concomitant antiplatelet medications have been introduced.¹⁰³

A new challenge occurred with the release of LMWH for general use in the United States in May 1993. At that time, labeled indications included thromboprophylaxis after major joint replacement. Approved dose scheduling was 30 mg every 12 hrs, with the first dose administered as soon as possible after surgery. The pharmacologic differences between LMWH and standard heparin were underestimated; more than 40 spinal hematomas were reported through the MedWatch system during a 5-year period.¹² The risk of spinal hematoma, based on LMWH sales, prevalence of neuraxial techniques, and reported cases, was estimated to be approximately 1 in 3000 continuous epidural anesthetics compared with 1 in 40,000 spinal anesthetics.¹⁰⁴ However, this is most likely an underestimation—in addition to the spinal hematomas that had been reported at the time of the first ASRA Consensus Conference, there were approximately 20 more that had occurred but were not yet reported to the MedWatch system. In total, nearly 60 spinal hematomas were tallied by the FDA between 1993 and 1998.

The marked increase in the frequency of spinal hematoma in patients anticoagulated with LMWH prompted a reevaluation of the relative risks and benefits of neuraxial blockade. For example, ASRA guidelines have consistently recommended against the administration of twice-daily LMWH in a patient with an indwelling epidural catheter.^{12,13} Although once-daily LMWH dosing in the presence of an epidural catheter is safe, caution was advised if the patient received an additional hemostasis-altering medications, including antiplatelet therapy.

Reports of Spinal Hematoma Since the 2003 ASRA Consensus Conference

Since 2003, there have been 5 cases of *spontaneous* spinal hematomas associated with LMWH.^{105,106} Four of these cases occurred with treatment dosing LMWH (enoxaparin 1 mg/kg twice daily). There have also been 6 cases of spinal hematoma after neuraxial block published as case reports.^{107–112} In addition to LMWH, 2 received an antiplatelet medication.

It is of interest that in 2 of the cases, the ASRA guidelines were followed regarding dosing intervals, but patient factors may have contributed to hematoma development.

Specifically, 1 case occurred in an 81-year-old woman whose clopidogrel had been discontinued for 7 days before elective fasciotomy under spinal anesthesia.¹¹¹ Lumbar puncture was traumatic and required multiple attempts/levels. She received 2 doses of enoxaparin (40 mg) 8 and 40 hrs after lumbar puncture. Four hours after the second dose, she had difficulty voiding, which progressed to numbness and weakness. The patient underwent decompressive laminectomy with only partial return. The authors concluded that the traumatic tap, residual clopidogrel effect, and moderately reduced renal function may have contributed to her outcome. The second case occurred in an 85-year-old woman presenting for epidural steroid injection.¹⁰⁸ She was taking warfarin for chronic atrial fibrillation and a St. Jude aortic valve. Warfarin was discontinued 6 days before the procedure (INR = 1.2), and she had received bridge therapy with enoxaparin 1 mg/kg every 12 hrs, with her last dose more than 24 hrs before the injection. In the evening after the uneventful procedure, she restarted her

warfarin. Enoxaparin was reinstated the following day (24 hrs after the procedure). The patient developed acute back pain 48 hrs after the procedure—an expanding hematoma was noted. In addition, the patient was noted to have sustained therapeutic anti-Xa levels even 12 hrs after her third enoxaparin dose, suggesting renal impairment as a contributing factor to her spinal hematoma.

When spinal hematoma occurs as a single case (or small series of cases), it is difficult to determine frequency or risk factors. However, the series by Moen et al³³ has markedly added to our understanding of patient and anesthetic risk factors. (Specific information on the 33 spinal hematomas included in this landmark investigation was graciously provided by Moen, Dahlgren, and Irestedt to promote the understanding of patient, anesthetic, and surgical risk factors). Of the 33 spinal hematomas reported, 8 patients had documented prophylaxis with LMWH. An additional 7 patients may have received LMWH because they had undergone orthopedic or general surgery (and received an unspecified agent for thromboprophylaxis; LMWH of which is the preferred agent). In 13 of these 15 patients, either the time interval between needle placement and catheter removal was insufficient (7 patients) or an additional hemostasis-altering medication such as dextran, ketorolac, or other nonsteroidal anti-inflammatory drug (NSAID) was administered (6 patients).

The 1:3600 frequency of spinal hematomas among women undergoing total knee replacement (with once-daily LMWH) in the survey by Moen et al is strikingly similar to the frequency associated with twice-daily administered LMWH calculated by Horlocker et al¹² in their initial series of 40 LMWH spinal hematomas. In addition, the series by Horlocker et al¹² contained only the cases of spinal hematoma, making it impossible to determine frequency or relative risk. However, 70% of the patients were elderly women. Moen et al³³ also postulated on the contribution of existing vertebral column pathology because many of the affected patients had undiagnosed spinal stenosis. This patient factor was also noted by Horlocker et al¹²; at the time of decompressive laminectomy, it was not unusual to have only a small collection of blood causing spinal cord ischemia.

Risk Factors for Spinal Hematomas With LMWH Thromboprophylaxis

On the basis of an examination of the published cases, MedWatch reports, and clinical experience in Europe and North

TABLE 8. Patient, Anesthetic, and LMWH Dosing Variables Associated With Spinal Hematoma

Patient factors
Female sex
Increased age
Ankylosing spondylitis or spinal stenosis
Renal insufficiency
Anesthetic factors
Traumatic needle/catheter placement
Epidural (compared with spinal) technique
Indwelling epidural catheter during LMWH administration
LMWH dosing factors
Immediate preoperative (or intraoperative) LMWH administration
Early postoperative LMWH administration
Concomitant antiplatelet or anticoagulant medications
Twice-daily LMWH administration

America, specific risk factors have been proposed.^{12,13,33} It is not possible to stratify the individual risk factors or determine interactions between risk factors (Table 8). In summary, age and sex seem 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 twice-daily dosing.³³ Thus, the characteristics of the reported cases support the previous recommendations of epidural catheter removal before the initiation of LMWH thromboprophylaxis and avoidance of concomitant antiplatelet/anticoagulant medications. Although the number of cases voluntarily reported has markedly declined, this may be a result of decreased reporting, improved management, or simple avoidance of all neuraxial techniques in patients receiving LMWH. Continued monitoring is necessary.

Therapeutic (Off-Label) Applications

Several off-label applications of LMWH are of special interest to the anesthesiologist. Low-molecular weight heparin has been demonstrated to be efficacious as a “bridge therapy” for patients chronically anticoagulated with warfarin, including parturients, patients with prosthetic cardiac valves, a history of atrial fibrillation, or preexisting hypercoagulable condition.^{62,113} In anticipation of surgery, warfarin is discontinued and the PT is allowed to normalize. During this time, the patient would be at risk for thromboembolic events and, historically, would be hospitalized and heparinized systemically. Outpatient LMWH is a suitable alternative. The doses of LMWH are those associated with DVT *treatment*, not prophylaxis, and are much higher. Needle placement should occur a minimum of 24 hrs after this level of LMWH anticoagulation. It is also important to determine when the first postoperative dose is anticipated because these patients are often aggressively anticoagulated postoperatively. In these cases, a spinal or a general anesthetic may be the safest alternatives.

Management Guidelines in Reducing the Risk of Spinal Hematoma

Perioperative management of patients receiving LMWH requires coordination and communication. Time intervals between neuraxial needle placement and administration of LMWH must be maintained. However, hospital staff often administer LMWH at a set time (usually 7–8 A.M. and 7–8 P.M.), unless otherwise specified. It is also important to note that even when protocols for dosing of LMWH and catheter management exist, they may not be closely followed. McEvoy et al¹¹⁴ reported a 52% noncompliance rate in the administration of LMWH in association with epidural analgesia. Clinicians are urged to develop protocols that “fit” within the normal practice standards at their institution, rather than deviate from the routine.

4.0 Anesthetic Management of the Patient Receiving LMWH

Anesthesiologists in North America can draw on the extensive European experience to develop practice guidelines for the management of patients undergoing spinal and epidural blocks while receiving perioperative LMWH. All consensus statements contained herein respect the labeled dosing regimens of LMWH as established by the FDA. Although it is impossible to devise recommendations that will completely eliminate the

risk of spinal hematoma, previous consensus recommendations have seemed to improve outcome. Concern remains for higher dose applications, where sustained therapeutic levels of anticoagulation are present.

4.1 The anti-Xa level is not predictive of the risk of bleeding.

We recommend against the routine use of monitoring of the anti-Xa level (Grade 1A).

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 (Grade 1A).

4.3 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 hrs postoperatively and that this consideration be discussed with the surgeon (Grade 2C).

4.4 Preoperative LMWH

4.4.1 Patients on preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, we recommend that needle placement should occur at least 10 to 12 hrs after the LMWH dose (Grade 1C).

4.4.2 In patients receiving higher (treatment) doses of LMWH, such as enoxaparin 1 mg/kg every 12 hrs, enoxaparin 1.5 mg/kg daily, dalteparin 120 U/kg every 12 hrs, dalteparin 200 U/kg daily, or tinzaparin 175 U/kg daily, we recommend delay of at least 24 hrs to ensure normal hemostasis at the time of needle insertion (Grade 1C).

4.4.3 In patients administered a dose of LMWH 2 hrs preoperatively (general surgery patients), we recommend against a neuraxial techniques because needle placement would occur during peak anticoagulant activity (Grade 1A).

4.5 Postoperative LMWH

Patients with postoperative LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule (Grade 1C).

4.5.1 Twice-daily dosing. This dosage regimen is associated with an increased risk of spinal hematoma. The first dose of LMWH should be administered no earlier than 24 hrs postoperatively, regardless of anesthetic technique, and only in the presence of adequate (surgical) hemostasis. Indwelling catheters should be removed before initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight, but must be removed before the first dose of LMWH. Administration of LMWH should be delayed for 2 hrs after catheter removal.

4.5.2 Single-daily dosing. The first postoperative LMWH dose should be administered 6 to 8 hrs postoperatively. The second postoperative dose should occur no sooner than 24 hrs after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10 to 12 hrs after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 hrs after catheter removal. No additional

hemostasis-altering medications should be administered due to the additive effects.

Oral Anticoagulants (Warfarin)

Warfarin Pharmacology

Oral anticoagulants, including warfarin, exert their anticoagulant effect indirectly by interfering with the synthesis of the vitamin K–dependent clotting factors, factor II (thrombin), VII, IX, and X. The effects of warfarin are not apparent until a significant amount of biologically inactive factors are synthesized and are dependent on factor half-life¹¹⁵:

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

An understanding of the correlation between the various vitamin K–dependent factor levels and the PT is critical to regional anesthetic management. Calculation of the INR allows for standardization/comparison of PT values between laboratories. Importantly, the INR is based on values from patients who were on stable anticoagulant doses for at least 6 weeks. Therefore, the INR is less reliable early in the course of warfarin therapy.¹¹⁵

Clinical experience with patients who, congenitally, are deficient in factors II, IX, or X suggests that a factor activity level of 40% for *each* factor is adequate for normal or near-normal hemostasis.¹¹⁶ Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. The PT is most sensitive to the activities of factors VII and X and is relatively insensitive to factor II. During the first few days of therapy, the PT reflects primarily a reduction of factor VII, the half-life of which is approximately 6 hrs. After a single dose, marked prolongation of the INR may occur, although adequate factor levels are still present. However, with additional doses, an INR greater than 1.4 is typically associated with factor VII activity less than 40% (and the potential for inadequate clotting).¹¹⁷ The reduction of factors X and II also contributes to the PT prolongation as therapy continues.¹¹⁵

Prolongation of the INR (INR >1.2) occurs when factor VII activity is reduced to approximately 55% of baseline, whereas an INR of 1.5 is associated with a factor VII activity of 40%.¹¹ Thus, an INR less than 1.5 during initiation of warfarin therapy should be associated with normal hemostasis. A corollary to this is the early recovery of factor VII after discontinuation of long-term warfarin therapy. Factor VII activity will rapidly increase, as demonstrated by a decrease in the INR. However, factors II and X activities recover much more slowly. Theoretically, there may be a time when the INR approaches a normal value because factor VII has been restored. However, factors II and X have not been restored to a hemostatic range of 40% activity.¹¹ In urgent/emergent situations, the effects of warfarin may be reversed by oral or intravenous of vitamin K and/or transfusion of fresh-frozen plasma (Table 4).²⁹

Factors Affecting Warfarin Response

The measured response to anticoagulant therapy at the initiation of treatment varies significantly. Some of the variability may be attributed to drug interactions, but in addition, there are patient variables such as age, female sex, and preexisting medical conditions (lower patient weight, liver, cardiac, and renal disease)

that are associated with an enhanced response to warfarin and/or a lower dose requirement for maintenance anticoagulation.^{82,115,118} Asian patients require lower doses than white patients during long-term therapy.^{115,118} In addition, there are many drug interactions described with warfarin therapy that potentiate the anticoagulant effect, including concomitant administration of antiplatelet medications, heparin, and LMWH.^{115,119,120} Recent clinical studies have demonstrated that patients with variations in the *CYP2C9* and/or *VKORC1* genes are at risk for increased bleeding and require lower doses of warfarin (approximately 20%–40% reduction in mean daily dose).¹¹⁵ The FDA recently changed the label to reflect this information (<http://www.fda.gov/cder/drug/infopage/warfarin/default.htm>). The ACCP recommends against the use of pharmacogenetic-based initial dosing owing to the lack of randomized trials.¹¹⁵

Warfarin is a drug with a narrow therapeutic range. Attention to the individual patient's response to warfarin therapy and maintenance of a consistent level of anticoagulation is paramount. Most medical laboratories have a method of contacting the caregiver in the event of an excessively prolonged PT/INR. However, further precautions may be warranted. Inclusion of pharmacy personnel may be one technique to add consistency in warfarin management. Because all warfarin orders are filled in by the pharmacy (and entered into a central computer), linking the pharmacy and laboratory results' computers will allow identification of patients with (1) a significant increase in the INR in a predefined time, (2) a subtherapeutic INR, and (3) warfarin therapy without INR assessment. The pharmacy then notifies the primary service and/or Pain Medicine Service so that appropriate action may be taken. To maintain the desired anticoagulant effect, the patient is instructed in a "warfarin" diet that contains foods with a consistent (low) level of vitamin K. These procedures have been successfully implemented at the Mayo Clinic. Web sites are also available to assist clinicians with the initiation of warfarin therapy and refine warfarin dosing (www.WarfarinDosing.org).

Neuraxial Techniques in the Chronically Anticoagulated Patient

Although no studies have directly examined the risk of procedure-related bleeding and the INR in patients recently discontinued from warfarin, careful consideration should be given before performing neuraxial blocks in these patients. Labeling of warfarin in the United States specifically lists spinal puncture and lumbar block anesthesia as contraindicated during warfarin therapy that is not interrupted before surgery (<http://www.fda.gov/cder/drug/infopage/warfarin/default.htm>). Wille-Jorgensen et al⁸² reported a case of difficult epidural placement in a patient fully anticoagulated with phenprocoumon. The anticoagulant therapy was unknown to the anesthesiologist. There was no bleeding observed during catheter placement, although placement was technically difficult. Satisfactory anesthesia developed and apparently resolved. Three days after surgery, the patient developed paresis of the lower extremities and impairment of the rectal and bladder sphincters. An epidural hematoma was evacuated from T11 to L1, but the extremity paresis was not reversed.

Timing of Neuraxial Catheter Removal During Warfarin Thromboprophylaxis

The management of patients requiring long-term anticoagulation (with recent discontinuation of warfarin in anticipation of surgery) and patients receiving warfarin perioperatively for thromboprophylaxis remains controversial. Adjusted-dose warfarin is the most common agent used for thromboembolism pro-

phylaxis after hip and knee replacement surgery (Table 1). Few data exist regarding the risk of spinal hematoma in patients with indwelling spinal or epidural catheters who are subsequently anticoagulated with warfarin. Bleeding may occur during catheter removal of the epidural catheter as a result of vascular trauma during catheter manipulation¹²¹ or dislodgment of an existing clot.¹²²

Several studies have examined the use of regional anesthesia and analgesia in patients who received warfarin during the perioperative period for thromboembolic prophylaxis. No spinal hematomas were reported in any of the studies; however, the power of these studies to detect a rare complication is low. Odoom and Sih¹²³ performed 1000 continuous lumbar epidural anesthetics in 950 patients undergoing vascular procedures who were receiving oral anticoagulants preoperatively. The thrombotest (a test measuring factor IX activity) was decreased, and the aPTT was prolonged in all patients before needle placement. A modest heparin infusion was administered intraoperatively. Epidural catheters remained in place for 48 hrs postoperatively; the coagulation status at time of catheter removal was not described. There were no neurologic complications. Although the results of this study are reassuring, the obsolescence of the thrombotest as a measure of anticoagulation combined with the unknown coagulation status of the patients at the time of catheter removal limits their usefulness.

The use of an indwelling epidural or intrathecal catheter and the timing of its removal in an anticoagulated patient are also controversial. Although the trauma of needle placement occurs with both single-dose and continuous catheter techniques, the presence of an indwelling catheter could theoretically provoke additional injury to tissue and vascular structures. A combined series of 651 patients reported no spinal hematomas in patients receiving neuraxial block in conjunction with low-dose warfarin therapy. The mean INR at the time of catheter removal was 1.4. However, marked variability in patient response to warfarin was noted.^{124,125}

There are 2 case reports in the literature describing spinal hematoma in patients who received perioperative warfarin for thromboembolic prophylaxis and regional anesthesia. Woolson et al¹²⁶ reported an 85-year-old woman who underwent total knee arthroplasty (TKA) with epidural anesthesia and analgesia. The patient was given a single preoperative dose of 10 mg of warfarin. Her epidural catheter was removed on the second postoperative day, at which time her INR was 6.3. She developed paraparesis of the lower extremities, which required laminectomy. Badenhorst¹²⁷ described a female patient who underwent bilateral TKA with epidural anesthesia and analgesia. This patient also received a preoperative dose of warfarin that was continued throughout the perioperative period. Her PT the morning of surgery was 14.3 sec (reference range, 11.2–14.4 sec; INRM not reported). On the third postoperative day, the epidural catheter was removed when her PT was 17.3 sec. At that time, she complained of blurred vision and tingling and weakness in her right leg. On postoperative day 4, she had bilateral lower extremity sensory and motor deficits. She underwent emergent decompressive laminectomy with near-complete recovery. Two cases of spinal hematomas in patients anticoagulated with warfarin were reported through the MedWatch system since 1998. The details are scant for both cases. The first patient was chronically anticoagulated with warfarin with a PT greater than 50 sec at the time of needle placement. The second patient received epidural analgesia and developed neurologic deficits 48 hrs later (with the catheter indwelling), at which time her INR was 1.6. Although a laminectomy was performed, neurologic outcome was not noted.

There have been no additional published cases of spinal hematoma in patients anticoagulated with warfarin in combination

with neuraxial block. Although ASRA has consistently recommended that epidural catheters be removed with an INR less than 1.5, this value has been questioned as being “conservative.” Although epidural catheters have been uneventfully removed with higher INRs,^{128,129} if this occurs within the first 48 hrs, it is likely there are adequate factor activity levels, particularly of factors II and X. Beyond this period, all vitamin K–dependent factors will be affected. There were no spinal hematomas in a series of 11,235 patients receiving epidural analgesia after total knee replacement.¹²⁹ Patients received warfarin (5–10 mg) starting the night of surgery. Epidural catheters were removed within 48 hrs. The mean INR in a subset of 1030 patients at the time of catheter removal was 1.5 (range, 0.9–4.3); the INR was less than 1.5 in nearly 40% of patients. These series suggest that not only the INR but also the duration of warfarin therapy must be considered and that prolongation within the first 48 hrs may represent a significant increase in risk.

5.0 Regional Anesthetic Management of the Patient on Oral Anticoagulants

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).

- 5.1 Caution should be used when performing neuraxial techniques in patients recently discontinued from long-term warfarin therapy. In the first 1 to 3 days after discontinuation of warfarin therapy, the coagulation status (reflected primarily by factor 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 reference limits. We recommend that the anticoagulant therapy must be stopped (ideally 4–5 days before the planned procedure) and the INR must be normalized before initiation of neuraxial block (Grade 1B).
 - 5.2 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, ticlopidine and clopidogrel, UFH, and LMWH (Grade 1A).
 - 5.3 In patients who are likely to have an enhanced response to the drug, we recommend that a reduced dose be administered. Algorithms have been developed to guide physicians in the appropriate dosing of warfarin based on desired indication, patient factors, and surgical factors. These algorithms may be extremely useful in patients at risk for an enhanced response to warfarin (Grade 1B).
 - 5.4 In patients receiving an initial dose of warfarin before surgery, we suggest that the INR should be checked before neuraxial block if the first dose was given more than 24 hrs earlier or if a second dose of oral anticoagulant has been administered (Grade 2C).
 - 5.5 In patients receiving low-dose warfarin therapy during epidural analgesia, we suggest that their INR be monitored on a daily basis (Grade 2C).
 - 5.6 Neurologic testing of sensory and motor function should be performed routinely during epidural analgesia for patients on warfarin therapy. To facilitate neurologic evaluation, we recommend that the type of analgesic solution be tailored to minimize the degree of sensory and motor blockade (Grade 1C).
- 5.7 As thromboprophylaxis with warfarin is initiated, we suggest that neuraxial catheters should be removed when the INR is less than 1.5. This value was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%. We suggest that neurologic assessment be continued for at least 24 hrs after catheter removal for these patients (Grade 2C).
 - 5.8 In patients with INR greater than 1.5 but less than 3, we recommend that removal of indwelling catheters should be done with caution and the medication record reviewed for other medications that may influence hemostasis that may not effect the INR (eg, NSAIDs, ASA, clopidogrel, ticlopidine, UFH, LMWH) (Grade 2C). We also recommend that neurologic status be assessed before catheter removal and continued until the INR has stabilized at the desired prophylaxis level (Grade 1C).
 - 5.9 In patients with an INR greater than 3, we recommend that the warfarin dose be held or reduced in patients with indwelling neuraxial catheters (Grade 1A). We can make no definitive recommendation regarding the management to facilitate removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during neuraxial catheter infusion (Grade 2C).

Antiplatelet Medications

Pharmacology of Antiplatelet Medications

Antiplatelet agents include NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa receptor antagonists (abciximab, eptifibatid, and tirofiban). It is important to note the pharmacologic differences among the drugs with antiplatelet effects.

Cyclooxygenase (COX) exists in 2 forms. Cyclooxygenase-1 regulates constitutive mechanisms, whereas COX-2 mediates pain and inflammation. Nonsteroidal anti-inflammatory drugs inhibit platelet cyclooxygenase 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 cyclooxygenase 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.^{130,131} As a result, low-dose aspirin (81–325 mg/d) is *theoretically* a greater risk factor for bleeding than higher doses. Spontaneous¹³² and postoperative (unrelated to neuraxial technique)¹³³ spinal hematomas have been reported with low-dose aspirin therapy.

It has been suggested that the Ivy bleeding time is the most reliable predictor of abnormal bleeding in patients receiving antiplatelet drugs. However, there is no evidence to suggest that a bleeding time can predict hemostatic compromise.¹³⁴ Platelet function is affected for the life of the platelet after aspirin ingestion; other nonsteroidal analgesics (naproxen, piroxicam, ibuprofen) produce a short-term defect that normalizes within 3 days.¹³⁵

Celecoxib (Celebrex) is an anti-inflammatory agent that primarily inhibits COX-2, an inducible enzyme that is not expressed in platelets and thus does not cause platelet dysfunction.¹³⁶ After single and multidosing, there have not been findings of significant disruption of platelet aggregation,

and there is no history of undesirable bleeding events. The concomitant use of COX-2 inhibitors and warfarin may increase the risk of hemorrhagic complications by increasing the PT.

The antiplatelet effect of the thienopyridine derivatives, ticlopidine, and clopidogrel results from the inhibition of adenosine diphosphate-induced platelet aggregation. These antiplatelet agents, used in the prevention of cerebrovascular thromboembolic events, affect both primary and secondary platelet aggregation. Ticlopidine (Ticlid) and clopidogrel (Plavix) also interfere with platelet-fibrinogen binding and subsequent platelet-platelet interactions.¹³⁷ Thienopyridine derivatives demonstrate both time- and dose-dependent effects; steady state is achieved within 7 days for clopidogrel and 14 to 21 days for ticlopidine, although this may be accomplished with higher loading doses (eg, clopidogrel 300 mg). For example, steady-state levels of clopidogrel are reached within 2 to 15 hrs with 300- to 600-mg loading doses.^{29,138} Although often administered in combination with aspirin, the concomitant use of clopidogrel or ticlopidine 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. Labeling of the thienopyridine derivatives recommends, "If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, clopidogrel should be discontinued 7 days and ticlopidine 10–14 days, prior to surgery." The ACCP recommends discontinuation of clopidogrel for 7 to 10 days,²⁹ whereas in patients at high risk for recurrent angina, 5 days have been suggested.¹³⁹ 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, and the clinical applicability of these tests remains undetermined at this time.^{140,141} The potency of these medications is demonstrated by recent reports of spontaneous spinal hematomas during clopidogrel therapy.^{142–144}

Platelet GP IIb/IIIa receptor antagonists, including abciximab (Reopro), eptifibatid (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.¹³⁷ Most clinical trials involving the GP IIb/IIIa antagonists have evaluated their use in the treatment of acute coronary syndrome (with or without percutaneous coronary intervention). 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 after discontinuation of therapy ranges from 8 hrs (eptifibatid, tirofiban) to 24 to 48 hrs (abciximab). During therapy with GP IIb/IIIa antagonists, labeling precautions recommend that puncture of noncompressible sites and "epidural" procedures be avoided.

Spinal Hematoma in Patients Receiving Antiplatelet Medications

At the previous ASRA Consensus Conferences on Neuraxial Anesthesia and Anticoagulation, it was concluded NSAIDs did not seem to present significant risk to patients for developing spinal epidural hematomas.^{13,16} Vandermeulen et al³⁴ implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia. These patients had received aspirin, indomethacin, or ticlopidine. Four additional case reports related to neuraxial techniques have been published in recent years, 2 involving ketorolac, and 2 involving a thienopyr-

idine derivative.^{145–148} The paucity of case reports is important, given the prevalence of NSAID use among the general population and that subset of patients with acute, chronic, and/or cancer pain-related problems who subsequently receive interventional therapy.

Several large studies have demonstrated the relative safety of central neural blockade in combination with antiplatelet therapy, although the total number of patients in this combined series is only 4714.¹⁶ If low-dose aspirin creates the greatest impact on platelet function, patients receiving 60 to 325 mg of aspirin would theoretically represent the greatest risk of significant bleeding. However, the Collaborative Low-dose Aspirin Study in Pregnancy Group included 1422 high-risk obstetric patients administered 60 mg of aspirin daily who underwent epidural anesthesia without any neurologic sequelae.¹⁴⁹ A recent prospective study evaluated the risk of neurologic complications after epidural steroid injection. There were no spinal hematomas among the 1214 patients, including the 32% of patients who reported NSAID use before injection.¹⁵⁰ These results confirm those of previous studies performed in obstetric and surgical populations.

No series involving the performance of neuraxial blockade in the presence of thienopyridine derivatives or platelet GP IIb/IIIa receptor antagonists have been performed. Although the data are inconsistent, increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel, and GP IIb/IIIa antagonists has been noted.^{151,152} In general, the cardiac surgical¹⁵² and interventional radiology literature recommend that elective surgery be delayed 24 to 48 hrs after abciximab and 4 to 8 hrs after eptifibatid or tirofiban.¹⁵³ Surgery performed within 12 hrs of abciximab administration with most likely necessitate a platelet transfusion. There have been 3 spinal hematomas attributed to neuraxial techniques and ticlopidine or clopidogrel, including 1 patient undergoing a series of epidural steroid injections.^{145,148,154} Two cases of severe bleeding after lumbar sympathetic blockade in patients on ticlopidine and clopidogrel were recently reported, which may warrant concern regarding the risk of anesthesia-related hemorrhagic complications.⁹

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.^{12,27,66} For example, in the series of 40 spinal hematomas associated with LMWH reported in 1998, 10 patients received concomitant antiplatelet medications.¹² The addition of antiplatelet therapy to postoperative thromboprophylaxis was implicated in a similar number of cases in the survey by Moen et al.³³ Likewise, in a case report of spinal hematoma after epidural steroid injection, Benzon et al¹⁴⁵ noted the patient had received multiple antiplatelet medications, including clopidogrel and aspirin.

6.0 Anesthetic Management of the Patient Receiving Antiplatelet Medications

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel) and platelet GP IIb/IIIa antagonists (abciximab, eptifibatid, tirofiban) 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. There is no

wholly accepted test, including the bleeding time, which will guide antiplatelet therapy. 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 bruisability/excessive bleeding, female sex, and increased age.

6.1 Nonsteroidal anti-inflammatory drugs seem to represent no added significant risk for 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-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring, or the timing of neuraxial catheter removal (Grade 1A).

6.2 In patients receiving NSAIDs, we recommend against the performance of neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as 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).

6.3 The actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown. Management is based on labeling precautions and the surgical, interventional cardiology/radiology experience (Grade 1C).

6.3.1 On the basis of labeling and surgical reviews, the suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. If a neuraxial block is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented.

6.3.2 Platelet GP IIb/IIIa inhibitors exert a profound effect on platelet aggregation. After administration, the time to normal platelet aggregation is 24 to 48 hrs for abciximab and 4 to 8 hrs for eptifibatid and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. Although GP IIb/IIIa antagonists are contraindicated

within 4 weeks of surgery, should one be administered in the postoperative period (after a neuraxial technique), we recommend that the patient be carefully monitored neurologically.

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.¹⁵⁵⁻¹⁵⁷ 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-warfarin (Table 9). Because the current regulatory mechanism for commercial herbal preparations sold in the United States does not adequately protect against unpredictable or undesirable pharmacological effects, it is especially important for anesthesiologists to be familiar with related literature on herbal medications when caring for patients in the perioperative period. Sources for reliable and updated information are important in helping anesthesiologists stay abreast of new discoveries about the effects of herbal medications in humans. Several resources are available on the World Wide Web as clinical aides. The Center for Food Safety and Applied Nutrition, Food and Drug Administration (<http://vm.cfsan.fda.gov/~dms/supplmnt.html>), and National Center for Complementary and Alternative Medicine, National Institutes of Health (<http://nccam.nih.gov>) Web sites contain fact sheets about alternative therapies, consensus reports, and databases. The FDA Web site may also be used to report adverse events.

Garlic

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk of developing atherosclerosis by reducing blood pressure, thrombus formation, and serum lipid and cholesterol levels.¹⁵⁸ The usual dosage is 4 g (~2 cloves) of fresh bulb or its equivalent as an extract or tincture per day. Garlic inhibits *in vivo* platelet aggregation in a dose-dependent fashion. The effect of one of its constituents, ajoene, seems to be irreversible and may potentiate the effect of other platelet inhibitors such as prostacyclin, forskolin,

TABLE 9. Three Herbal Medications With the Greatest Impact on Hemostasis*

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

From Horlocker et al,¹³ with permission.

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

indomethacin, and dipyridamole.^{159,160} Although these effects have not been consistently demonstrated in volunteers, there is 1 case in the literature of an octogenarian who developed a spontaneous epidural hematoma that was attributed to heavy garlic use.¹⁶¹

Ginkgo

Ginkgo is derived from the leaf of *Ginkgo biloba*. It has been used in cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness.^{162,163} The compounds believed to be responsible for its pharmacological effects are the terpenoids and flavonoids. The usual dosage is 120 to 240 mg of standardized extract per day, in 2 or 3 divided doses. Ginkgo seems to inhibit platelet-activating factor.¹⁶⁴ Clinical trials in a small number of patients have not demonstrated bleeding complications, but 4 reported cases of spontaneous intracranial bleeding^{165–168} have been associated with ginkgo use. A single case report of post-laparoscopic bleeding attributed to *Ginkgo biloba* has also been reported.¹⁶⁹

Ginseng

Among the several species used for pharmacological effects, Asian ginseng and American ginseng are the most commonly described. Ginseng has been labeled an “adaptogen” because it reputedly protects the body against stress and restores homeostasis.¹⁷⁰ The usual dosage is 1 to 2 g of root or 200 mg of standardized extract per day. Ginseng has a broad but incomplete pharmacological profile because it has many heterogeneous and sometimes opposing effects of different ginsenosides.¹⁷¹ There is a concern of ginseng’s effect on coagulation pathways. Ginsenosides inhibit platelet aggregation *in vitro*^{172,173} and prolong both thrombin time and aPTT in rats.¹⁷⁴ These findings await confirmation in humans. Although ginseng may inhibit the coagulation cascade, ginseng use was associated with a significant decrease in warfarin anticoagulation in 1 reported case.¹⁷⁵

Overall, there does not seem to be a clinically significant increase in surgical bleeding or spinal hematoma in patients receiving herbal medications. However, 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.

7.0 Anesthetic Management of the Patient Receiving Herbal Therapy

Herbal drugs, by themselves, seem to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. This is an important observation because it is likely that a significant number of our surgical patients use alternative medications preoperatively and perhaps during their postoperative course.

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

New Anticoagulants

New antithrombotic drugs that target various steps in the hemostatic system, such as inhibiting platelet aggregation, blocking coagulation factors, or enhancing fibrinolysis, are

continually under development. The most extensively studied are antagonists of specific platelet receptors and direct thrombin inhibitors. Many of these antithrombotic agents have prolonged half-lives and are difficult to reverse without administration of blood components. It is likely that orally bioavailable agents will be introduced in the near future. The administration of these medications in combination with neuraxial anesthesia must be carefully considered. Importantly, until large series become available, we can apply lessons learned from the LMWH experience to develop initial management recommendations. For example, the early postoperative dosing, prolonged half-life, exaggerated response in patients with comorbidities, and increased risk with concomitant administration of other medications affecting coagulation were all identified as risk factors for spinal hematoma (as well as surgical bleeding). The presence of these factors is likely to increase the risk with new and more efficacious (ie, potent) medications of thromboprophylaxis.

Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)

Recombinant hirudin derivatives, including desirudin (Revasc), lepirudin (Refludan), 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 heparin-induced thrombocytopenia and as an adjunct to angioplasty procedures.^{176,177} Desirudin is approved for prevention of DVT/PE after hip replacement.¹⁷⁸ The anticoagulant effect of thrombin inhibitors is monitored by the aPTT and is present for 1 to 3 hrs after intravenous 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. Owing to the lack of information available and the approved applications of these agents (typically patients with heparin-induced thrombocytopenia who will need therapeutic levels of anticoagulation and are therefore poor candidates for neuraxial blockade), no statement regarding risk assessment and patient management can be made. Identification of cardiology and surgical risk factors associated with bleeding after invasive procedures may be helpful.

8.0 Anesthetic Management of Patients Receiving Thrombin Inhibitors (Desirudin, Lepirudin, Bivalirudin, and Argatroban)

- 8.1 In patients receiving thrombin inhibitors, we recommend against the performance of neuraxial techniques (Grade 2C).

Fondaparinux

Fondaparinux, an injectable synthetic pentasaccharide, was approved in December 2001. The FDA released fondaparinux (Arixtra) with a black box warning similar to that of the LMWHs and heparinoids. Fondaparinux produces its antithrombotic effect through factor Xa inhibition. The plasma half-life of fondaparinux is 21 hrs, allowing for single-daily dosing, with the first dose administered 6 hrs postoperatively.¹⁷⁹ 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).^{179,180} No additional spinal hematomas were reported in the combined series of 3600 patients who underwent spinal or epidural anesthesia

in combination with fondaparinux thromboprophylaxis. However, the conditions for performance of neuraxial block were strictly controlled. Patients were included in subsequent clinical trials only if needle placement was atraumatic and accomplished on the first attempt. In addition, indwelling epidural catheters were removed 2 hrs before fondaparinux administration. These strict parameters suggested that neuraxial blockade in patients with planned fondaparinux thromboprophylaxis may not be feasible in clinical practice. For example, in a prospective series, less than 40% of neuraxial blocks were successful with 1 pass.³⁵ A recent series of 1631 patients undergoing continuous neuraxial or deep peripheral block reported no serious hemorrhagic complications. However, the catheters were removed 36 hrs after the last dose of fondaparinux, and subsequent dosing was delayed for 12 hrs after catheter removal.¹⁸¹ Although these results are reassuring, the deviation from the manufacturer's suggested dosing guidelines is of concern.

9.0 Anesthetic Management of the Patient Receiving Fondaparinux

The actual risk of spinal hematoma with fondaparinux is unknown. Consensus statements are based on the sustained and irreversible antithrombotic effect, early postoperative dosing, and the spinal hematoma reported during initial clinical trials. Close monitoring of the surgical literature for risk factors associated with surgical bleeding may be helpful in risk assessment and patient management.

9.1 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.

Oral Direct Thrombin and Activated Factor Xa Inhibitors in Development

It is beyond the scope of this review to discuss all antithrombotic agents that are currently in development. However, there are 2 (oral) medications intended for use as thromboprophylaxis after total knee and/or hip replacement that are in phase 3 clinical trials in the United States (and already released for use in Canada and Europe). These anticoagulants, namely dabigatran etexilate and rivaroxaban, inhibit thrombin and factor Xa, respectively.

Dabigatran Etexilate

Dabigatran etexilate is a prodrug that specifically and reversibly inhibits both free and clot-bound thrombin. The drug is absorbed from the gastrointestinal tract with a bioavailability of 5%.¹⁸² Once absorbed, it is converted by esterases into its active metabolite, dabigatran. Plasma levels peak at 2 hrs. The half-life is 8 hrs after a single dose and up to 17 hrs after multiple doses. It is likely that once-daily dosing will be possible for some indications because of the prolonged half-life. Because 80% of the drug is excreted unchanged by the kidneys, it is contraindicated in patients with renal failure.¹⁸³ Dabigatran etexilate prolongs the aPTT, but its effect is not linear and reaches a plateau at higher doses. However, the ecarin clotting time and thrombin time are particularly sensitive and display a linear dose-response at therapeutic concentrations. Reversal of anticoagulant effect is theoretically possible through administration of recombinant factor VIIa, although this has not been attempted clinically.¹⁸³

Clinical trials comparing dabigatran etexilate (150 or 220 mg, with the first dose administered 1 to 4 hrs postoperatively) with enoxaparin (40 mg daily with first dose 12 hrs preoperatively) noted little difference in efficacy or bleeding.¹⁸⁴⁻¹⁸⁶ Preliminary results comparing a higher dose of enoxaparin (30 mg every 12 hrs, starting 12 to 24 hrs after surgery) with a later institution of dabigatran etexilate (8 hrs after surgery) report a higher frequency of thromboembolism with dabigatran etexilate.¹⁸² Among published series, there has been no attempt to randomize patients with respect to anesthetic technique or to impose exclusion criteria based on the performance of neuraxial block, including the presence of an indwelling epidural catheter or traumatic needle/catheter placement.¹⁸⁴⁻¹⁸⁶ Although there have been no reported spinal hematomas, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach.

Rivaroxaban

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor, with an oral bioavailability of 80%. Phase 3 clinical trials have been completed in the United States. Like dabigatran etexilate, it is approved for use in Canada and Europe for thromboprophylaxis after total hip or knee replacement.¹⁸³ Rivaroxaban is generally administered once daily for thromboprophylaxis. After administration, the maximum inhibitory effect occurs 1 to 4 hrs; however, inhibition is maintained for 12 hrs. The antithrombotic effect may be monitored with the PT, aPTT, and Heptest, all of which demonstrate

TABLE 10. Inherited Thrombophilias in Pregnancy

Thrombophilia	Prevalence, % (Healthy Subjects)	Risk of Thrombosis
AT-III deficiency	0.02–0.10	<ul style="list-style-type: none"> • Most common congenital clotting disorder in women • 70%–90% lifetime risk of thrombosis • 60% chance of thrombosis during pregnancy and 33% during the puerperium
Factor V Leiden		
Heterozygous	3.6–6.0	<ul style="list-style-type: none"> • 10%–15% during pregnancy and 20% during puerperium in heterozygous • Risk of thrombosis increased >100-fold if homozygous
Homozygous	0.1–0.2	<ul style="list-style-type: none"> • Mutation rate varies among ethnic groups
Protein C deficiency	0.2–0.5	<ul style="list-style-type: none"> • 5% during pregnancy and 20% during puerperium
Protein S deficiency	0.03–1.3	<ul style="list-style-type: none"> • 5% during pregnancy and 20% puerperium • Protein S declines during normal pregnancy
Prothrombin G2010A	1–4	<ul style="list-style-type: none"> • Risk of thrombosis in asymptomatic pregnant carrier is 0.5% • Homozygosity carries a significant risk of thrombosis

From Kopp et al,²³⁴ with permission.

linear dose effects. Rivaroxaban is cleared by the kidneys and gut. The terminal elimination half-life is 9 hrs in healthy volunteers and may be prolonged to 13 hrs in the elderly owing to a decline in renal function (hence a need for dose adjustment in patients with renal insufficiency and contraindicated in patients with severe liver disease).

Overall, clinical trials comparing rivaroxaban (5–40 mg daily, with the first dose 6 to 8 hrs after surgery) with enoxaparin (40 mg, beginning 12 hrs before surgery) demonstrate similar rates of bleeding and a comparable efficacy.^{187–190} A recent comparison of once-daily rivaroxaban 10 mg with enoxaparin reported superiority with the rivaroxaban regimen (and the simplicity of oral administration).¹⁸⁹ Although a “regional anesthetic” was performed in more than half of the patients included in the clinical trials, no information regarding needle placement or catheter management was included. Although there have been no reported spinal hematomas, the lack of information regarding the specifics of block performance and the prolonged half-life warrants a cautious approach.

Antithrombotic Therapy and Pregnancy

Despite decreased maternal mortality over the past 70 years, pulmonary embolism continues to be one of the most common causes of maternal death in both the United States and the United Kingdom.¹⁹¹ The age-adjusted incidence of VTE ranges from 5 to 50 times higher in pregnant versus nonpregnant women.¹⁹²

Common risk factors that increase the incidence of thrombosis in pregnant women include increasing age, prolonged immobilization, obesity, thrombophilia, previous thromboembolism, and cesarean delivery^{193–196} (Table 10). The puerperium, defined as the 6-week period after delivery, is associated with a higher rate of thrombosis and pulmonary embolism than that associated with pregnancy itself.^{191,192}

Although there is an increased risk of thrombosis during normal pregnancy, in most women, the benefits of thromboprophylaxis do not outweigh the maternal and fetal risks. The exception is the pregnant woman with an acquired or inherited thrombophilia. The use of anticoagulation for prevention of thromboembolism in patients with hereditary or acquired thrombophilia is becoming more frequent and has been addressed by the ACCP for more than a decade. The ACCP guidelines on the use of antithrombotic agents during pregnancy have not recommended anticoagulation in pregnant women without thrombophilia or women *with* thrombophilia in the absence of a history of thromboembolism or poor pregnancy outcome. Owing to the high risk of thrombosis, the exceptions to this recommendation are as follows: women with (1) AT deficiency, (2) homozygosity for the factor V Leiden mutation, (3) homozygosity for the prothrombin gene G20210A mutation, or (4) heterozygosity for both mutations.¹⁷ The degree and duration of prophylaxis are dependent on risk of thromboembolism in the antepartum and postpartum periods (Table 11).

TABLE 11. Antithrombotic Therapy During Pregnancy

Thrombotic Disorder	Anticoagulant
Treatment of VTE during pregnancy or long-term anticoagulation before pregnancy (eg, mechanical heart valve)	Antepartum: adjusted-dose LMWH <i>or</i> adjusted-dose UFH Postpartum: therapeutic anticoagulation
History of thrombophilia <i>without</i> prior VTE	Surveillance
History of single episode of VTE <i>without</i> thrombophilia	Antepartum: surveillance Postpartum: LMWH/UFH prophylaxis
History of single episode of VTE <i>with</i> thrombophilia	Antepartum: Prophylactic LMWH/UFH <i>or</i> intermediate-dose LMWH/UFH <i>or</i> surveillance Postpartum: LMWH/UFH prophylaxis
No history of VTE <i>and</i> AT deficiency	Antepartum: LMWH/UFH prophylaxis Postpartum: LMWH/UFH prophylaxis
History of VTE <i>and</i> higher-risk thrombophilia AT deficiency Prothrombin G20210A <i>and</i> factor V Leiden Homozygotes for the above disorders	Antepartum: prophylactic <i>or</i> intermediate-dose LMWH <i>or</i> intermediate-dose UFH Postpartum: LMWH/UFH prophylaxis
Multiple (≥2) episodes of VTE	Antepartum: prophylactic, intermediate <i>or</i> adjusted-dose LMWH/UFH Postpartum: LMWH/UFH prophylaxis
Antiphospholipid antibodies <i>and</i> history of multiple pregnancy complications*	Prophylactic <i>or</i> intermediate-dose UFH <i>or</i> Prophylactic LMWH plus aspirin

Prophylactic UFH: 5000 U of subcutaneously (SC) every (q) 12 hours (h).

Intermediate-dose UFH: UFH SC q12h in doses adjusted to target and anti-Xa level of 0.1 to 0.3 U/mL.

Adjusted-dose UFH: UFH SC q12h in doses adjusted to target a mid interval aPTT into the therapeutic range.

Prophylactic LMWH: dalteparin 5000 U SC q24h *or* enoxaparin 40 mg SC q24h (extremes of weight may require dose modification).

Intermediate-dose LMWH: dalteparin 5000 U SC q12h *or* enoxaparin 40 mg SC q12h.

Adjusted-dose LMWH: weight-adjusted, full-treatment doses of LMWH administered once *or* twice daily (dalteparin 200 U/kg q24h, *or* 100 U/kg q12 hrs, *or* enoxaparin 1 mg/kg q12 hrs).

Postpartum anticoagulants: warfarin for 4 to 6 weeks with a target INR of 2.0 to 3.0, with initial UFH *or* LMWH overlap until INR is 2.0 *or* higher.

Adapted from Bates et al.¹⁷

*Pregnancy complications = multiple early pregnancy losses, one *or* more late pregnancy loss, preeclampsia, abruption, intrauterine growth retardation.

The peripartum management of the anticoagulated parturient represents a significant clinical challenge to both the obstetrician and the anesthesiologist. Unfortunately, there is a paucity of data regarding the efficacy of anticoagulants in pregnancy. Recommendations are based largely on small case series and case reports. From the neuraxial anesthetic standpoint, there is even less information regarding safety or risk. In addition, the lack of a suitable alternative to labor analgesia, as well as the desire for women to participate in the birth during cesarean delivery further complicates management decisions. Finally, the administration of LMWH (which is preferred over UFH)¹⁷ during pregnancy is an off-label application. Without manufacturer-specified dosing guidelines, the management may markedly vary even within an institution, further complicating patient care.

Spinal Hematoma in the Obstetric Patient

The frequency of spinal hematomas in the obstetric population is unknown. Bleeding may occur in the absence of a neuraxial block. In a case report of a spontaneous thoracic epidural hematoma in a preeclamptic woman, Dobljar and Schumacher¹⁹⁷ present an additional 6 cases of *spontaneous* epidural hematoma in *healthy* parturients. A subsequent case of spontaneous hematoma in a parturient has been reported.¹⁹⁸ The etiology of these spontaneous hematomas is not currently

understood, although if not treated appropriately and expeditiously, the outcome can be devastating for these young mothers. There also is a case of spontaneous spinal hematoma in a pregnant patient with factor Leiden mutation and anticardiolipin antibodies (27 weeks' gestation) who was receiving enoxaparin 60 mg twice per day. A laminectomy was performed, and LMWH was restarted at enoxaparin 40 mg daily. The patient subsequently underwent an uncomplicated cesarean delivery (general anesthesia).¹⁰⁵

The incidence of spinal hematoma after neuraxial blockade (with or without altered hemostasis) is very difficult to determine, although it is widely reported that obstetric patients have a significantly lower incidence of complications than their elderly counterparts.^{33,199} Moen et al³³ reported 2 spinal hematomas among 200,000 epidural blocks for pain relief in labor; one after a subarachnoid block and one after the removal of an epidural catheter. Interestingly, signs of severe coagulopathy were present in both patients. The authors reported the incidence of spinal hematoma after obstetric epidural blockade was 1:200,000, which was significantly lower than the incidence of 1:3600 elderly females undergoing TKA. Among the published case reports of parturients who have experienced a spinal hematoma after neuraxial blockade, a significant proportion of patients had altered coagulation at the time of block placement

TABLE 12. Spinal Hematoma After Neuraxial Block in Obstetric Patient

Author (Reference)	Year	Technique	Coagulopathy	Outcome	Miscellaneous
Nguyen ²⁰⁴	2006	Epidural	Postpartum hemorrhage	Recovered	• Epidural catheter inadvertently removed while coagulopathic
			Thrombocytopenia		
			Elevated thrombin time		
Lee ³⁸	2004	Epidural	Severe preeclampsia (1 patient)	Permanent paraplegia	
Lee ³⁸	2004	Unknown	None	Permanent paraplegia	Evidence of cord trauma above L1
Lee ³⁸	2004	Unknown	None	Permanent paraplegia	Evidence of cord trauma above L1
Moen et al ³³	2004	Epidural	HELLP*	Unknown	• Epidural catheter removed in setting of coagulopathy
Moen et al ³³	2004	Subarachnoid	HELLP*	Unknown	• Evidence of coagulopathy
Esler ²⁰¹	2001	Epidural	None	Recovered	• Neurofibromatosis
Yuen ²⁰⁹	1999	Epidural	Severe preeclampsia	Recovered	• Presented on second postpartum day
			Thrombocytopenia		• Presented within hrs
Yarnell ²⁰⁸	1996	Epidural	Elevated aPTT	Mild weakness of right leg	• Surgical laminectomy
			Elevated PT		• Presented 12 hrs after epidural
Lao ²⁰²	1993	Epidural	Preeclampsia and lupus anticoagulant	Residual urinary and bowel dysfunction	• Surgical treatment
			Abnormal aPTT		• Surgical treatment
Scott ²⁰⁶	1990	Epidural	Not reported	Improving	• Surgical treatment
Sibai ²⁰⁷	1986	Epidural	Thrombocytopenia	Unknown	• No information
Crawford ¹⁹⁹	1985	Epidural	Unknown	Recovered	• Presented several weeks postpartum
Roscoe ²⁰⁵	1984	Epidural	None	Residual leg weakness	• Epidural ependymoma
					• Presented 3 d postpartum
Newman ²⁰³	1983	Epidural	None	Minimal weakness and paresthesia	• Surgical treatment
					• Presented 2 hrs after delivery
Ballin ²⁰⁰	1981	Epidural	None	Recovered	• Spinal stenosis

Adapted from: Kopp et al,²³⁴ with permission.

*Syndrome of hemolysis, elevated liver enzymes, and low platelets.

TABLE 13. Hemorrhagic Complications After Plexus and Peripheral Block in Patients Without Antithrombotic Therapy

Author, Year (Reference)	Patient Information	Block Type	Clinical Course/Outcomes
Ben-David, 1999 ²¹⁵	38 y-old healthy man, procedure on palmar surface of wrist	Axillary (transarterial)	<ul style="list-style-type: none"> • Large axillary hematoma causing paresthesias and radial nerve weakness • Electromyogram at 4 wk demonstrated signs of neuropraxia • Complete recovery after 6 mo • Patient developed small (<2 cm) hematoma • Resolved without sequelae • Patient developed axillary hematoma • Resolved spontaneously without sequelae • Large, obstructing subserosal hematoma, which presented as intestinal obstruction 5 d postoperatively • Diagnostic laparoscopy and bowel resection with an uneventful recovery • Hematoma (2 cm in diameter) in the wall of the terminal ileum noted on opening peritoneum • Hematoma was nonobstructing • Uneventful recovery • Three hrs after block placement, patient returned to emergency department 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 • Patient developed hematoma at the puncture site
Stan, 1995 ²²²	No information	Axillary (transarterial)	
Bergman, 2003 ²¹⁶	No information	Continuous axillary catheter	
Amory, 2003 ²¹⁴	6 y-old healthy boy, left herniorrhaphy	Ilioinguinal/iliohypogastric	
Frigon, 2006 ²¹⁹	6 y-old healthy girl, appendectomy	Ilioinguinal/iliohypogastric	
Vaisman, 2001 ²²⁴	40 y-old man with left testicular pain	Ilioinguinal	
Borgeat, 2001 ²¹⁷	No information	Infraclavicular (modified approach of the Raj technique)	
Ekatodramis, 2001 ²¹⁸	48 y-old woman with chronic regional pain syndrome of the right hand	Continuous interscalene catheter	
Ekatodramis, 2001 ²¹⁸	20 y-old healthy female undergoing right shoulder Bankart repair	Continuous interscalene catheter	<ul style="list-style-type: none"> • No information about outcome • 3 d postoperatively, the patient complained of blurred vision and painful swelling on right side of neck • Ultrasound of neck revealed 4 × 5-cm hematoma • Neurologic investigation confirmed Horner syndrome • Catheter removed immediately • 6 mo later, Horner syndrome began to improve • Complete resolution at 1 y • Postoperative day 1, patient noted visual disturbances and neck swelling • Ultrasound of the neck revealed 3 × 4-cm hematoma • Neurologic investigation confirmed Horner syndrome • Catheter removed immediately • 6 mo later, only slight ptosis present • Complete resolution at 1 y

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TABLE 13. (Continued)

Author, Year (Reference)	Patient Information	Block Type	Clinical Course/Outcomes
Wheatley, 1984 ²⁵	59 y-old woman with chronic pelvic pain	4 lumbar sympathetic blocks during a 5-d period (paravertebral approach, 5 cm lateral to the second lumbar vertebrae)	<ul style="list-style-type: none"> • 30 mins 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, 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) • Technical difficulty during block placement, with blood aspiration on second pass of the needle
Thomas, 1999 ²²³	65 y-old woman undergoing thoracotomy for recurrent esophageal hernia	Paravertebral (loss of resistance to saline technique)	<ul style="list-style-type: none"> • 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
Kurzel, 1996 ²²⁰	17 y-old admitted for induction of labor	Bilateral pudendal block	<ul style="list-style-type: none"> • Postpartum day 3, patient complained of abdominal distention, back pain, pain in right inguinal area, and fever • Patient was discharged and readmitted 2 d later with increasing abdominal pain radiating to right lower quadrant and flank • CT scan revealed an infected, right retroperitoneal hematoma • Treated with broad-spectrum antibiotics and dismissed after 3 d when fever and pain resolved
Mishio, 1998 ²²¹	62 y-old woman with sudden deafness	4 sequential (on alternate days) stellate ganglion blocks at C7, anterior paratracheal approach	<ul style="list-style-type: none"> • 30 mins after the fourth block, patient complained of discomfort in her throat • Patient was noted to have a Horner syndrome • 2 hrs later, patient complained of dyspnea and difficulty swallowing • Magnetic resonance imaging revealed massive hemorrhage from clivus to the diaphragm • Patient required emergency tracheotomy owing to glottic swelling and narrowing • Multiple complications during the hospitalization • Stoma closed on 33rd postoperative day and discharged on 41st day after the block

TABLE 14. Hemorrhagic Complications After Plexus and Peripheral Block in Patients Receiving Antithrombotic Therapy

Author, Year (Reference)	Patient Information	Anticoagulant/Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Nielsen, 1989 ²³⁰	<ul style="list-style-type: none"> • 80-y-old man • Cholecystectomy with severe postoperative pain 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • Warfarin preoperatively <p><i>Postoperative</i></p> <ul style="list-style-type: none"> • PT on operative day 13 sec • Heparin 5000 U subcutaneously every 8 hrs (started 8 hrs postoperatively and discontinued on POD 2) • POD 2, heparin bolus 4500 U intravenously followed by continuous infusion (PTT ranged from 99 to 29 sec) 	<ul style="list-style-type: none"> • Intercostal nerve blocks bilaterally T7 to T11 • Placed 20 hrs postoperatively • Blocks repeated 4 times (approximately every 7 hrs) 	<ul style="list-style-type: none"> • Small chest wall hematoma noted on POD 3 at T7 before the last block was placed • During the next 2 d, hematoma increased to 30 × 65 cm and covered a large area of the posterior and lateral chest wall down to flank and upper thigh • Required transfusion of 8 U of packed red blood cells • Heparin infusion was stopped • Patient recovered uneventfully but had pain for 4 wk in the area of the hematoma
Wiegel, 2007 ²³¹	<ul style="list-style-type: none"> • No information 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • Aspirin 1 g/d 	<ul style="list-style-type: none"> • Continuous femoral catheter 	<ul style="list-style-type: none"> • Patient complained of inguinal pain, numbness, weakness of the thigh on the sixth postoperative day • CT scan revealed a retroperitoneal hematoma • Retroperitoneal hematoma required surgical intervention • No further information • Low back pain became more intense 1 d after the last block
Aida, 1996 ²²⁶	<ul style="list-style-type: none"> • 71-y-old woman • Pain due to herniated lumbar disc 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • None <p><i>Postoperative</i></p> <ul style="list-style-type: none"> • Pain treated with mefenamic acid (NSAID) 	<ul style="list-style-type: none"> • Lumbar plexus block • Performed 4 times for 4 wk • Level of L3 using loss of resistance technique 	<ul style="list-style-type: none"> • Difficulty walking for several days • Pain still present 10 d after the block • CT scan and ultrasonography revealed renal subcapsular hematoma • Microscopic hematuria resolved after 2 wk • Back pain resolved after 3 wk • Hematoma resorbed spontaneously within 4 mo
Aida, 1996 ²²⁶	<ul style="list-style-type: none"> • 68-y-old woman • Severe low back pain due to spinal spondylosis 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • None <p><i>Postoperative</i></p>	<ul style="list-style-type: none"> • Lumbar plexus block at the level of L3 using loss of resistance technique 	<ul style="list-style-type: none"> • Low back pain became more intense 1 d after the block • Pain remained severe and patient could not ambulate for several days • 3 d after block, CT scan and ultrasonography revealed a renal subcapsular hematoma

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TABLE 14. (Continued)

Author, Year (Reference)	Patient Information	Anticoagulant/Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Maier, 2002 ⁹	• 71-y-old man	• Pain treated with 200 mg intravenous diclofenac (NSAID)	• Left-sided lumbar sympathetic block using radiographic control	• Microscopic hematuria resolved after 1 wk
	• Left leg claudication	<i>Preoperative</i>	• 6 d after the first block, a second block was performed	• Pain markedly decreased after 2 wk
		<i>Postoperative</i>	• Radiographic control using contrast medium confirmed intravascular needle position	• Discharged after a 10-d hospitalization
		• Ticlopidine stopped 2 d after the first block	• Needle was repositioned	• Pain resolved after 6 wk, hematoma resorbed within 4 mo
Maier, 2002 ⁹	• 79-y-old woman	<i>Preoperative</i>	• Diagnostic lumbar sympathetic block at the L3 level	• No vascular puncture during first block
	• Generalized peripheral arterial disease	• Clopidogrel 75 mg/d		• Within 12 hrs complained of numbness on medial side of thigh and groin pain
	• Severe pain in lower extremities	• Discontinued 3 d before block		• 2 d later, widespread skin hematoma was noted
		<i>Postoperative</i>		• The night after the second block, the patient complained of severe groin pain and decrease in blood pressure
Weller, 2003 ¹⁰	• 85-y-old woman	• None	• Single-injection sciatic (Labat approach) and continuous lumbar plexus block (posterior approach)	• CT scan revealed large retroperitoneal hematoma
	• Unicompartamental right knee arthroplasty	• No anticoagulant medication	• Blood was aspirated, catheter withdrawn 2 cm and flushed with saline, aspiration then negative	• Patient required a blood transfusion of an unknown amount
		<i>Postoperative</i>	• Supplemental sciatic block at the midpoint between the ischial tuberosity and greater trochanter, and a femoral block at the groin	• Discharged 5 d later without major complaints
				• No intravascular injection recognized

<ul style="list-style-type: none"> • Treated with morphine • POD 3, right paravertebral pain, no neurological deficit • POD 4, 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 • POD 5, extensive ecchymosis and pain in flank and hip • Dismissed from hospital on POD 20 • POD 3, patient complained of back pain at the site of the lumbar plexus block 		<ul style="list-style-type: none"> • POD 2 at 0900 enoxaparin 30 mg • Enoxaparin continued 30 mg every 12 hrs • Enoxaparin discontinued on POD 4
<ul style="list-style-type: none"> • Single-injection lumbar plexus block (posterior approach) and single-injection sciatic block • No technical difficulty noted 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • Warfarin 5 mg/d 	<p>Weller, 2003¹⁰</p> <ul style="list-style-type: none"> • 65-y-old man • Left knee arthroscopy • Mechanical aortic valve
<ul style="list-style-type: none"> • CT scan revealed moderate-sized retroperitoneal hematoma that appeared to originate in the psoas muscle • Transfused 2 U of packed red blood cells • Discharged on POD 10 with plan to restart anticoagulation 2 wk after discharge 	<ul style="list-style-type: none"> • Aspirin 81 mg twice a day • Patient admitted with INR 5.19, coumadin stopped, and heparin started • Next day INR measured 9.27, given 10 mg of vitamin K and 1 U of fresh-frozen plasma • Morning of surgery INR 0.92 <p><i>Postoperative</i></p> <ul style="list-style-type: none"> • Heparin infusion initiated at 1200 U/hr 8 hrs after the lumbar plexus block • aPTT on POD 1 was 77.7 sec • Coumadin restarted evening of POD 1 • POD 3, aPTT > 100 sec and INR 1.4 • Heparin adjusted and POD 4 aPTT 60.2 sec • POD 5, anticoagulation discontinued and vitamin K 1 mg subcutaneously and 2 U of fresh-frozen plasma given 	

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TABLE 14. (Continued)

Author, Year (Reference)	Patient Information	Anticoagulant/Antiplatelet Agent(s)	Block Type	Clinical Course/Outcomes
Aveline, 2004 ²²⁷	<ul style="list-style-type: none"> • 72-y-old woman • Total hip replacement 	<ul style="list-style-type: none"> • Heparin infusion initiated at 1200 U/hr 8 hrs after the lumbar plexus block • <i>Preoperative</i> • Phenylindanedione stopped 5 d before surgery 	<ul style="list-style-type: none"> • Lumbar plexus block via the posterior approach • Unable to be placed after 3 attempts 	<ul style="list-style-type: none"> • POD 17, the patient complained of progressive left leg motor deficit and left lumbar back pain • Extensive ecchymosis on the left side of her back with sensory and motor deficit in the distribution of the femoral nerve and lateral cutaneous nerve of the thigh (INR 3.5) • CT scan revealed large left retroperitoneal hematoma with anterior displacement of the left kidney and diffusion of the hematoma into the left psoas and iliac muscles • Patient received 3 U of packed red blood cells and vitamin K • Motor function started to progressively recover on POD 19 • Recovery was complete on POD 45
Klein, 1997 ²²⁹	<ul style="list-style-type: none"> • 67-y-old woman • Repair of open right calcaneal fracture • Patient underwent 3 operative procedures during a 6-d period 	<ul style="list-style-type: none"> • Heterozygous Leyden mutation • Enoxaparin 60 mg twice daily started 5 d before surgery and held 24 hrs before surgery • INR and aPTT normal • <i>Postoperative</i> • Anticoagulation initiated at 14 hrs with enoxaparin 40 mg and then increased to 60 mg once daily on POD 2 • Phenylindanedione restarted on POD 3 and enoxaparin stopped on POD 7 • <i>Preoperative</i> • Aspirin 325 mg/d • <i>Postoperative</i> • POD 1 enoxaparin 30 mg twice a day and aspirin 325 mg/d • Enoxaparin continued 30 mg every 12 hrs • Third operative procedure was 19.5 hrs after last dose of enoxaparin 	<ul style="list-style-type: none"> • Fascia iliaca compartment block on first attempt • <i>Night of admission</i> • Incision and drainage of ankle • Sciatic block (Labat approach), saphenous nerve block posterior to the sartorius muscle • <i>Hospital day 3 (second procedure)</i> • Open reduction internal fixation of ankle • Sciatic block (Raj approach) and lumbar plexus block (femoral approach) 	<ul style="list-style-type: none"> • Hospital day 7 (1 d after below the knee amputation), patient complained of right hip pain • Hospital day 14, severity of pain worsened • Hospital day 15 patient was unable to move right leg • Abdominal CT revealed a large retroperitoneal hematoma involving the right psoas muscle • Patient regained motor function during the next 5 d • No subjective or objective evidence of sensory deficit at the 4-mo follow-up visit

Bickler, 2006 ^{2,28}	<ul style="list-style-type: none"> • 49-y-old man • Right total knee replacement 	<p><i>Hospital day 6 (third procedure)</i></p> <ul style="list-style-type: none"> • First postoperative enoxaparin dose (after third procedure) 4.5 hrs after block placement • Enoxaparin discontinued on hospital day 15 after CT scan <p><i>Preoperative</i></p> <ul style="list-style-type: none"> • Right below knee amputation • Lumbar plexus block (posterior approach)—unable to place despite multiple attempts • Lumbar plexus block (femoral approach) and sciatic block (Raj approach) • Continuous sciatic nerve catheter (lateral, mid femoral region) • Continuous femoral catheter <p><i>Postoperative</i></p> <ul style="list-style-type: none"> • No anticoagulant medication • POD 2, enoxaparin 40 mg/d subcutaneously • POD 5, enoxaparin discontinued 	<ul style="list-style-type: none"> • No difficulty noted with either catheter placement • Nerve catheters removed on POD 3 approximately 3 hrs after the enoxaparin dose • At the time of catheter removal, swelling and discoloration were noted both at the femoral and at the sciatic insertion sites • POD 4, massive swelling of right thigh and extensive ecchymoses at both sites • Sensation and strength were unaffected • Patient discharged on POD 7, which was 2 d later than expected • No specific treatment of the hematoma • No difficulty noted with either catheter placement
Bickler, 2006 ^{2,28}	<ul style="list-style-type: none"> • 78-y-old woman • Total knee replacement 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • No anticoagulant medication <p><i>Postoperative</i></p> <ul style="list-style-type: none"> • POD 1, enoxaparin 40 mg/d subcutaneously 	<ul style="list-style-type: none"> • POD 2, 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 during the next 24 hrs • No significant neurologic impairment at the time of discharge on POD 5 • No difficulty noted with either catheter placement
Bickler, 2006 ^{2,28}	<ul style="list-style-type: none"> • 48-y-old female • Total knee replacement 	<p><i>Preoperative</i></p> <ul style="list-style-type: none"> • No anticoagulant medication <p><i>Postoperative</i></p> <ul style="list-style-type: none"> • POD 1, enoxaparin 40 mg/d subcutaneously 	<ul style="list-style-type: none"> • POD 2, the dressings over the femoral catheter insertion site were soaked with 15–20 mL of blood, no hematoma noted • The catheters were removed on POD 2 and the femoral site continued to ooze blood and soaked another dressing • No further bleeding on POD 3 • No delay in discharge

POD, postoperative day.

TABLE 15. Neuraxial* Anesthesia in the Patient Receiving Thromboprophylaxis

	Antiplatelet Medications	UFH		LMWH
		Subcutaneous	Intravenous	
German Society for Anaesthesiology and Intensive-Care Medicine†	NSAIDs: no contraindication; hold LMWH, fondaparinux 36–42 hrs Thienopyridines and GP IIb/IIIa are contraindicated	Needle placement 4 hrs after heparin; heparin 1 hr after needle placement or catheter removal	Needle placement and/or catheter removal 4 hrs after discontinuing heparin, heparinize 1 hr after neuraxial technique; delay bypass surgery 12 hrs if traumatic	Neuraxial technique 10–12 hrs after LMWH; next dose 4 hrs after needle or catheter placement Delay block for 24 hrs after therapeutic dose
Belgian Association for Regional Anesthesia‡	NSAIDs: no contraindication Discontinue ticlopidine 14 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 87–48 hrs in advance	Not discussed	Heparinize 1 hr after neuraxial technique Remove catheter during normal aPTT; reheparinize 1 hr later	Neuraxial technique 10–12 hrs after LMWH; next dose 4 hrs after needle or catheter placement Delay block for 24 hrs after therapeutic dose
American Society of Regional Anesthesia and Pain Medicine	NSAIDs: no contraindication. Discontinue ticlopidine 14 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 8–48 hrs in advance	No contraindication with twice-daily dosing and total daily dose <10,000 U, consider delay heparin until after block if technical difficulty anticipated. The safety of neuraxial blockade in patients receiving doses greater than 10,000 units of UFH daily, or more than twice daily dosing of UFH has not been established.	Heparinize 1 hr after neuraxial technique, remove catheter 2–4 hrs after last heparin dose; no mandatory delay if traumatic	Twice-daily dosing: LMWH 24 hrs after surgery, regardless of technique; remove neuraxial catheter 2 hrs before first LMWH dose Single-daily dosing: according to European statements BUT with no additional hemostasis-altering drugs Therapeutic dose: delay block for 24 hrs
American College of Chest Physicians§	NSAIDs: no contraindication Discontinue clopidogrel 7 d before neuraxial block.	Needle placement 8–12 hrs after dose; subsequent dose 2 hrs after block or catheter withdrawal	Needle placement delayed until anticoagulant effect is minimal	Needle placement 87–12 hrs after dose; subsequent dose 2 hrs after block or catheter withdrawal. Indwelling catheter safe with twice-daily dosing Therapeutic dose: delay block for 18+ hrs

*For patients undergoing deep plexus or peripheral block, follow ASRA recommendations for neuraxial techniques.

†Adapted from the German Society of Anesthesiology and Intensive Care Medicine Consensus guidelines.¹⁰³

‡Adapted from the Belgian Association for Regional Anesthesia. Working party on anticoagulants and central nerve blocks.⁶⁸

§Adapted from the American College of Chest Physicians.⁷

or epidural catheter removal^{33,38,199–209} (Table 12). To date, there have been no published cases of spinal hematoma in a parturient associated with antithrombotic therapy (with or without neuraxial block)!

Obstetrical Management

A major component of management is for delivery (and needle/catheter placement) to occur during normal hemostasis. Consequently, the delivery should be scheduled whenever possible. In general, it is recommended that (1) no later than 36 weeks, oral anticoagulants should be switched to LMWH or UFH with similar dosing and monitoring as when used for anticoagulation throughout pregnancy; (2) at least 36 hrs before induction of labor or cesarean delivery, LMWH should be discontinued and the patient converted to intravenous or

subcutaneous UFH if needed; (3) intravenous UFH should be discontinued 4 to 6 hrs before anticipated delivery.²¹⁰ The pregnant patient on LMWH should be advised to withhold her heparin injection if she believes she may be in labor until evaluated by her obstetrician. If it is determined that she is in labor, further doses are usually held until after delivery. When possible, an induction or elective cesarean delivery should be scheduled. Adherence to these guidelines also facilitates the performance of neuraxial techniques for labor and delivery.

The plan for reinitiating anticoagulation postpartum must also be considered when planning the anesthetic management, and is often the limiting factor when determining the safety of a neuraxial technique. Typically, resumption of prophylaxis (eg, 5000 U of UFH every 12 hrs, 40 mg of enoxaparin once daily) should be held until at least 12 hrs after abdominal delivery, or

Warfarin	Fondaparinux	Direct Thrombin Inhibitors	Thrombolytics	Herbal Therapy
INR <1.4 for needle/catheter insertion and withdrawal	Needle placement 36–42 hrs after last dose, wait 6–12 hrs after catheter removal for subsequent dose	Needle placement 8–10 hrs after dose; delay subsequent doses 2–4 hrs after needle placement	Absolute contraindication	No contraindication
INR <1.4 for needle/catheter insertion and withdrawal	Needle placement 36 hrs after last dose. Indwelling epidural catheter not recommended	Needle placement 8–10 hrs after dose; delay subsequent doses 2–4 hrs after needle placement	Absolute contraindication	Not discussed
Normal INR (before neuraxial technique); remove catheter when INR ≤ 1.5 (initiation of therapy)	Single injection, atraumatic needle placement or alternate thromboprophylaxis. Avoid indwelling catheters.	Insufficient information. Suggest avoidance of neuraxial techniques	Absolute contraindication	No evidence for mandatory discontinuation before neuraxial technique; be aware of potential drug interactions
Avoid or limit epidural analgesia to <48 hrs. Remove catheter when INR <1.5	Single-injection spinal safe. Avoid epidural analgesia	Not addressed	Not addressed	Not addressed

epidural removal, whichever is later. After cesarean delivery, thromboprophylaxis should be held for at least 24 hrs.^{210,211} If higher levels (eg, enoxaparin 1 mg/kg every 12 hrs or adjusted-dose UFH for therapeutic aPTT) are required, prophylaxis should be delayed for 24 hrs, regardless of mode of delivery. These are consistent with recommendations for the nonpregnant patient.

10.0 Anesthetic Management of the Anticoagulated Patient

10.1 In the absence of a large series of neuraxial techniques in the pregnant population receiving prophylaxis or treatment of VTE, we suggest that the ASRA guidelines (derived from mainly from surgical patients) be applied to parturients (Grade 2C).

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 after plexus and peripheral techniques remains undefined. There are few investigations that examine the frequency and severity of hemorrhagic complications after plexus or peripheral blockade in anticoagulated patients. However, few reports of serious complications after neurovascular sheath cannulation for surgical, radiological, or cardiac indications have been reported. For example, during interventional cardiac procedures, large bore catheters are placed within brachial or femoral vessels. Heparin, LMWH, antiplatelet medications, and/or thrombolytics are subsequently administered. In a series

of 4879 patients undergoing cardiac catheterization and/or coronary angioplasty, the frequency of vascular complications was 0.39%. Size of the catheter (5F versus 7F catheter) and degree of anticoagulation influenced the frequency of complications.²¹² No neurologic complications occurred as a result of the vascular injury; 1 patient required transfusion. The largest (and most significant) study involving the risk of hemorrhagic complications associated with peripheral blocks included 670 patients undergoing continuous lumbar plexus blocks who were anticoagulated with warfarin.²¹³ Nearly all catheters were removed on the second postoperative day. At the time of catheter removal, 36% of patients had an INR greater than 1.4. One case of local bleeding was noted in a patient with corresponding INR of 3.0, which was treated with local pressure.

All published cases of clinically significant bleeding/bruising after plexus or peripheral techniques in patients with normal^{214–225} and abnormal^{226–231} hemostasis are reported in Tables 13 and 14. In all patients with neurodeficits, neurologic recovery was complete within 6 to 12 months. Thus, whereas 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 13 patients with bleeding complications after peripheral or plexus block in patients without anticoagulation, 5 were serious and required hospitalization, transfusion, and/or surgical intervention (including 1 emergency tracheostomy after traumatic stellate block; Table 13). Of the 13 complications, 2 occurred after lumbar sympathetic or paravertebral techniques. There were also 13 cases of hemorrhagic complications associated with peripheral or plexus block in patients receiving antithrombotic therapy before and/or after block (Table 14). Twelve of these complications were serious, including 1 death due to massive hemorrhage after lumbar sympathetic block in a patient receiving clopidogrel. In all but 1 patient, hospitalization was complicated and prolonged. Nearly half of the patients received enoxaparin within 24 hrs of the technique. Although this may implicate LMWH, it is also representative of the orthopedic patients who undergo lower extremity block and are subsequently undergo thromboprophylaxis. Three of the patients were receiving NSAIDs only.

This series of 26 patients is insufficient to make definitive recommendations. However, trends that may assist with patient management are evolving. For example, these cases 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 after the deep plexus/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. Although needle/or catheter placement was described as difficult, there is often no evidence of vessel trauma (including the patient death from massive bleeding).

11.0 Anesthetic Management of the Patient Undergoing Plexus or Peripheral Block

- 11.1 For patients undergoing deep plexus or peripheral block, we recommend that recommendations regarding neuraxial techniques be similarly applied (Grade 1C).

German and Belgian Guidelines for Thromboembolism Prophylaxis and Regional Anesthesia

Every year, several million neuraxial blocks are performed in Europe, the majority on patients undergoing inpatient surgery

who receive thromboembolic prophylaxis, usually with either unfractionated or LMWH. The reported incidence of clinically important spinal bleeding resulting in permanent neurological lesions is extremely low. It is important to note that 70% to 75% of neuraxial blocks performed in Europe are single-dose spinal anesthetics; continuous epidural techniques account for only 19% of central blocks.⁹⁹

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.²³² A comparison of the Belgian Association for Regional Anesthesia⁶⁸ with those of the German Society for Anaesthesiology and Intensive Care¹⁰³ and those of ASRA reveals several similarities as well as differences (Table 15). The management of patients receiving thrombolytics, UFH, and antiplatelet therapy is remarkably similar. As expected, the ASRA guidelines for LMWH are much more conservative than the corresponding European statements owing to the large number of hematomas in North America. It is notable that an indwelling epidural catheter during single-daily dosing of LMWH is still considered safe in Europe. However, if the patient is receiving antiplatelet therapy, LMWH will not be administered 24 before needle placement and/or catheter removal. An additional major difference is the management of the patient receiving fondaparinux. The German guidelines allow maintenance of an indwelling epidural catheter, although this is recommended against in both the Belgian and the ASRA statements. Finally, both European guidelines support neuraxial techniques (including continuous epidural analgesia) in the presence of direct thrombin inhibitors. However, this is relatively contraindicated by the ASRA guidelines owing to the prolonged half-life (particularly in patients with renal insufficiency), narrow therapeutic window and limited available safety information. Finally, only the ASRA guidelines address management of plexus and peripheral blocks in the anticoagulated patient. The ACCP⁷ has informally collaborated with ASRA on the performance of neuraxial and peripheral nerve blocks in patients receiving antithrombotic drugs.

The ACCP recommendations are included in Table 15 and reflect a somewhat more conservative approach with warfarin (limit epidural analgesia <48 hrs) and more liberal recommendations with LMWH (epidural analgesia allowed with twice-daily dosing). The ACCP also recommends that deep peripheral blocks be managed similar to neuraxial techniques.

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 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 in 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. This “pharmacy fail-safe” allows the Pain Service to participate proactively in the timing of catheter removal and subsequent anticoagulation as well as to closely monitor the patient’s neurologic status.²³³

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 neuraxial anesthesia and anticoagulation. They are based on case reports, clinical series, pharmacology, hematology, and risk factors for surgical bleeding. 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 should be made on an individual basis, weighing the small, although definite risk of spinal hematoma with the benefits of regional anesthesia for a specific patient. Alternative anesthetic and analgesic techniques exist for patients considered an unacceptable risk. 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 seems 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 the series of Vandermeulen et al,³⁴ although 87% of patients had a hemostatic abnormality or difficulty with needle puncture, 13% had no identifiable risk factor. Vigilance in monitoring is critical to allow early evaluation of neurologic dysfunction and prompt intervention. Protocols must be in place for urgent magnetic resonance imaging and hematoma evacuation if there is a change in neurologic status. We must focus not only on the prevention of spinal hematoma but also on rapid diagnosis and treatment to optimize neurologic outcome.

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