There is limited evidence to discontinue antiplatelet therapy with platelet aggregation inhibitors to avoid bleeding and epidural hematomas and/or to continue antiplatelet therapy clopidogrel (Plavix), ticlopidine (Ticlid), or prasugrel (Effient) during interventional techniques to avoid cerebrovascular and cardiovascular thromboembolic fatalities.

There is limited evidence in reference to newer antithrombotic agents dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) to discontinue to avoid bleeding and epidural hematomas during interventional techniques and to continue to avoid cerebrovascular and cardiovascular thromboembolic events.

Recommendations: The recommendations derived from the comprehensive assessment of the literature and guidelines are to continue NSAIDs and low dose aspirin, and phosphodiesterase inhibitors (dipyridamole, cilostazol, Aggrenox) during interventional techniques. However, the recommendations for discontinuation of antiplatelet therapy with platelet aggregation inhibitors (clopidogrel, ticlopidine, prasugrel) is variable with clinical judgment to continue or discontinue based on the patient's condition, the planned procedure, risk factors, and desires, and the cardiologist's opinion. Low molecular weight heparin (LMWH) or unfractionated heparin may be discontinued 12 hours prior to performing interventional techniques. Warfarin should be discontinued or international normalized ratio (INR) be normalized to 1.4 or less for high risk procedures and 2 or less for low risk procedures based on risk factors. It is also recommended to discontinue Pradaxa for 24 hours for paravertebral interventional techniques in 2 to 4 days for epidural interventions in patients with normal renal function and for longer periods of time in patients with renal impairment, and to discontinue rivaroxaban for 24 hours prior to performing interventional techniques.

Limitations: The paucity of the literature.

Conclusion: Based on the available literature including guidelines, the recommendations in patients with antithrombotic therapy for therapy prior to interventional techniques are provided.

Key words: Perioperative bleeding, bleeding risk, practice patterns, anticoagulant therapy, antithrombotic therapy, interventional techniques, safety precautions

Among various issues facing interventional pain physicians on a daily basis, bleeding risk and perioperative management of patients on anticoagulants and antithrombotic therapy is one of the major ones without appropriate guidance or literature to support the existing opinions. The majority of guidelines developed thus far are not based on appropriate evidence, due to the paucity of evidence in this area. Cardiovascular and cerebrovascular diseases are among the leading causes of morbidity and mortality (1-5), and chronic persistent pain is the leading cause of disability and functional impairment across the globe (6-13). Thus, chronic persistent pain and cardiovascular disease are associated with significant impairment of physical and psychological health and performance of social responsibilities, including work and family life (1-13). Antithrombotic therapy has been established with a favorable risk benefit ratio for prevention of cardiovascular disease and in limiting the present and future burden of cardiovascular and cerebrovascular disorders (14-36). It has been estimated that a significant proportion of patients with cardiovascular, cerebrovascular, or peripheral vascular disease, receiving antithrombotic therapy, undergo surgical interventions including interventional techniques.

Interventional techniques are performed with increasing frequency to manage chronic persistent pain, even though it is often debated in reference to their effectiveness, safety, and appropriate indications (37-80). Based on a recent survey it appears that the majority of interventional pain physicians discontinue antiplatelet therapy and anticoagulant therapy (81), even though continuation of antithrombotic therapy is considered as "safe" (82-84). Based on the multiple guidelines published with evidence derived from case reports, it has been generally accepted to stop antiplatelet therapy and is considered as standard of care by some (85-95). However, there is also significant disagreement among the guidelines. Even though, epidural hematomas have been reported in one in 150,000 of all epidurals, the incidence has been higher in cervical and thoracic spine. There is also a trend of increasing epidural hematoma cases following neuraxial blocks (81,88,89,96,97); however, one report indicates decreasing tendencies (98). Epidural hematoma is a serious complication that may result in spinal cord injury but only occurs with proce-

dures that involve placing a needle into the spinal canal (i.e. posterior interlaminar epidural steroid injection). Epidural hematoma is not a risk of injections of the exterior spine such as medial branch blocks.

The risks of withdrawing antiplatelet therapy include cardiovascular, cerebrovascular, and peripheral vascular thrombosis which may results in ominous consequences including stroke and death. In a systematic review and meta-analysis of the hazards of discontinuing or not adhering to aspirin regimens among patients at risk for coronary artery disease (14), noncompliance or withdrawal of aspirin treatment was associated with significant complications in those with or at moderate to high risk for coronary artery disease. This study showed aspirin non-adherence or withdrawal being associated with a 3-fold higher risk of major adverse cardiac events which was magnified in patients with intracoronary stents with the conclusion that aspirin discontinuation in such patients should be advocated only when bleeding risk clearly overwhelms that of atherothrombotic events. In a study of the evaluation of incidence of death and acute myocardial infarction (MI) associated with the discontinuation of clopidogrel (Plavix®) after acute coronary artery syndrome (19), the authors observed a clustering of adverse events in the initial 90 days after discontinuation among both medically treated and percutaneous coronary intervention treated patients with acute coronary syndrome, supporting the possibility of clopidogrel rebound effect. It has been described that more than two-thirds of the sudden cardiac events (acute coronary syndrome or sudden cardiac death) (99-101) and half of the postoperative MIs (99,102-105) are due to the disruption and thrombosis of an unstable plaque. The data on cerebrovascular events are not known; however, acute coronary syndrome is linked with pro-inflammatory and pro-thrombotic conditions that involve an increase in fibrinogen, C-reactive protein, and plasminogen activator inhibitor (106). Thus, in the postoperative setting, the risk of acute coronary syndrome is further aggravated by augmented release of endogenous catecholamines, increased platelet adhesiveness, and decreased fibrinolysis, which are characteristic of the acute phase reaction (104,107,108).

It has also been described that stoppage of antiplatelet therapy may result in either hypercoagulability with thrombosis or bleeding complications (14,17,18,109-148). Studies assessing the risk of maintaining antiplatelet therapy have shown increased surgical blood loss of 2.5% to 20% with aspirin and 30% to 50% with aspirin and clopidogrel (126,149). However, no increase in surgical mortality has been linked to the increased bleeding, except during intracranial surgery (115,126). An average increase of 30% in transfusion rate with a complication rate of red blood cell transfusion in only 0.4% of the patients (150) and mortality linked directly to massive surgical blood loss of less than 3% has been reported (151). However, the risks of withdrawing the antiplatelet therapy also have been described with a rebound effect with increased platelet adhesiveness (130,132,136,137); simultaneously, the systemic inflammatory syndrome and the acute phase reaction to surgery increases platelet adhesiveness and decreases fibrinolysis (27,99,104); and some pathologies, such as carcinoma and diabetes, are accompanied by hyper-coagulability. It has also been shown that infarction and death rates in acute coronary syndrome were doubled (136). Further, during the re-endothelialization phase of coronary stents, a myocardiac infarction rate of up to 85% due to stent thrombosis has been reported in one postoperative study (141) with an increase of the perioperative cardiac death rate by 5 to 10 times, compared to the average stent thrombosis of 35% and the average mortality of stent thrombosis of 20% to 40% (17,99,138,152) without noncardiac surgery.

Based on the available information, the risks of coronary events from withdrawing patients from antiplatelet agents in the perioperative period are generally higher than those of maintaining them through the perioperative period. Thus, Chassot et al (99) recommended that it is necessary to modify the approach of withdrawing patients from all antiplatelet agents 7 to 10 days before surgery, except when bleeding might occur in a closed cavity. After a comprehensive literature review, they (99) also proposed that even if large prospective studies with a high degree of evidence are still lacking on different antiplatelet regimens during noncardiac surgery, apart from low coronary risk situations, patients on antiplatelet drugs should continue their treatment throughout surgery, except when bleeding might occur in a closed space. They also recommended consideration of a therapeutic bridge with shorter-acting antiplatelet drugs. In fact, multiple guidelines have provided variable guidance (81-86,90-95,153-166). In a systematic review, Dunn and Turpie (156) after evaluating 31 reports concluded that most patients can undergo dental procedures, arthrocentesis, cataract surgery, and diagnostic endoscopy without alteration of their anticoagulant regimen; however, for

other invasive and surgical procedures, oral anticoagulation needs to be withheld and the decision whether to pursue an aggressive strategy of perioperative administration of intravenous heparin or subcutaneous low LMWH should be individualized. In a 2003 publication (167), current practice in the use of antiplatelet agents in the perioperative period by vascular surgeons showed that the general consensus of opinion from their survey suggested that most vascular surgeons do not stop antiplatelet drugs preoperatively. In fact, multiple recent publications also illustrated that endoscopy (160,163), peripheral vascular surgery (161), and ophthalmic surgery (165) show no evidence of increased bleeding when the antiplatelet agents were continued through the perioperative period. In addition, Gerstein et al (166) also showed that for many operative procedures, the risk of perioperative bleeding while continuing aspirin is minimal, as compared with the concomitant thromboembolic risks associated with aspirin withdrawal. Lip et al (165), in evaluating perioperative management of ophthalmic patients taking antithrombotic therapy, based on the current evidence, recommended the continued use of aspirin and, with some exceptions, warfarin in the perioperative period. They described that the risk of thrombosis-related complications and disruption of anticoagulation may be higher than the risk of significant bleeding by continuing its use for most types of ophthalmic surgery. With the increasing performance of interventional procedures over the years, the number of patients undergoing interventional techniques, with not only coronary artery stenting, but a multitude of other cardiovascular, peripheral vascular, and cerebrovascular risk factors may be increasing. Thus, interventional pain physicians managing these patients are confronted with the complex issue of weighing the risks of hemorrhagic complications when continuing the antiplatelet agents in the perioperative period against the risk of cerebral and cardiovascular events if the drugs are discontinued abruptly. Even though data suggest that traditional attitude of discontinuing the medication 7 days before interventions poses considerable risk, multiple guidelines recommend these polices and it has been a general practice to discontinue these drugs (81-99). A recent evaluation by Manchikanti et al (82) of over 18,000 procedures with over 12,000 encounters and over 3,000 patients, showed no significant prevalence of adverse events observed in those who continued with or ceased antithrombotic therapy. In addition, another issue related to interventional pain management is that most

reports are related to regional anesthesia for surgical procedures, with few reports of epidural hematoma in patients undergoing interventional techniques for chronic pain with or without antithrombotic therapy – continued or discontinued.

Thus, this comprehensive review with best evidence synthesis is undertaken to evaluate the role of the risk of bleeding in interventional pain management, with a best evidence synthesis of practice patterns and perioperative management of anticoagulant and antithrombotic therapy.

1.0 Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and a meta-analysis of randomized trials and observational studies (168-170), and Standards for Reporting Observational Studies (STROBE) (170).

1.1 Criteria for Considering Studies for This Review

1.1.1 Types of Studies
Randomized controlled trials
Non-randomized observational studies
Case reports and reviews

1.1.2 Types of Facilities
Hospital outpatient facilities, ambulatory surgery centers (ASCs), and office practices performing interventional techniques were included.

1.1.3 Types of Interventions
All types of interventions, from simple injections to major procedures such as disc decompression and implantables, were included.

1.1.4 Types of Outcome Measures
The primary objectives were to assess overall bleeding risk and risk of thrombosis in patients receiving anticoagulant or antiplatelet therapy undergoing interventional techniques.

1.2 Literature Search
Searches were performed from the following sources without language restrictions:
1. PubMed from 1966
   www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
2. EMBASE from 1980

www.embase.com
3. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
4. U.S. National Guideline Clearinghouse (NGC)
   www.guideline.gov
5. Previous systematic reviews and cross references
6. Clinical Trials
   www.clinicaltrials.gov
7. FDA
   www.fda.gov

The search period was from 1966 through December 2012.

1.3 Search Strategy

The search strategy emphasized bleeding risk, antithrombotics, antiplatelets, cardiovascular events, cerebrovascular events, thrombotic events, interventional techniques, bleeding complications, and epidural hematoma related to interventional techniques.

At least 2 of the review authors independently, in an unblinded standardized manner, performed each search. Accuracy was confirmed by a statistician. All searches were combined to obtain a unified search strategy. Any disagreements between reviewers were resolved by a third author and consensus.

1.4 Data Collection and Analysis

The review focused on all types of reports including case reports and reviews.

1.4.1 Selection of Studies

♦ In an unblinded standardized manner, 2 review authors screened the abstracts of all identified studies.

♦ All articles with possible relevance were then retrieved in full text for comprehensive assessment.

1.4.2 Methodological Quality or Validity Assessment

Due to the inherent difficulty with the literature describing adverse effects such as bleeding and rare occurrence of fatal complications of thrombosis and bleeding, all available literature was included without methodologic quality or validity assessment. However, critical assessment of the literature was performed.

Each study was evaluated by at least 2 authors and any disagreements about conclusions were discussed with a third reviewer. Authors with a perceived conflict of interest for any manuscript were recused from reviewing the manuscript.

1.4.3 Data Extraction and Management

Two review authors independently, in an unblinded standardized manner, extracted the data from the included studies. Disagreements were resolved by discussion between the 2 reviewers; if no consensus could be reached, a third author was called in to break the impasse.

1.5 Summary Measures

Summary measures included fatal thrombotic and bleeding events and other complications.

1.6 Analysis of Evidence

Due to the nature of the issue and available literature, criteria developed by the United States Preventive Services Task Force (USPSTF) (171) or other criteria could not be utilized, thus, the evidence was analyzed based on a preponderance indicating causal relationship.

2.0 Results

An extensive search of the literature yielded multiple manuscripts (81-98,172-400). The majority of the reports were case reports except for some guidelines and studies of assessment of bleeding and thromboembolic risk.

2.1 Risk of Bleeding with Interventional Techniques

Table 1 shows multiple studies conducted to assess the risk of bleeding and thrombolic events (81-84,91,96,173,174, 195,197,218,229,255,298).

2.2 Case Reports of Spontaneous or Traumatic Epidural Hematoma

Table 2 shows the case reports of spontaneous epidural hematoma or bleeding complications.

Overall, there were 41 case reports which were available with descriptions (181,202,203,207,208,223,225,231,232,245,260,261,263,275, 278, 295,319,334,335,337,343-345,348-352,357,358, 362,365,367,368,373,376,378-380,383,385). Some case reports were not available (347,347). Further, many of them may not have been reported. There were 5 case reports of spontaneous epidural hematoma following chiropractic manipulation and strenuous activity (203,208,231,383,385).

Table 3 shows the case reports of bleeding and epidural hematoma associated with interventional techniques in the absences of antithrombotic therapy. At least 8 case reports of epidural hematoma associated with antithrombotic therapy with interventional

Table 1. *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Manchikanti et al, 2012 (81)	An online physician survey of antithrombotics in interventional pain management was designed incorporating various aspects of practices including practice setting, limits on international normalized ratio (INR) when patients were on warfarin, routine practices on stopping Coumadin, practice patterns on discontinuing antithrombotic or related agents such as aspirin and other agents, experience with complications when antiplatelet therapy was continued or it was discontinued, any testing utilized for assessment of antiplatelet therapy, and finally, total number of procedures performed per year and the number of years in the practice. The online survey was e-mailed to 2,300 physicians and 325 replied.	The results illustrate an overwhelming pattern of discontinuing antiplatelet and warfarin therapy as well as aspirin and other NSAIDs prior to performing interventional pain management techniques. However, thromboembolism complications may be 3 times more prevalent than epidural hematomas (162 versus 55 events). It is concluded that clinicians must balance the risks of thromboembolism and bleeding in each patient prior to the routine discontinuation of antiplatelet therapy.	Even though, there is an overwhelming pattern of discontinuing antiplatelet and warfarin therapy as well as aspirin and other NSAIDs prior to performing interventional pain management techniques, thromboembolism complications may be 3 times more prevalent than epidural hematomas (162 versus 55 events). The authors concluded that clinicians must balance the risks of thromboembolism and bleeding in each patient prior to the routine discontinuation of antiplatelet therapy.	This study essentially shows that even though there is no evidence of increased risk of epidural hematoma, the majority of physicians discontinue antiplatelet therapy despite increased risk of thromboembolic complications. While this study shows a direction that discontinuation of antithrombotic therapy may not be the ideal, it does not provide conclusive evidence that they should be continued without potential risks.
Manchikanti et al, 2011 (82)	The prospective evaluation was performed utilizing the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement which was developed with recommendations to improve the quality of reporting observational studies. Measurable outcomes employed were intravascular entry of the needle, bruising, local bleeding, profuse bleeding, local hematoma, oozing, and postoperative soreness.	The results of this study illustrated that in one-quarter (3,087) of patient encounters utilizing interventional pain management techniques, antithrombotic therapy was included. Among these, for approximately 55%, or 1,711 encounters, antithrombotic therapy was continued during the interventional techniques, whereas, for 45%, or 1,376 encounters, antithrombotic therapy was discontinued.	Overall, these results illustrate that while intravascular penetration and oozing were higher in patients with continued antithrombotic therapy, bruising and local bleeding were higher in patients with discontinued antithrombotic therapy without any difference either statistical or clinical in any of the other aspects, either intraoperative, post procedure in the recovery room, or postoperative period.	This study essentially shows that there is no significant difference in bleeding patterns whether antithrombotic agents are continued or discontinued except for warfarin with no fatal incidents in a large proportion of patients.
Horlocker et al, 1995 (83)	1,000 orthopedic procedures performed under spinal or epidural anesthesia in 924 patients were studied prospectively. Preoperative antiplatelet therapy was defined as aspirin one week prior to surgery or any other nonsteroidal antiinflammatory drug such as ibuprofen, naproxen, piroxicam, and diclofenac 3 days prior to surgery. Anesthetic technique (spinal or epidural, single-dose or continuous catheter), needle gauge, approach (midline, paramedian, or both), and duration of an indwelling epidural catheter (if used) was noted.	There were 511 (51%) surgical procedures performed on males and 489 (49%) on females. There were no documented major hemorrhagic complications – spinal hematomas. Preoperative antiplatelet therapy did not increase the incidence of minor hemorrhagic complications. Female gender, increased age, history of excessive bruising/bleeding, surgery to the hip, continuous catheter anesthetic technique, large needle gauge, multiple needle passes, and moderate or difficult needle placement were all significant risk factors.	The lack of correlation between antiplatelet medications and bloody needle or catheter placement (producing clinically insignificant collection of blood in the spinal canal or epidural space) is strong evidence that preoperative antiplatelet therapy is not a significant risk factor for the development of neurologic dysfunction from spinal hematoma in patients who undergo spinal or epidural anesthesia while receiving these medications.	The results of this study strongly show that discontinuation of antiplatelet therapy is not essential and is not associated with major hemorrhagic complications, even though discontinuation is associated with minor hemorrhagic complications. The interesting aspect is that this was performed in patients with chronic pain undergoing epidural injections. However, this does not include chronic pain management and interventional techniques.

Table 1 (cont). *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Horlocker et al, 1990 (84)	Hospital records of 805 patients given 1,013 epidural or spinal anesthetics who were undergoing orthopedic procedures were retrospectively studied. Preoperative antiplatelet medications were administered before 391 (39%) of the operations, and 113 of 391 were receiving multiple drugs.	No patient developed signs of spinal hematoma or postoperative neurological deficits. The combination of increased age and epidural, but not spinal, anesthesia was associated with a 4.5% incidence of minor hemorrhagic complications.	Patients receiving antiplatelet medications had increased incidences only of minor hemorrhagic complications with no major hemorrhagic complications with spinal hematoma or postoperative neurological deficits. Aspiration of blood through the spinal or epidural needle may not imply an increased risk for serious hemorrhagic complications.	Overall authors concluded that patients receiving preoperative antiplatelet medications can safely undergo major regional anesthesia, however, the disadvantage for this study is that this was performed in patients undergoing surgical interventions rather than interventional techniques for chronic pain management.
Bugada et al, 2011 (91)	To evaluate how Italian anesthesiologists use different antithrombotic drugs in relation with different regional anesthetic techniques, both neuraxial and peripheral nerve blocks. Data were collected from a questionnaire sent, in March 2011, to anesthesiologists from 66 hospitals, with a response rate of 45.45%. The sampled data (a total of 203,542 surgical procedures performed in 201) were derived from a wide variety of hospitals with many different surgical settings.	Regional analgesia/anesthesia was used in 38.9% of the procedures. The results showed 43.3% of the respondents do not discontinue aspirin and 67% do not discontinue other NSAIDs. Whereas 56.7% did discontinue aspirin and other NSAIDs before performing the block for a mean duration of 4.93 days, ranging from 1 to 10 days. 47% of respondents also stated that they use bridging-therapy with low molecular weight heparin while patients are not taking aspirin. All of them (100%) discontinued antiplatelet drugs before performing neuraxial blocks, with a mean time of 9.76 days before and 89.5% using a bridging therapy to surgery with low molecular weight heparin.	The authors concluded that more studies and guidelines are required to provide a better knowledge on the use of antithrombotic drugs, in order to lead to more accurate guidelines and to reduce hemorrhagic risk. Authors are also extremely concerned that not all the responders strictly followed the guidelines. Further, they concluded that in many cases authors from different countries do not agree with each other and suggest different behaviors.	This study is related to Italian anesthesiologist's practice patterns when providing regional anesthesia. There is no consensus except that all respondents discontinue antiplatelet drugs and also add a bridging therapy with low molecular weight heparin even for aspirin.
Horlocker et al, 2002 (96)	A total of 1,214 epidural steroid injections in ambulatory pain centers were prospectively studied. The presence of antiplatelet effect was defined by the duration of platelet inhibition as measured by response to adenosine diphosphate, epinephrine, and/or collagen, i.e., one week for aspirin and one day for ibuprofen. However, no actual platelet function studies were performed. Regional technique (single dose or continuous epidural), level of needle placement (cervical, thoracic, lumbar, or caudal), needle gauge, needle approach (midline or paramedian), and elicitation of a paresthesia during needle/catheter placement were noted. The presence of blood or blood-tinged fluid in the needle or catheter (minor spinal bleeding) was recorded. Bleeding from obvious trauma to soft tissue was not included. The number of needle passes by pain center personnel was assessed.	32% of the patients were receiving nonsteroidal antiinflammatory agents including 34 patients on multiple medications. Aspirin was the most common NSAID and was noted by 158 patients including 140 patients on 325 mg or less per day. There were no major hemorrhage complications with spinal hematomas. There were minor hemorrhagic complications with blood during the needle or catheter placement in 5.2% of the patients. NSAIDS did not increase the frequency of minor hemorrhagic complications. Increased age, needle gauge, needle approach, needle insertion at multiple interspaces, number of needle passes, volume of injectate, and accidental dural puncture were all significant risk factors for minor hemorrhagic complications.	Authors concluded that these results confirm those of previous studies performed in obstetric and surgical populations that document the safety of neuraxial techniques in patients receiving NSAIDS. They concluded that epidural steroid injection is safe in patients receiving aspirin-like antiplatelet medications. Minor worsening of neurologic function may occur after epidural steroid injection and must be differentiated from etiologies requiring interventions.	The results of this study strongly show that discontinuation of antiplatelet therapy is not essential and is not associated with major hemorrhagic complications, even though discontinuation is associated with minor hemorrhagic complications. The interesting aspect is that this was performed in patients with chronic pain undergoing epidural injections.

Table 1 (cont). *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Lee et al, 2004 (173)	The American Society of Anesthesiologists Closed Claims Project is a structured evaluation of adverse anesthetic outcomes collected from closed anesthesia malpractice insurance claims of professional liability companies. An in-depth analysis of 1980–1999 regional anesthesia claims was performed with a subset comparison between obstetric and non-obstetric neuraxial anesthesia claims. Of the total 1,005 regional anesthesia claims, neuraxial blockade was used in 368 obstetric claims and 453 of 637 non-obstetric claims (71%).	The study reported 36 cases of hematomas associated with vascular (56%), orthopedic (22%), general surgery (11%), obstetrics (8%), and urologic procedures (3%). There were no neuraxial injuries associated with hematoma. Epidural hematoma claims were 33 of total 1,005 regional anesthesia claims. Overall, hematoma was considered as the most common cause of neuraxial injury, and the majority (72%) of these cases was associated with either intrinsic or iatrogenic coagulopathy.	Authors concluded that neuraxial cardiac arrest and neuraxial hematomas associated with coagulopathy remain sources of high-severity injury.	The results of this study for regional anesthesia show epidural hematomas mostly related to catheters in patients with coagulopathy. No significant data is available in reference to discontinuation of antiplatelet therapy.
Cook et al, 2009 (174)	A 2 week national census estimated the number of central neuraxial block procedures performed annually in the UK National Health Service. All major complications of central neuraxial blocks performed over one year (vertebral canal abscess or hematomas, meningitis, nerve injury, spinal cord ischaemia, fatal cardiovascular collapse, and wrong route errors) were reported. Each case was reviewed by an expert panel to assess causation, severity, and outcome. "Permanent" injury was defined as symptoms persisting for more than 6 months. Efforts were made to validate denominator (procedures performed) and numerator (complications) data through national databases. The study also included 27,975 procedures performed for chronic pain patients.	The census phase produced a denominator of 707,455 central neuraxial blocks. Eighty-four major complications were reported, of which 52 met the inclusion criteria at the time they were reported. This study reported a total of 20 epidural abscesses, 5 cases of epidural hematomas.	Authors concluded that the data are reassuring and suggest that central neuraxial blockade has a low incidence of major complications, many of which resolve within 6 months. Authors reported a total of 5 vertebral canal hematomas were reported, all in patients receiving epidural or spinal injection. No details were available in reference to anticoagulant status in the patients developing epidural hematoma.	Authors reported 5 cases of vertebral canal hematomas from a total of 52 cases meeting the inclusion criteria; however, no particulars are given and these hematomas developed in patients undergoing regional anesthesia.
Wu & Perkins, 1996 (195)	A retrospective review was made of the charts of 459 patients who underwent hip pinning or hip or knee replacement under regional anesthesia and received postoperative epidural analgesia and warfarin thromboembolism prophylaxis. The number of patients receiving preoperative antiplatelet therapy and warfarin, as well as baseline coagulation parameters, was documented. For patients who had postoperative epidural analgesia, the prothrombin time on the day of epidural catheter removal was obtained. Neurologic complications during the hospital stay were noted.	Blood on needle or catheter insertion was noted in 21 patients, all of whom were taking antiplatelet medication and/or warfarin. Epidural catheters remained postoperatively for a mean of 43.6 +/- 12.5 hours (range 5 - 118 hours). The mean prothrombin time on the day of epidural catheter removal was 14.1 +/- 3.2 seconds. Four postoperative peripheral neuropathies were detected. There was no clinical evidence of spinal hematoma in any patient.	Authors concluded that epidural catheter placement and removal in patients taking oral anticoagulants appears to be safe; however, careful monitoring of patients for evidence of spinal hematoma after epidural catheter removal is recommended.	This reported hematoma formation in regional anesthesia in patients on antiplatelet therapy as well as warfarin therapy with no occurrence of epidural hematomas.
Liu et al, 2011 (197)	Over 4,300 patients undergoing total joint replacement followed by daily warfarin thromboprophylaxis were enrolled in this observational study. All nonsteroidal anti-inflammatory drugs and anticoagulants were held before surgery, and all patients had normal coagulation test results before surgery. Only patients with INR greater than 1.4 at the time of removal of epidural catheter were included. Neurologic checks were performed for 24 hours after removal.	A total of 4,365 patients were included, and 79% underwent knee replacement and 18% hip replacement. Mean age was 68 years, and mean weight was 81 kg. Mean (SD) duration of epidural analgesia was 2.1 (0.6) days. Mean (SD) INR at the time of epidural removal was 1.9 (0.4), ranging from 1.5 to 7.1. No spinal hematomas were observed (0% incidence with 95% confidence interval, 0% - 0.069%).	Authors concluded that in their series of 4,365 patients catheter removal was uncomplicated despite INRs ranging from 1.5 to 5.9.	This study indicates that epidural catheter may be removed even when INR is high.

Table 1 (cont). *Studies assessing the risk of thrombosis and bleeding with interventional pain management techniques.*

Study/Year	Methods	Results	Conclusions by the Study Authors	Author Conclusions of the Review
Horlocker et al, 1994 (218)	The relative safety of epidural catheter placement and the risk of neurologic sequelae in patients receiving warfarin perioperatively were assessed retrospectively. The study also assessed the risk of spinal hematoma in patients receiving postoperative epidural analgesia while receiving low dose warfarin after total knee replacement. All patients received low dose warfarin to prolong the prothrombin time to 15 to 17.3.	There were 192 epidural catheters placed in 188 patients. In addition to warfarin, 36 patients with indwelling catheters received nonsteroidal antiinflammatory drugs. Epidural catheters were left indwelling for 13 to 96 hours. The mean PT was not increased beyond the normal range until the third postoperative day and did not reach 15 seconds until the seventh postoperative day. There were no signs of spinal hematoma.	Authors concluded that even though epidural catheter placement and subsequent anticoagulation with warfarin appears relatively safe, there is a large variability in patient response to warfarin. Consequently, coagulation status should be monitored to avoid excessive prolongation of the PT, and the patient should be watched closely for evidence of spinal hematoma.	This is a small study performed earlier by the same authors with larger studies later on concluding there is large variability in the warfarin metabolism. Consequently, coagulation status should be monitored to avoid excessive prolongation of the PT and potential spinal hematoma. The study was conducted for regional anesthesia in the perioperative period.
Wulf, 1996 (229)	Authors evaluated epidural anesthesia and spinal hematoma and conducted a comprehensive review of case reports.	51 confirmed spinal hematomas associated with epidural anesthesia were found. Most were related to the insertion of a catheter, a procedure that was graded as difficult or traumatic in 21 patients. Risk factors were fibrinolytic therapy in 2 patients, previously unknown spinal pathology in 2 patients, low molecular weight heparin in 2 patients, aspirin or other NSAID in 3 patients, epidural catheter inserted during general anesthesia in 3 patients, thrombocytopenia in 5 patients, ankylosing spondylitis in 5 patients, preexisting coagulopathy in 14 patients, and intravenous heparin therapy in 18 patients.	Authors concluded that coagulopathies or anticoagulant therapy were the predominant risk factors, whereas low-dose heparin thromboprophylaxis and NSAID treatment were rarely associated with spinal bleeding complications. Ankylosing spondylitis was identified as risk factor.	This comprehensive review assessed 51 confirmed spinal hematomas associated with epidural anesthesia. There were no reports related to epidurals performed for chronic pain.
Parvizi et al, 2007 (255)	Authors retrospectively ascertained, by chart review, the incidence of epidural hematoma in 11,235 patients having 12,991 knee arthroplasties. Patients were receiving oral anticoagulants and epidural anesthesia for their surgery with the exception of 212 patients where the epidural catheter was removed within 48 hours of surgery.	Based on clinical examination, there were no epidural hematomas. In patients where the detailed analysis was confirmed it was shown that mean INR at the time of the removal of the catheter was 1.54, ranging from 0.93 to 4.25.	Based on clinical examinations there were no epidural hematomas. Authors identified no other complications related to the coadministration of epidural anesthesia and warfarin. They concluded that even though administration of epidural anesthesia in patients with coagulopathy can be detrimental, there were no recognized cases of epidural hematoma causing neurologic symptoms in patients receiving controlled oral anticoagulation after total knee arthroplasty.	The study was conducted in regional anesthesia patients receiving warfarin in reference to removal of the catheter.
Fitzgibbon et al, 2004 (298)	Data from 5,475 claims in the American Society of Anesthesiologists Closed Claims Project database between 1970 and 1999 were reviewed to compare liability related to chronic pain management with that related to surgical or obstetric anesthesia. Acute pain management claims were excluded from analysis. Outcomes and liability characteristics between 284 pain management claims and 5,125 surgical/obstetric claims were compared.	Claims related to chronic pain management increased and accounted for 10% of all claims in the 1990s. Nerve injury with 53 claims was the most common outcome in invasive pain management claims. Epidural steroid injections was 40% of all chronic pain management claims. 32 of 63 nerve injury claims were related to spinal cord injury. Pneumothorax was also common. 2 claims for hematoma involving administration of epidural steroids in patients who received anticoagulants.	Authors concluded that frequency and payments of claims associated with chronic pain management by anesthesiologists increased in the 1990s. However, 2 of the 276 claims were related to epidural hematoma involving administration of epidural steroids in patients who received anticoagulants; however, no further information is provided in reference to if they were discontinued or continued.	American Society of Anesthesiologists claims analysis in chronic pain management shows epidural hematoma is a rare complication leading to malpractice claims. No conclusions regarding specific risk factors can be drawn from this study.

Table 2. *Descriptions of reports of spontaneous or traumatic bleeding.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Anderson & Donaldson, 1989 (181)	A patient with a spontaneous cervical spinal epidural hematoma was described. There was complete clinical and radiological resolution with non-operative treatment. This is the fifth recorded case of spontaneous resolution of spinal epidural hematoma as of publication of this case report in 1989.	Even though surgical decompression is generally recorded as mandatory, in selected patients with incomplete and non-progressing deficit, conservative management may be possible.	This case illustrates spontaneous cervical spinal epidural hematoma which is successfully managed conservatively without surgical intervention.
Urculo Bareño & Arrazola Schlamich, 1987 (202)	The author reported one case of spontaneous spinal epidural hematoma in the cervical spine of unknown etiology extending over C3 to C6. Cervical epidural hematoma was diagnosed by CT. The clinical picture was characterized by sudden onset of severe cervical or intrascapular pain, associated with radicular radiation into the upper extremities, followed by development of progressive signs of spinal cord compression with varying degree of motor and sensory paralysis. Complete recovery was accomplished after surgical treatment, within 36 hours after the onset of symptoms.	The authors emphasized the importance of an early diagnosis easily possible with CT in 1987. They also described that the CT findings are similar to intracranial acute epidural hematoma, showing a characteristic hyperdense lenticular collection, typically localized in the dorsal lateral spinal epidural space. They felt that the surgical indication is absolute.	This case report in 1987 is in contrast to the one published in 1989 which mandates surgical intervention.
Zupruk & Mehta, 1989 (203)	Post traumatic cervical epidural hematoma is an uncommon entity. This case report in 1989 presented post traumatic cervical epidural hematoma manifesting as Brown-Séquard syndrome which manifested after chiropractic manipulation of the neck. Both are rarities, namely cervical epidural hematoma as well as Brown-Séquard syndrome. The diagnosis was made with CT scanning and surgical evaluation of the hematoma was followed by full recovery.	The authors concluded that it is a rare phenomenon to have cervical epidural hematoma after chiropractic manipulation and at the same time to present with Brown-Séquard syndrome.	Chiropractic manipulation can cause cervical epidural hematoma specifically in patients with severe cervical spondylosis.
Crabbe et al, 1992 (207)	A healthy 20-year old male developed an extradural hematoma in his cervical spinal canal after an episode of "disco dancing" and "head banging." The following day he complained of neck pain, and 36 hours after this, he presented to the hospital complaining of weakness of his left arm and leg with sensory loss in his right leg. CT scan of the cervical spine showed an extradural hematoma located in the left side of the spinal canal between the levels of C4 and C6. The patient had symptoms of Brown-Séquard syndrome. The patient was treated with intravenous steroids and improved without surgical intervention.	The authors concluded that cervical spinal extradural hematoma causing a transient Brown-Séquard syndrome resolved with steroid therapy.	The study indicates either spontaneous epidural hematoma without needle placement or surgery with usual movements in dancing resolved with conservative management.
Whedon et al, 2006 (208)	A 79-year-old man with a past medical history of polymyalgia rheumatica, congestive heart failure, and atrial fibrillation, for which he was undergoing long-term anticoagulant therapy and underwent chiropractic manipulation.

Soon after his treatment, the patient developed signs of cord compression. Investigations showed injury to the cord. The patient was treated with fresh frozen plasma and vitamin K and underwent C4/5 laminectomies. Postoperatively, the patient slowly regained his strength; he was discharged to a rehabilitation center on postoperative day 5. At follow-up, several months after discharge, he had nearly full strength. | Authors concluded that practitioners of spinal manipulative therapy should be aware of spinal epidural hematoma as a possible complication of manipulation in patients at risk and should exercise caution in the care of patients undergoing anticoagulant therapy. | This case report shows chiropractic manipulation resulting in epidural hematoma in a patient with multiple cervical spine abnormalities despite appropriate diagnosis and surgical intervention the result was borderline taking several months to recover. |
| Nourbakhsh & Garges, 2007 (223) | This is a case report of hematoma of the lumbar spinal synovial joint in a 67-year old man on anticoagulant therapy who presented with progressive neurologic symptoms in the right lower extremity. MRI revealed a lesion which was thought to be a synovial joint cyst; however, during surgery, it was proven to be epidural hematoma originating from the synovial joint. The patient recovered completely with surgical decompression. | The authors stated that this was the first report of synovial cyst hematoma due to anticoagulant therapy but spontaneous without trauma. | The case report indicates that epidural hematoma can masquerade in many forms occurring without needle placement or surgery and proper diagnosis will yield appropriate recovery. |
| Song & Lee, 2005 (225) | This report presents 2 patients who had acute paraplegia with sensory loss due to spontaneous spinal epidural hematoma. One had myocardial infarction and the other had deep vein thrombosis and the former was treated with anticoagulants and the latter was treated with thrombolytic agent.

Postoperatively, both showed no improvement of neurological symptoms, and on follow-up of 12 months, one showed no neurological improvement and the other showed insignificant improvement of lower extremity muscle power. | The authors thought that this poor outcome was due to delayed operation, which was done more than 24 hours after symptom onset. The outcome in spontaneous spinal epidural hematoma is essentially determined by the time taken from symptom onset to operation, therefore they concluded early and precise diagnosis such as careful history taking and MRI evaluation is necessary. | The authors emphasize the prompt recognition and surgical decompression of epidural hematoma even in case of spontaneous epidural hematoma. |

Table 2 (cont.). *Descriptions of reports of spontaneous or traumatic bleeding.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Heiner, 2009 (231)	Cervical epidural hematoma after chiropractic spinal manipulation was reported in a healthy 38-year old female 4 hours after the short-term onset of numbness and pain in her neck and arms during cervical spinal manipulation therapy by a chiropractor. The diagnosis was made by MRI and MR angiography of the neck without contrast. This showed a right-sided epidural hematoma extending from the level of the foramen magnum to the C4 level with associated mass effect upon the spinal cord.	The patient was managed conservatively and 2 weeks after discharge, symptoms had completely resolved with minimal residual paraesthesias along the posterior part of her neck.	This case report illustrates conservative management in some cases is effective.
Abe et al, 2009 (232)	Spinal epidural hematoma after stretch exercise was reported in a 60-year old man with development of severe neck pain and rapidly progressing weakness of left arm. Appropriate diagnosis was made by MRI and the patient underwent surgical intervention with evacuation of hematoma. However, upper extremity weakness did not completely resolve.	They concluded that early diagnosis and treatment can confer a significant prognostic advantage to patients with spinal cord hematoma.	Spontaneous epidural hematoma successfully treated with proper diagnosis and appropriate intervention.
Ohaegbulam et al, 2008 (245)	Three cases were reported of lumbar epidural hematoma associated with spondylolysis. The first case was a 15-year old athletic male patient developing spontaneous epidural hematoma at the level of pars fracture. Diagnosis was made by MRI and the patient was managed conservatively, followed by physical therapy program for strengthening. The second patient was an 18-year old male ice hockey player who had experienced low back pain for 2 years prior to the onset. The diagnosis of spontaneous hematoma was diagnosed by MR imaging. It was managed conservatively with full recovery. Hematoma was at the level of spondylolisthesis. The third case was a 35-year old active male who experienced onset of back tightness the morning after playing soccer. Epidural hematoma was diagnosed. MR imaging obtained one month after symptoms developed showed an epidural collection of dorsolateral hematoma at L2/3 to the left with mild thecal sac compression. A CT scan of his lumbar spine revealed bilateral pars defects but no spondylolisthesis. The patient improved with conservative management.	The authors concluded that their report described the clinical and imaging findings in 3 cases of an epidural hematoma associated with spondylolysis. All cases resolved without surgery and without neurological deficit. This diagnostic possibility should be considered in the young active patient who experiences new or increased back or leg pain and it may be reasonable to avoid surgery in such cases in which there is reasonable certainty that the lesion noted on MR imaging is a hematoma and there is no progressive neurological deficit.	This study once again shows spontaneous epidural hematoma which can be resolved with conservative management.
Borges et al, 2000 (260)	Acute cervical epidural hematoma was reported in a 74-year old patient with a nocturnal onset of neck and chest pain which progressed to a flexed paralysis of the 4 extremities. Initially lumbar puncture was performed. Subsequently CT scan was done showing a large cervical epidural bleeding in the posterolateral region of C4/5 extending from C7 to T1 along with a C6 vertebral body hemangioma. A normal selective angiography of multiple arteries was observed. Spontaneous spinal epidural hematoma was diagnosed. The patient recovered completely.	The authors demonstrated that a rare case of spinal cord decompression and complete neurological recovery may supervene when the decompression is performed. They concluded that spontaneous spinal epidural hematoma is a rare condition with a rather unfavorable prognosis if left untreated.	Even though authors performed lumbar puncture and symptoms were relieved, MRI is the choice of assessment for the diagnosis.
Costabile et al, 1984 (261)	The authors reported 3 cases of spinal epidural hematoma, one lumbar, one cervical, and one thoracic. All were dorsolaterally localized, the first and third were dependent on the anticoagulant therapy and the second was spontaneous. The patients developed sudden onset of spinal pain, flaccid paralysis, and loss of sphincter control. The second case, with involvement of the cervical spine, also had a cervical anterior spinal cord syndrome with preoperative transient improvement, followed by the development of Brown Séquard syndrome with subsequent deterioration. The postoperative course was satisfactory in all patients with complete recovery in 2.	The authors opined that epidural hematoma may develop with or without anticoagulant therapy spontaneously and the cervical epidural hematoma may lead to Brown Séquard syndrome with subsequent deterioration.	This reports 3 cases of spontaneous epidural hematoma in 2 patients on anticoagulant therapy and in one patient without anticoagulant therapy.
Ng et al, 2002 (263)	The authors reported spinal epidural hematoma in a patient with thrombocytopenia with traumatic epidural hematoma presenting with right hemiparesis which progressed to complete tetraplegia. Postoperatively the patient improved significantly.	The authors opined that MRI is an important modality in the early diagnosis of spinal epidural hematoma and can facilitate emergent decompression surgery which offers the best chance of neurological improvement.	This case shows the importance of early diagnosis and decompression. The epidural hematoma developed without interventional techniques, but was related to trauma.

Table 2 (cont.). *Descriptions of reports of spontaneous or traumatic bleeding.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
	A 19-year-old male who presented with a 2-month history of neck pain and weakness of the upper and lower limbs without sensory deficit was reported. MRI showed features of anteriorly located cervical epidural hematoma. As the patient had started improving by the time he sought neurosurgical consultation, he was treated conservatively, and he improved over a period of 2 months. This case illustrates that, though rare, chronic spontaneous spinal epidural hematoma should be entertained in the differential diagnosis of cervical cord compression.	The authors concluded that chronic spontaneous spinal epidural hematoma is a rare cause of cervical cord compression. However, it should be entertained in the differential diagnosis of chronic cervical compressive myelopathy. Since spontaneous spinal epidural hematomas are known to resolve spontaneously, in properly selected cases, surgical intervention may not always be necessary.	Conservative management was effective treatment in this case.
Takano et al, 1994 (278)	The authors reported a rare case of acute cervical epidural hematoma caused by the hemorrhage from extradural arterio-venous malformation. The patient was a 74-year-old Japanese man with a past history of total gastrectomy after being diagnosed as having gastric cancer 12 years before. Six hours prior to admission, the patient had experienced a sudden episode of severe nuchal pain radiating to both scapular areas, followed by rapid development of left-side Brown-Sequard Syndrome below the C4 cord level, and urinary incontinence. Plain cervical X-ray films did not show any destructive lesion suggesting a metastatic tumor. T1 and T2 weighted images of MRI demonstrated a high intensity mass lesion, suggesting an acute epidural hematoma, extending from C3 to C6 and compressing severely the left side spinal cord posteriorly. Twelve hours after the onset of symptoms, an emergency laminectomy from C3 to C6 was performed and a fresh epidural clot with small vascular tissue was totally removed. Histological examination of the small vascular tissue in the hematoma revealed arterio-venous malformation. The postoperative recovery of the patient was dramatic. He regained full muscle strength and there was complete disappearance of sensory deficits 2 weeks after the operation.	The authors concluded that even though acute spinal epidural hematoma caused by extradural arterio-venous malformation is a rare clinical entity, MRI is the most helpful diagnostic tool for this condition. Further, they stressed that accurate neuroradiological diagnosis and prompt surgical decompression of the spinal cord are essential to obtain an excellent surgical outcome.	The study emphasizes once again that a high level of suspicion with appropriate diagnosis and rapid intervention results in avoidance of neurological dysfunction in many cases.
	The authors present the case of an adult woman, otherwise in good health, who developed Brown-Séquard syndrome after cervical spinal manipulation therapy. Decompressive surgery performed within 8 hours after the onset of symptoms allowed for complete recovery of the patient's preoperative neurological deficit.	The unique feature of this case was the MRI showing increased signal intensity in the paraspinal musculature consistent with a contusion, which probably formed after spinal manipulation therapy.	Another case of epidural hematoma after manipulation shows diagnosis could be occasionally difficult such as paraspinal musculature contusion coincidental with manipulative therapy.
Gundag et al, 2012 (319)	The authors reported a spontaneous resolution of paraparesis because of acute spontaneous thoracolumbar epidural hematoma. The patient presented 3 days after sudden onset of back pain, numbness, and weakness. MRI revealed a posterior thoracolumbar epidural hematoma extending from the level of T10 to L2 with significant cord compression. Decompression was recommended, but patient refused surgery and was managed conservatively. One month later, weakness totally disappeared and hematoma was absent on MRI.	Spontaneous epidural hematoma may be resolved spontaneously in some patients; however, these should always be considered in the differential diagnosis of other conditions. Since this was mild paralysis and he was recovering gradually, conservative treatment was a success.	Conservative management may be helpful in managing spontaneous epidural hematoma.
Kamo et al, 2012 (334)	The authors reported a case of subdural hematoma in the lumbar spine in a 75-year-old woman. MRI showed lesions of homogeneous high intensity in the spinal canal, findings closely resembling those for lipomatosis; however, epidural hematoma was diagnosed and patient was managed conservatively with full recovery after 2 weeks.	Authors share their experience of encountering of subacute phase of spinal subdural hematoma that mimicked spinal epidural lipomatosis of MR imaging. Even though it is extremely rare, authors caution that, subdural hematoma should be considered among the differential diagnosis for progressive spinal compressive syndrome.	Lipomatosis may present as spinal subdural hematoma and in this case improve with conservative management only.

Table 2 (cont.). *Descriptions of reports of spontaneous or traumatic bleeding.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Matsumoto et al, 2012 (335)	The authors reported 2 cases with spontaneous spinal epidural hematoma with hemiparesis mimicking acute cerebral infarction. In one case, the presentation was neck pain and in the other case, it was Lhermitte's sign; brain MRI and MR angiography were negative for signs of ischemic infarction, hemorrhage, or arterial dissection. Cervical MRI was performed and demonstrated spontaneous spinal epidural hematoma.	The authors concluded that clinicians who perform intravenous thrombolytic treatment with alteplase need to be aware of this possible contraindication.	It is essential to be cautious and entertain various types of diagnosis and manage appropriately.
Lo et al, 2012 (337)	A 61-year old female after finishing worshipping Buddha presented with sudden onset of severe neck and back pain followed by quadriparesis, sensory deficits below C4 level, and sphincter dysfunction. MRI demonstrated acute extensive epidural hematoma of cervicothoracic spinal segments. Idiopathic spontaneous spinal epidural hematoma was diagnosed and emergency decompressive laminectomy with hematoma evaluation was performed within 12 hours of symptom onset. Good functional and neurological outcomes were obtained.	The authors concluded that spontaneous spinal epidural hematoma is a rare but disabling or even fatal entity. Early diagnosis and prompt surgery improve the neurological and functional outcome.	A case of spontaneous spinal epidural hematoma with no risk factors with full recovery with surgical decompression.
Russman & Kazi, 1971 (343)	A 53-year old white female without trauma, but with hypertension developed an epidural hematoma at C6. Preoperative neurological lesion was on the left side at L5. The diagnosis was performed by myelogram and the patient deteriorated during myelogram. The patient developed residual Brown-Séquard syndrome.	The authors concluded that the syndrome is most commonly associated with penetrating trauma of the spinal cord or intramedullary lesions and in this case, its occurrence was associated with extramedullary lesion.	The authors caution that epidural hematoma can be originating from extramedullary lesion. Even myelography can deteriorate the patient's condition manifesting in fatal results.
Mustafa & Bernstein, 1987 (344)	A 70-year old female with no history of trauma developed a cervical spinal hematoma at C5/6 with factor 11 deficiency. Diagnosis was by myelogram with full recovery.	Another case of cervical epidural hematoma with Brown-Séquard syndrome which was spontaneous in nature.	Another case of spontaneous epidural hematoma resulting in Brown-Séquard syndrome.
Mattle et al, 1987 (345)	A 46-year old male with no history of trauma on anticoagulant therapy after myocardial infarction developed a cervical epidural hematoma at C7/T1 resulting in Brown-Séquard syndrome. The diagnosis was made by myelogram with full ambulation.	This is a case of anticoagulant therapy leading to spontaneous hematoma without trauma with full ambulation with continued deficiency.	Epidural hematoma in a patient with anticoagulant therapy but no trauma with significant recovery.
Yang et al, 2012 (348)	A case of spinal epidural hematoma during breath-hold diving was reported in a 47-year old male who presented with severe frontal headache and intense cervical pain which developed during a protracted spear fishing session. A cervical spine MRI performed 12 days after symptoms onset showed a small epidural blood collection on the left side of the spinal canal at the C7/T1 level. One week later, blood was no longer present and the asymptomatic patient was discharged.	The authors concluded that protracted minor trauma with neck flexion and repeat Valsalva maneuvers might have played a role in the genesis of this event. The role of decompression is important; however, this patient improved with conservative management.	Spontaneous hematomas can occur with any type of activity without risk factors and be managed conservatively or surgically.
Tremolizzo et al, 2012 (349)	This is a report of a case of non-traumatic spinal epidural hematoma in a female after breath-hold diving.	The authors postulated that protracted minor trauma (neck flexion) and repeated Valsalva manoeuvres might have played a role in the genesis of this event.	This case illustrates necessity for a high level of suspicion and proper diagnosis and management.
Kim et al, 2012 (350)	A 51-year old man developed spontaneous spinal epidural hematoma related to low dose aspirin use. The patient was successfully treated with medical management.	The authors concluded that this indicates that low dose aspirin could induce spontaneous spinal epidural hematoma and that conservative treatment with close observation and repeated imaging studies should be considered in cases with neurological improvement or mild deficits.	Even though the patient was on low dose aspirin, no causal relationship could be established due to spontaneous epidural hematoma occurring in many other cases.
Fuster et al, 2012 (351)	The authors reported a spontaneous chronic epidural hematoma of the lumbar spine mimicking an extradural spine tumor. A 61-year-old woman was evaluated after 18 month history of pain, dysesthesias, and mild weakness in both lower extremities with significant radicular symptoms on the right side associated to neurogenic claudication. A CT scan revealed a nodular image of soft tissue density located in the right anterolateral epidural space at L4-L5 level. MRI studies revealed epidural hematoma. Patient underwent surgery and recovered.	The authors concluded that spontaneous chronic epidural hematomas are rare, even more when they produce scalloping of bone structures, a diagnostic challenger. They should always be considered as a differential diagnosis in patients with extradural chronic compression taking into account that also chronic epidural hematomas can cause bone involvement.	Appropriate diagnosis and proper management with surgical decompression or conservative management is essential.

Table 2 (cont.). *Descriptions of reports of spontaneous or traumatic bleeding.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Yabe et al, 2012 (352)	The authors present a case report in an elderly patient who developed spontaneous spinal epidural hematoma during warfarin therapy. Since the patient was on warfarin laboratory testing was performed and based on MRI findings of a space occupying lesion on the dorsal side of the spinal canal, compression of spinal cord epidural hematoma was suspected. Patient was treated with oral vitamin K to prevent expansion of the hematoma. Surgical intervention was contraindicated due to old age and delayed diagnosis. Consequently, conservative management was carried out. Eventually he recovered to operate an electric wheelchair and underwent rehabilitation.	Spontaneous epidural hematoma must be considered specifically in patients with sudden onset of unexplained cervical or back pain or subsequent radicular symptoms during anticoagulant therapy. Immediate MRI is essential for early diagnosis and treatment.	High level of suspicion with appropriate diagnosis in patients who are on warfarin therapy is essential with proper management when indicated.
Shima et al, 2012 (357)	The authors reported a case of a spinal epidural hematoma with symptoms mimicking cerebral stroke in an 84-year-old female with nuchal pain and right hemiparesis. CT scan of the neck demonstrated a spinal epidural hematoma. She was managed conservatively and her symptoms improved significantly.	The authors emphasized that cervical spinal lesions should be considered in the differential diagnosis for patients with acute onset hemiparesis, when they are associated with neck pain. They also stated that even though MRI is a gold standard, a CT scan is also useful for quick screening for spontaneous cervical epidural hematoma.	CT scan will be helpful and patients may be treated conservatively, however, the differential diagnosis and high level of suspicion is of paramount importance.
Gwyn & Shinton, 2012 (358)	The authors presented a case report of an 80-year-old gentleman presenting with right arm weakness with sudden onset of right-sided neck pain at rest radiating to his right shoulder and back, leading to immediate numbness and tingling down right arm and associated heaviness, with no history of trauma. His medications included aspirin, 75 mg once a day and dipyridamole sustained release 200 mg twice a day. MRI evaluation showed a right-sided shallow fluid collection projecting into the spinal canal from the posterolateral aspect of the canal, diagnosed either as hematoma or abscess, without a known cause. Patient was managed conservatively and was discharged with full recovery and epidural hematoma resolved after 3 weeks.	Authors concluded that this report highlights the importance of considering a spontaneous epidural hematoma in any patient presenting with neck pain and limb weakness. They also emphasized that specific attention must be paid to any antiplatelet medication as this may put the patient at higher risk.	Even though patients may need surgical intervention, this patient responded well to conservative management. High level of suspicion and differential diagnosis are essential.
Schwartz et al, 2012 (362)	The authors reported a spontaneous cervical epidural hematoma associated with thunderclap headache in an 80-year-old woman who abruptly developed an explosive, severe headache in the bilateral occipital and frontal regions associated with neck pain/stiffness while sitting on her couch watching television. After multiple evaluations involving the head, MRI of the cervical spine was performed which showed cervical epidural hematoma. Patient was on warfarin, aspirin, and clopidogrel, all 3 antithrombotic agents. The headache and neck pain resolved several days after withholding anticoagulation and treating with empiric intravenous antibiotics.	The authors concluded that this, to the best of their knowledge, is the first reported case of spontaneous cervical epidural hematoma presenting with a thunderclap headache. Thus, the recognition of spinal epidural hematoma with thunderclap headache has important clinical implications.	A high level of suspicion in patients with headache or cerebral symptoms, associated neck symptomatology with assessment with MRI is essential.
Yang et al, 2011 (365)	The authors reported a case of spontaneous spinal epidural hematoma associated with myocardial infarction treatment in a 56-year-old man. Patient was treated with nitroglycerin, aspirin, low molecular weight heparin, and clopidogrel. MRI showed epidural hematoma despite emergent decompressive surgery, paraplegia was not improved 7 months after surgery.	The authors concluded that a spontaneous spinal epidural hematoma should be considered when patients complain of abrupt, strong, and non-traumatic back and neck pain, particularly if they have not known spinal pain history.	Despite aggressive intervention, prognosis was poor.
Kim et al, 2012 (367)	The authors reported a chronic pure radiculopathy in a 52-year-old male without antithrombotic therapy and without injury with organizing epidural hematoma around C8 nerve root. MRI scan showed small space-occupying lesion around eighth cervical nerve root. After surgery, the authors confirmed chronic organizing epidural hematoma.	The authors concluded that this is only the second reported case in the worldwide literature of pure radiculopathy in a patient with chronic spontaneous cervical epidural hematoma.	Epidural hematomas can present in many ways, consequently, a high level of suspicion is essential along with appropriate management.
Jacob et al, 2012 (368)	The authors presented a case report of acute epidural spinal hemorrhage from vasculitis which resolved with immunosuppression in a 61-year-old female presenting with sudden onset of back pain and headache.	Immunomodulating therapy should be considered in the management of select patients with spinal vasculitis which may lead to improved clinical outcome and potentially disease resolution.	A difficult case of epidural spinal hemorrhage managed with immunomodulating therapy.
Nakanishi et al, 2011 (373)	The authors reported 3 cases of hemiparesis caused by spontaneous cervical spinal epidural hematoma in a 73-year-old woman, a 62-year-old man, and a 60-year-old woman with all of them presenting with symptoms of hemiparesis and eventually diagnosed with cervical spinal epidural hematoma. First 2 patients were treated with surgical decompression, whereas, third patient was treated with conservative management, with all of them improving.	The authors concluded that these cases suggest that acute cervical spinal epidural hematoma should be considered as a differential diagnosis in patients presenting with clinical symptoms of sudden neck pain and radicular pain with progression to hemiparesis.	A high level of suspicion with appropriate diagnosis and either surgical or conservative management is the mainstay of management.

Table 2 (cont.). *Descriptions of reports of spontaneous or traumatic bleeding.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Puah et al, 2012 (376)	The authors reported a spontaneous cervical spinal epidural hematoma in the postpartum period in a 31-year-old Chinese woman who underwent a lower segment cesarian section. She presented with sudden onset of neck pain and lower limb weakness with no trauma 3 weeks after discharge. MRI showed cervical epidural hematoma. She was treated with intravenous dexamethasone and an emergency cervicothoracic laminectomy and evacuation of the hematoma. The patient recovered fully after one year even though she required self-catheterization once daily for bladder dysfunction.	The authors concluded that early recognition and intervention for their patient allowed for neurological recovery with a spontaneous cervical spinal epidural hematoma in the postpartum period.	Sudden onset of neck pain in the postpartum period with neurological dysfunction must be treated with high suspicion. Appropriate diagnosis and treatment are essential.
Cai et al, 2011 (378)	Authors described a case of spontaneous epidural hematoma of the thoracic spine presenting as Brown-Séquard syndrome in a healthy 35-year-old male with insidious development of intrascapular pain without trauma. MRI identified spontaneous epidural hematoma and patient was offered prompt surgical intervention. The patient opted for conservative treatment which was followed by rapid resolution.	Authors conclude that prompt surgical decompression is an absolute surgical indication widely accepted for patients with progressive neurological deficit. Successful non-operative care in this case does not make it a standard of care and surgical decompression remains the standard treatment for spontaneous epidural hematoma.	Even though case illustrates a rare presentation and spontaneous recovery, surgical intervention must always be considered.
Kim & Kim, 2011 (379)	This is a case report of an epidural hematoma in a 63-year-old man with a 25-year history of ankylosing spondylitis. After a minor fall, MRI showed a large posterior epidural hematoma with cord compression. Prompt surgical decompression was carried out, however, the patient died.	Authors concluded that a good outcome depends on prompt diagnosis and surgery, even though outcome was poor in this patient.	Prompt diagnosis and treatment is essential in epidural hematoma of any origin.

Table 3. *Reports of bleeding and epidural hematoma associated without antithrombotic therapy with interventional techniques.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Williams et al, 1990 (178)	A diagnosis of cervical epidural hematoma was made and was confirmed by CT scan after a seventh epidural in several years in a patient who was taking indomethacin. Immediate surgery revealed an epidural hematoma. During the operation blood results became available showing that INR was 1.0, the clotting time was 41 seconds with a control of 40 seconds, and the platelet count was within normal limits. Bleeding time was not measured. His recovery was complicated with wound breakdown requiring a skin graft and urinary retention which required prostatectomy. Subsequently he made a full recovery.	Authors concluded that repeated epidural steroid injections should preferably be performed in centers equipped to accurately to diagnose and promptly treat this rare but serious complication.	In this case there were no major antithrombotics utilized (except for indomethacin), however, patient suffered with cervical spondylosis. All the bleeding parameters were appropriate. Even then, patient developed cervical epidural hematoma. Further, there are no recommendations to stop indomethacin in the majority of the guidelines.

Table 3 (cont.). *Reports of bleeding and epidural hematoma associated without antithrombotic therapy with interventional techniques.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Stoll & Sanchez, 2002 (180)	A healthy 34-year old man with no evidence of coagulopathy and not taking antiplatelet medication suddenly had onset of acute cervical myelopathy from a large cervical epidural hematoma 8 days after cervical epidural steroid block. The patient developed a Brown-Séquard type of myelopathy manifesting by severe weakness of the left arm and leg and right-sided numbness and loss of temperature appreciation. The diagnosis was made by CT scan. Because of the severe neurological deficit, the patient was directly taken to surgery with MRI scan. The surgical exposure showed a large, discreet sausage-shaped extradural hematoma, appearing darkish and somewhat organized. There was no active bleeding nor were any abnormal vessels seen. Following prompt surgical evaluation of the clot, the patient made a near complete recovery.	The authors concluded that this case illustrated that epidural hematoma may occur in the absence of known risk factors. The delayed onset and the absence of risk factors have implications for the use of epidural steroid injection in chronic pain management.	This case again illustrates that epidural hematoma can occur in patients without antiplatelet therapy (ibuprofen discontinued). The size of the needle, the technique, and number of attempts were not available. It is unknown if vigorous physical therapy or epidural injection caused the epidural hematoma.
Yagi et al, 1998 (187)	The authors described a case of 41-year old man with prior anterior cervical fusion who underwent an epidural block at C7/T1 for shoulder pain. Two hours after cervical twisting, he had onset of severe neck pain and bilateral shoulder pain. This was followed by asymmetrical quadriparesis. An MRI showed an epidural hematoma from C3 to C7. At operation, no active bleeding or vascular abnormality was found and he made a good recovery.	The authors of this case report attributed the hematoma to cervical twisting, noting the spinal puncture was not difficult and no impairment of coagulation was found.	Whatever the cause is, it is essential to recognize that epidural hematoma can happen at any time, even in the best hands, and appropriate care must be taken.
Lee et al, 2011 (193)	A 58-year old woman presented with quadriparesis and neck pain after dry needling. MRI of the spine revealed a hyperintense mass in the T2 weighted at C2-T2 level, which proved to be an epidural hematoma. The diagnosis was made with MRI and decompression was carried out. The patient recovered completely.	The authors concluded that even though it is rare, epidural hematoma is a possible complication in needling therapies. The authors concluded the spinal hematoma caused by dry needling in this case was probably the result of unintentional needling of the spinal canal, similar to that caused by central neural blockade. However, there were no risk factors and the patient was not on antiplatelet therapy.	The epidural hematoma may develop following dry needling without major interventional techniques and may be treated appropriately with prompt diagnosis.
Ozdemir et al, 2007 (204)	A 40-year old man was admitted with severe persistent headache and vomiting after epidural steroid injection for right leg pain. Epidural steroid injection was performed with a #18 gauge Tuohy needle which revealed a dural puncture. The second attempt at L3/4 level was successful. It appears that epidural steroid injection was performed without fluoroscopy. MRI showed a right frontal subdural hematoma. His headache was relieved after strict bedrest, intravenous hydration, and analgesics. The patient was discharged with full recovery after one week without neurological dysfunction.	The authors concluded that intracranial subdural hematoma for accidental dural puncture during epidural steroid injection is a rare complication, even though there were no risk factors in this patient.	Intracranial subdural hematoma can develop in patients without any risk factors.
Lee et al, 2007 (222)	A healthy 38-year-old woman after motor vehicle injury developed upper extremity radiculopathy. She underwent a series of right transforaminal epidural injections at the C7-T1 level. Approximately 4 days after the final injection, she awakened with severe upper thoracic back pain and progressive loss of sensation in the lower extremities. By late that morning, patient had progressive neurological symptoms and onset of weakness and she was promptly referred to the emergency department for evaluation. MRI of the spine showed a large hematoma extending from T1 to T5. The patient underwent surgical decompression. Within 6 months patient regained full strength and sensation in both lower extremities.	Authors concluded that interventional pain physicians must appreciate the possibility of catastrophic complications and discuss with the patient prior to the procedure. They also cautioned that the physician should be aware that symptoms from a slowly developing epidural hematoma can present even days after an injection.	The study shows that apart from various other complications with cervical transforaminal epidural injections, a spinal epidural hematoma, even without risk factors, is possible. Appropriate management can address these issues if patients do develop complications.
Bose, 2005 (276)	This case report described severe adverse effects (quadriplegia and respiratory arrest) associated with an epidural injection into the C6-C7 space. Although the patient's symptoms improved somewhat with supportive care, quadriparesis appears irreversible. No reports of quadriparesis after cervical epidural injection were found in the literature, although other adverse effects have been reported.	The authors concluded that although evidence is not conclusive, this patient may have suffered a vascular event from a cervical epidural injection.	The study shows that patients may suffer with vascular events from cervical epidural injections, thus, a high level of suspicion and caution are essential.

techniques were identified (178,180,187,193,204,222, 276,391). In addition, the survey by Manchikanti et al (81) showed there were multiple cases of epidural hematoma in patients who were not on antiplatelet and warfarin therapy.

Table 4 shows the reports of bleeding and epidural hematoma related to the patients with discontinuation of antiplatelet and antithrombotic therapy in chronic pain with interventional techniques (189,190,201). Manchikanti et al (81) also showed epidural hematoma in 29 patients with discontinuation of antiplatelet and warfarin therapy compared to 26 patients with continued antiplatelet therapy. However, they also showed the prevalence of thromboembolic events were 153 in patients with discontinuation of antiplatelet therapy compared to 9 in patients with continued antiplatelet therapy.

Table 5 shows the reports assessing bleeding complications and epidural hematoma in patients with continuation of antiplatelet therapy and interventional techniques. There were only 3 reports of bleeding complications when anticoagulant therapy was continued for interventional techniques (176,177,388). However, there is an abundance of literature with complications related to anesthesia and surgery (209,212-214,216,217,219,220,224,226-228,230,242,248,253,258,259,262). Further, Manchikanti et al (81), in assessing the frequency of adverse effects during interventional pain management techniques, showed bleeding complications with epidural hematoma in 26 instances compared to 29 instances where antiplatelet and warfarin therapy was discontinued. However, with continuation of antiplatelet therapy, thromboembolic events were only 9 compared to 153 with discontinuation of antiplatelet and warfarin therapy.

2.3 Analysis of Evidence

Based on the review of the comprehensive literature without methodological quality assessment of the presented studies and case reports, the evidence appears as follows:

- There is good evidence for the risk of thromboembolic phenomenon in patients who discontinue antithrombotic therapy.
- There is good evidence spontaneous epidural hematomas occur with or without traumatic injury in patients with or without anticoagulant therapy associated with stressors such chiropractic manipulation, diving, and anatomic abnormalities such as ankylosing spondylitis.
- There is good evidence for the lack of necessity of discontinuation of NSAIDs, including low dose aspirin, prior to performing interventional techniques.
- There is fair evidence that excessive bleeding, including epidural hematoma formation may occur with interventional techniques when antithrombotic therapy is continued.
- There is fair evidence that the risk of thromboembolic phenomenon is higher than the risk of epidural hematomas with discontinuation of antiplatelet therapy prior to interventional techniques, even though both risks are significant.
- There is fair evidence that anatomic conditions such as spondylosis, ankylosing spondylitis, and spinal stenosis, and procedures involving the cervical spine; multiple attempts; and large bore needles increase the risk of epidural hematoma.
- There is fair evidence that rapid assessment and surgical or nonsurgical intervention to manage patients with epidural hematoma can avoid permanent neurological complications.
- There is fair evidence of the lack of necessity of discontinuation of phosphodiesterase inhibitors (dipyridamole [Persantine], cilostazol [Pletal], and Aggrenox [dipyridamole plus aspirin]) prior to performing interventional techniques.
- There is limited evidence to discontinue antiplatelet therapy (clopidogrel [Plavix®], ticlopidine [Ticlid®], and prasugrel [Effient®]) to avoid bleeding and epidural hematomas.
- There is limited evidence to continue antiplatelet therapy during interventional techniques including epidural injections to avoid thromboembolic fatalities.

3.0 Discussion

This comprehensive review of the literature about the role of antithrombotic and antiplatelet therapy in interventional pain management assessed numerous manuscripts, without randomized trials. There is substantial literature, though mostly consisting of observational studies and case reports. There is no literature available in reference to monitoring platelet function under antiplatelet therapy in reference to interventional techniques or its application during intraoperative treatment (401-406).

The results of this assessment showed good evidence for increased risk of thromboembolic phenomenon in patients who discontinue antithrombotic

Table 4. *Reports of bleeding and epidural hematoma related to patients with discontinuation of antiplatelet and antithrombotic therapy with interventional techniques in chronic pain management.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Xu et al, 2009 (189)	A 78-year-old woman with history of diabetes mellitus, atrial fibrillation, myocardial infarction status after coronary stent placement, and who was on a regimen of aspirin and warfarin, stopped her warfarin and aspirin 6 days before the third epidural procedure and was bridged over to enoxaparin 1 mg/kg twice daily. She received her last enoxaparin dose at 7 a.m. one day before the procedure. The lumbar epidural injection was performed atraumatically by using the loss of resistance technique. She received her usual warfarin dosing 8 hours after the procedure and initiated her enoxaparin shots at 7 p.m. the following day, 30 hours after the procedure, after an INR was found to be within normal range. The following morning after the second shot of enoxaparin, she developed excruciating radicular pain and presented to the emergency room. CT scan of the lumbar spine was inconclusive. Subsequently, she underwent an MRI which showed a lumbar epidural clot that spanned from L2 to L5 causing severe thecal sac compression. Patient underwent surgical decompression. She recovered almost completely with rehabilitation.	The authors concluded that despite the overall low incidence of hemorrhagic complications associated with epidural steroid injections, because of the potential catastrophic outcome of epidural hematomas, it is extremely important to watch for these complications, specifically in patients on anticoagulants prior to procedure. They believe that early reintroduction of warfarin may have been responsible in this patient.	Even though all anticoagulants were discontinued prior to procedure resulting in normal INR, early reintroduction of warfarin may have resulted in lumbar epidural hematoma..
Ain & Vance, 2005 (190)	An 85-year-old woman underwent epidural steroid injection. She was on enoxaparin which was withheld per guidelines. Prior to that she was taking warfarin for chronic atrial fibrillation and a St. Jude aortic valve. Warfarin was withheld 6 days before the epidural steroid injection and patient received 1 mg/kg subcutaneous enoxaparin every 12 hours for 4 days before her appointment. On the day before her appointment, she received only her morning dose. At the time of the injection, it was more than 24 hours since her last dose. Her INR was 1.2. Epidural steroid injection was performed atraumatically with use of 18-gauge Tuohy needle and the loss of resistance technique into the L4-L5 interspace. The vertebral level of the injection was not confirmed radiologically, thus it is possible that the injection was performed at the L3-L4 interspace. No paresthesias or blood were encountered during needle placement. Methylprednisolone, 80 mg, was injected into the epidural space. Enoxaparin regimen was reinstated 24 hours after the procedure. The patient had received a total of 3 doses when, 48 hours after the procedure, she reported intractable back pain at the location of the epidural steroid injection. MRI showed epidural hematoma. Repeat MRI showed increasing size of the epidural hematoma. Patient underwent decompressive laminectomy and intravenous steroids were continued. Patient recovered completely.	The authors concluded that this case emphasized that even a low dose of enoxaparin administered over the course of days could produce a very long prolonged anticoagulation effect such as that even 36 hours after its discontinuation the patient may remain anticoagulated. Patient's renal insufficiency may have been a factor. Thus, authors concluded that current ASRA recommendations for treatment of patients receiving low molecular weight heparin may not apply to patients with renal insufficiency.	Epidural hematoma occurred despite appropriate precautions and the results with full recovery after surgical decompression.
Reitman & Watters, 2002 (201)	A 62-year old woman underwent cervical epidural steroid injection by an experienced anesthesiologist. She responded well to the first injection. Consequently, she underwent a second injection. She was on Fiorinal on a regular basis for headaches; this was discontinued for a week prior to epidural steroid injection. She developed acute onset of axial pain followed by progressive quadriparesis within a matter of 8 hours. She underwent a CT scan which showed anterior spinal hematoma from C3 to C5. After surgery the patient was initially quadriplegic, but rapidly gained full function in the left upper and lower extremities. She was making steady progress, but she developed meningitis, about 8 days after the surgery. Subsequently, she suffered a cardiopulmonary arrest. The first time she was successfully resuscitated, but remained critically ill with no evidence of neurological function. Six days later she had a second cardiac arrest and could not be resuscitated.	Authors concluded that spinal hematoma can occur after cervical epidural steroid injection. Prompt recognition and treatment could improve the prognosis for recovery. The patient suffered devastating complications in this study; however, there were no risk factors in this patient. The only remote risk factor was Fiorinal therapy which was discontinued.	The devastating complications of epidural hematoma can occur even without known risk factors or anticoagulant therapy..

Table 5. *Reports assessing bleeding complications and epidural hematoma in patients with continuation of antiplatelet therapy with interventional techniques.*

Study/Year	Case Report	Conclusions by the Study Authors	Author Conclusions of the Review
Maier et al, 2002 (176)	Two cases were presented with lumbar sympathetic blockade in 2 patients under medication with irreversible platelet aggregation inhibitors. The first patient was a 71-year-old male patient with intermittent claudication and a trophic leg ulcer due to progressive peripheral arterial disease. He was on ticlopidine 500 mg/day for stroke prevention in the presence of carotid artery stenosis. Patient underwent left-sided lumbar sympathetic block under fluoroscopy. There was no known vascular puncture. Two days later, a widespread skin hematoma was recognized. Four days later a second block was performed under fluoroscopic visualization which involved intravascular needle penetration. That is 6 days after the first block. Following this, the patient developed a large retroperitoneal hematoma. He was managed conservatively. The second case involved a 79-year-old female patient with generalized peripheral arterial disease, polyneuropathy, coronary artery sclerosis, and a history of stroke with treatment with 75 mg per day of clopidogrel. Clopidogrel was discontinued 3 days prior to lumbar sympathetic block. 72 hours later, the coagulation parameters, including bleeding time, were within normal limits. Lumbar sympathetic blocks were performed at L3 level with attempts with no intravascular injection. She complained of burning groin and medial thigh pain. Her pain was improved with opioid. She was walking on the ward without complaints. An hour later she was found pulseless and resuscitation attempts were unsuccessful. The autopsy revealed a massive coagulated hematoma beneath the left psoas muscle with enlarged retroperitoneal hemorrhage. There were no visible puncture lesions in larger vessels.	The authors concluded that irreversible platelet inhibitors should be discontinued for at least 7 days prior to any invasive technique, and any hemorrhage is not controllable by external compression. They also concluded that in case of high thrombotic risk, patients should be switched to a different therapeutic regimen with heparin up to 6 hours prior to blockade. They believe that groin pain and, particularly, pain at the medial side of the thigh, seem to be early signs of bleeding complications of lumbar sympathetic block.	In the first case report, ticlopidine was not stopped, and a retroperitoneal hematoma was observed. Nonetheless, conservative management was appropriate without fatal complications. In the second case, even though clopidogrel was discontinued prior to lumbar sympathetic block, coagulation parameters were appropriate, and bleeding time was appropriate, the result was fatal. Thus, no conclusions could be reached.
Benzon et al, 1999 (177)	This case report describes a patient with acute onset of quadriparesis admitted to a teaching hospital with a large cervical epidural hematoma, developing numbness and weakness of his arms and legs within 30 minutes after the performance of the cervical epidural steroid injection. At the time of injection, he was taking several clopidogrel, possibly aspirin, and diclofenac that had been started after a prior coronary angioplasty. He also had a prior uneventful cervical epidural steroid injection 11 days before the incident in question, but it is not clear if he was taking these antiplatelet drugs then. His PT, INR, and PPT were within normal limits. His platelet count was appropriate. The last doses of antiplatelet drugs were unclear. He underwent an emergency C3-T3 laminectomy and evacuation of cervical epidural hematoma. Approximately 14 hours after the epidural injection postoperatively upper extremity strength improved, but his lower extremities remained paralyzed. Three months after the surgery he had regained his strength in his upper extremities, but the paralysis of his lower extremities remained.	The authors of this case report cautioned that these drugs inhibit platelet adhesion to the vascular endothelium and shear stress-induced platelet aggregation and section. After discontinuation of clopidogrel therapy, platelet aggregation and bleeding time returned to baseline within 5 days. Authors stated that there has been no case report of spinal hematoma after neuraxial block in patients receiving clopidogrel; however, there was a case report with ticlopidine. They recommended that neuraxial blocks be postponed for 5 - 7 days in patients who are receiving several antiplatelet drugs.	This is another case report showing risks of antiplatelet therapy with multiple antiplatelet drugs. Even with prompt surgical intervention results were poor.

therapy; fair evidence for excessive bleeding, including epidural hematoma formation, may occur with interventional techniques when antithrombotic therapy is continued; good evidence that spontaneous epidural hematomas occur with or without traumatic injury in patients with or without anticoagulant therapy. These spontaneous epidural hematomas are more likely associated with stressors such as chiropractic manipulation, diving, and anatomic abnormalities such as ankylosing spondylitis. There is fair evidence that the risk of thromboembolic phenomenon is higher than the risk of epidural hematomas with discontinuation of antiplatelet therapy prior to interventional techniques, even though both risks are significant.

In addition, there is good evidence that discontinuation of NSAIDs, including low dose aspirin, prior to performing interventional techniques does not reduce bleeding risk; fair evidence that continuation of phosphodiesterase inhibitors (dipyridamole [Persantine], cilostazol [Pletal], and Aggrenox [aspirin and dipyridamole]) prior to performing interventional techniques does not increase bleeding risk; limited evidence that discontinuing antiplatelet therapy with clopidogrel (Plavix), ticlopidine (Ticlid), or prasugrel (Effient) reduces risks of bleeding and epidural hematomas during interventional procedures but increases the risk of cerebrovascular and cardiovascular thromboembolic fatalities.

Further, there is fair evidence that anatomic conditions such as spondylosis, ankylosing spondylitis, spinal stenosis, and procedures involving the cervical spine; multiple attempts, and large bore needles increase the risk of epidural hematoma; and rapid assessment and surgical or nonsurgical intervention to manage patients with epidural hematoma can avoid permanent neurological complications.

There is limited evidence in reference to newer antithrombotic agents dabigatran (Pradaxa) and rivaroxaban (Xarelto) to discontinue to avoid bleeding and epidural hematomas and are continued during interventional techniques to avoid cerebrovascular and cardiovascular thromboembolic events.

While the preparation of guidelines for interventional pain management (73-77,79,80) has been difficult, the question of whether or not to continue antithrombotic and antiplatelet therapy for interventional procedures is especially difficult to answer. Recommendations are made based on observational studies and case reports. Thus, the Institute of Medicine (IOM) considers most guidelines as not based on evidence (407).

The IOM has released methodology standards for clinical guidelines, which when followed, result in guidelines that can be trusted (407). In this manuscript the IOM describes multiple challenges in developing guidelines. The IOM states that the literature assessing the best methods for guideline development have evolved dramatically in the 20 years since the IOM's first report on the subject.

The issue of conflicting guidelines is a major issue in the era of comparative effectiveness research and evidence-based medicine (408-414). A publication, based on IOM standards, on adverse events in hospitals showed they were not accurately measured (415). In fact, they developed a new standard and illustrated that many years and much expense, due to the extensive measures proposed by IOM standards, have not improved care by reducing the number of adverse events in hospitals, but that adverse events in hospitals may be 10 times greater than previously measured (415). Multiple issues related to various regulations and guidelines since the enactment of the American Recovery and Reinvestment Act (ARRA) (416) and the Patient Protection and Affordable Care Act (ACA) (43,44,46-49,417) along with various guidelines (72,73,79,80) have been questioned. These guidelines are not only related to subjects such as infection control, but also to mammography, prostate cancer screening, fraud and abuse, and even the administering sedation during procedures, as issues affecting medical practices in the modern era (38,418-460).

Our literature search showed a large number of spontaneous occurrences of hematoma. In addition, there have been some case reports of epidural hematoma during interventional techniques (majority with regional anesthesia) whether antiplatelet therapy was continued or discontinued (80-98,171-398,461,462). Spontaneous spinal epidural hematoma is a rare, but recognized, entity. The causes of spontaneous spinal epidural hematoma vary but may be higher in patients with bleeding disorders, therapy with anticoagulants following thrombolysis for MI and spinal arteriovenous malformation, chiropractic manipulation, diving, hypertension, Paget's disease, and ankylosing spondylitis (181,185,202,203,207,208,223, 225,231,232,245,260,275,278,295,297,319, 343-345,348-352,357,358,362,365,368,373,376,378-380,463-481). Even when thromboembolic or hematoma events occur and are temporally related to an interventional procedure, a spontaneous event cannot be ruled out.

Groen and van Alphen (471), in 1996, reviewed

333 cases of spontaneous spinal epidural hematoma reported in the literature, including 3 of their own patients. Since then, multiple other case reports have been published. From their analysis it was evident that, among the 333 cases, the majority were in the posterior and posterolateral spinal epidural space. Due to the anatomical characteristics of the internal vertebral plexus, they postulated that the spinal epidural venous network was the major source of epidural hematoma.

Spontaneous spinal epidural hematoma usually presents with acute onset of spinal pain, which may rapidly progress to quadriparesis or paraparesis (265). However, several cases of Brown-Séquard syndrome due to cervical spontaneous spinal epidural hematoma have been reported (180,203,207,278,295,343-345,378,474). However, occasionally the pain produced by cervical spontaneous spinal epidural hematoma may be attributed to cardiac disease (277), which may result in a double jeopardy as these patients might receive thrombolytic therapy, which might aggravate the spontaneous spinal epidural hematoma. Symptoms may also mimic stroke (357). The majority of the cases report (471) reveal a classic clinical picture consisting of acute onset of severe, often radiating, back pain, followed by signs and symptoms of a rapidly evolving nerve root and/or spinal cord compression. Only 9 of 333 cases presented in a chronic manner. Among these 9 patients, only one had a lesion in the cervical region (471). The best diagnostic tool for spontaneous epidural hematoma is MRI. Resolution of spontaneous spinal epidural hematoma is well known (181,319,378,398,469,471-481). In fact, some cases have improved within a few hours of onset of the symptomatology (398). Even then, among the 333 cases reported (471), surgery was performed in 327 patients. The authors concluded that in patients who underwent surgery, the factors that determined the outcome were interval between the onset of the symptoms and the extent of preoperative neurological deficit. In patients with complete sensory motor loss, the results were better if surgery was performed less than 36 hours after onset of neurological deficit. In patients with incomplete sensory motor deficit, favorable outcomes correlated highly with surgery carried out less than 48 hours following onset.

The development of epidural hematoma with or without anticoagulant or antithrombotic therapy is a grave complication even though it is extremely rare in interventional pain management. Spinal hematoma is relatively more common complication associated with regional anesthesia. In fact, Wulf (229) reported 51 confirmed spinal hematomas associated with epidural anesthesia in 1996. However, Horlocker et al (85), in American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines for regional anesthesia, described that while these complications may be common, the actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with central neural blockade is unknown. In an extensive review of the literature, Tryba (482), in 1993, identified 13 cases of spinal hematoma after 850,000 epidural anesthetics and 7 cases among 650,000 spinal techniques. Consequently, on the basis of these observations, the calculated incidence has been estimated to be approximately less than 1 in 150,000 epidural and less than one in 220,000 spinal anesthetics (97). However, these estimates represent the upper limit of the 95% confidence interval (CI), the actual frequency should be much less. The series involved in these calculations were conducted before the implementation of routine perioperative thromboprophylaxis. Further, later case series and epidemiologic surveys suggest that the risk has increased (262,396,397).

Hemorrhaging to the spinal canal most commonly occurs in the epidural space, most likely because of the prominent epidural venous plexus, even though variables such as needle size, catheter placement, number of attempts, the type and volume of injectate, may also affect the site of clinically significant bleeding (83-85,96,296). In a literature review between 1906 and 1994, Vandermeulen et al (262) reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia; 60% of the 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. The review by Wulf (229) included an additional 16 cases. Vandermeulen et al (262) showed that 25 of the 61 patients in their report had received intravenous or subcutaneous unfractionated or LMWH, whereas an additional 5 patients were presumably administered heparin because they were undergoing a vascular surgical procedure. However, only 12 of 61 patients had evidence of coagulopathy or thrombocytopenia or were treated with antiplatelet medications such as aspirin, indomethacin, ticlopidine, oral anticoagulants, thrombolytics (urokinase), or dextran 70 immediately before or after the spinal or epidural anesthetic. In 25% of the patients, needle or catheter placement was reported to be difficult. All in all, in 87% of the 61 cases, either a clotting abnormality or needle placement difficulty was

present. Consequently, only 13% of the patients were without any coagulopathy or placement difficulties.

In our assessment, we found multiple cases of epidural hematoma in patients undergoing interventional techniques. In addition, 2 studies assessing bleeding risk of interventional techniques in chronic pain (82,96) showed the lack of increased risk with continued administration of antiplatelet therapy. However, multiple surveys of interventional techniques (81,83-85) have uniformly illustrated that in the majority of the patients, antiplatelet therapy is discontinued. Cases have been reported despite proper adherence to guidelines of antiplatelet therapy (175,176,178,180,187,189,190,193,201,204,222,276) and also in patients who have never had antiplatelet therapy. Further, it is also important to remember that the majority of these cases are related to spontaneous occurrence.

Multiple factors described include anatomy of the epidural space, spinal anatomy, coexisting pathology, coagulation status, needle placement, and injectate. A meta-analysis of over 600 spinal hematoma including both spontaneous and iatrogenic cases, revealed anticoagulation to be the second most common underlying etiology for spontaneous hematoma formation, following idiopathic occurrence with no readily identifiable cause (483). In this meta-analysis, spinal and epidural anesthetic procedures in combination with anticoagulation were the fifth highest cause of epidural hematomas. However, among this group of patients, spinal hematomas were most commonly encountered in those receiving continuous and not single-shot epidural anesthesia (70,71).

Consequently, the majority of the interventionalists believe that the relative contribution of anticoagulation to hemorrhagic risk for patients receiving epidural steroid injections or other interventional techniques is unknown. Xu et al (189) in a 2009 publication reported that there were 8 cases ever published based on the English language literature in PubMed and MedWatch (177,178,180,190,391,396). Their review showed that excluding one case in which the location of the hematoma was unknown, 4 cases involved the cervical spine. Interestingly, all 4 cases were associated with NSAID usage (199). However, current concepts and guidelines conclude that there is not a significantly increased risk for hemorrhage complications in patients on NSAIDs receiving neuraxial anesthesia, even though NSAID usage may increase the likelihood of developing minor complications or prolonging existing side effects (83-85,96,97,199,201,218,396,405,461,462,484-495).

Xu et al (189) postulated that the evidence for such guidelines is based on studies such as that conducted by Horlocker et al (96), which were limited in patient population size and quantity of NSAID coverage, the only study published until 2011. In 2011, Manchikanti et al (82) published a larger study with 12,000 encounters which included all types of interventional techniques. However, this will also be considered a smaller sample size. However, Xu et al (189) considered these studies provided skewed results as smaller number of patients are on antiplatelet medications, specifically drugs such as indomethacin. Consequently, as they state, the relative contribution of each medication to the risk of spinal hematoma may be variable, especially for a relatively rare complication. However, a retrospective assessment of complications by Manchikanti et al (82,461,462) revealed no epidural hematomas or major bleeding incidents in 120,000 interventional techniques performed in patients without antiplatelet therapy, with continued antiplatelet therapy, and discontinued antiplatelet therapy. Nevertheless, it is important to acknowledge that prospective well controlled long-term studies are essential and other factors may also contribute to the epidural hematomas. In the case report by Benzon et al (177), the patient had therapeutic doses of diclofenac, clopidogrel, and possibly aspirin during the epidural steroid injection, and there exists no study that examines whether multiple NSAIDs or antiplatelet drugs may elevate the risk of hemorrhage. The patients reported by Ghaly (391), Stoll and Sanchez (180), and Williams et al (178) only received one NSAID each (diclofenac, ibuprofen, and indomethacin, respectively). Cervical epidural steroid injections, in general, are potentially associated with a higher risk of complications due to anatomical considerations (88,201,262,485-488). In fact, an in vitro study of 10 cadavers revealed that cervical epidural steroid injections were at particularly high risk for hemorrhagic complications due to the anatomical variation in the location of arteries within the spinal canal (461,462,489,490). In addition, the anatomy of the ligamentum flavum varies significantly with its absence and extensive vasculature in the cervical spine (496-517).

Xu et al (189) also described that among the 3 epidural steroid injections in patients on a regimen of anticoagulation therapy that resulted in lumbar or thoracolumbar epidural hematomas, the case report by Snarr (392) documented a dural puncture, suggesting an increased likelihood of trauma in the spinal canal during the procedure. The patient also had a history of

receiving several epidural steroid injections in the area in addition to being on warfarin therapy, both of which are known risk factors for hematoma development after epidural analgesia (85). Repeated epidural steroid injections, along with anatomical variations including post surgery syndrome, are major issues in interventional pain management. Many of the patients present with spinal stenosis, spondylosis, facet arthrosis, and post surgery syndrome often with multiple surgical interventions. These patients also suffer with comorbid medical disorders requiring antiplatelet therapy and many of the patients in interventional pain management settings are obese. Xu et al (189) also discussed that the case reported by Horlocker and Wedel (396) involved a patient taking enoxaparin and aspirin, but there is no additional information on dosage, timing, or injection technique to evaluate the risk factors for hematoma development. The case by Ain and Vance (190) was considered most similar to the case by Xu et al (189). The patient was an 85-year old woman who was taking warfarin for atrial fibrillation and aortic valve replacement (190). Warfarin was withheld 6 days before the epidural steroid injection, and the patient received 1 mg per kg enoxaparin every 12 hours for 4 days before her appointment. A traumatic epidural steroid injection was performed greater than 24 hours after her last enoxaparin dose. The patient resumed her warfarin treatment on the evening of the injection and continued to take 1 mg/kg subcutaneous enoxaparin every 12 hours starting the second day after the procedure. Two days later, she experienced excruciating back pain, which was revealed to be an L2/4 hematoma on MR imaging. Similarly, Xu et al's (189) patient developed an epidural hematoma after epidural steroid injections, despite having following the ASRA's most current guidelines for patients receiving neuraxial anesthesia who are on a regimen of LMWH. These guidelines state that patients should discontinue warfarin for 4 - 5 days before neuraxial procedures, and recommend performing the procedure later than 24 hours after the last dose of bridging LMWH. If needle placement is traumatic or if blood is encountered during needle placement, a 24-hour delay is recommended before restarting LMWH.

The debate also continues with ophthalmic surgeries (165,253,518-526). Research in ophthalmic surgery is based on perioperative management focusing on cataract surgery (527-536). However, cataract surgery has been described to be of lower risk of hemorrhage by virtue of small incision techniques and the use of topical anesthesia when compared to glaucoma surgery (165,253). Patients undergoing glaucoma surgery often start with high intraocular pressure, experience a sudden drop in intraocular pressure or a period of hypotony, and may require an iridectomy. Consequently, these factors post an increased risk of intraoperative or delayed bleeding in the form of hyphema, vitreous or retinal hemorrhage, or choroidal hemorrhage (513,534,535). In addition, complications may also be related to the type of anesthesia (536). A study of 347 patients (eyes) who were on anticoagulant therapy or antiplatelet therapy prior to glaucoma surgery (253) showed a higher rate of hemorrhagic complications than 347 control patients with hemorrhagic complications of 10.1% versus 3.7%. Patients on coagulant therapy had a higher rate of hemorrhagic complications than patients on antiplatelet therapy (22.9% versus 8%).

The risk of thromboembolic phenomenon may be even more significant than the risk of epidural hematoma. The regional anesthesia and interventional pain management literature has only focused on the risks of epidural hematoma paying scant attention to thromboembolic events. However, multiple guidelines of other specialties have described continuation of antiplatelet therapy during surgical interventions including peripheral vascular surgery with exceptions (108-130,141-143,146,151-165,253).

In a systematic review and meta-analysis of the hazards of discontinuing or not adhering to aspirin among patients at risk for coronary artery disease (14), noncompliance or withdrawal of aspirin treatment was illustrated with ominous prognostic implications in those at moderate-to-high risk for coronary artery disease. This study showed aspirin nonadherence or withdrawal being associated with a 3-fold higher risk of major adverse cardiac events which was magnified in patients with intracoronary stents with the conclusion that aspirin discontinuation in such patients should be advocated only when bleeding risk clearly overwhelms that of atherothrombotic events. In a study of the evaluation of incidence of death and acute MI associated with discontinuation of clopidogrel (Plavix) after acute coronary syndrome (19), the authors observed a clustering of adverse events in the initial 90 days after discontinuation among both medically treated and percutaneous coronary intervention treated patients with acute coronary syndrome, supporting the possibility of a clopidogrel rebound effect.

It has been shown that approximately 5% of patients who have undergone percutaneous coronary

interventions will undergo noncardiac surgery within the first year after stenting (537). However, the proportion of patients undergoing other invasive procedures such as interventional techniques may be even higher (37-41,43-78,81-88,92,97,98,390,537). The physicians managing such patients are confronted with the complex issue of the risk of hemorrhagic complications when continuing the antiplatelet agents in the perioperative period and the risk of cerebral and cardiovascular events if the drugs are discontinued abruptly (14,37-41,43-78,81-88,92,97,98,143,390,537-561).

The data suggest the traditional attitude of discontinuing the medication 10 days before interventions poses considerable danger (108-130,139-146,537). Multiple guidelines recommend discontinuation and this has been a general practice to discontinue these drugs (85). Thus, despite the lack of evidence of significant risk of bleeding during interventional techniques in patients with antithrombotic therapy (83-85,96), they are routinely discontinued. However, neither the continuation or discontinuation of antithrombotic therapy are without risk (85,86,172-177,296,397). While most of the reports are related to regional anesthesia for surgical procedures, there have also been multiple reports of epidural hematoma in patients undergoing interventional techniques for chronic pain with or without antithrombotic therapy – continued or discontinued (81-96,176-178,180,187,189,190,193,201,204,222,276,388,391).

Appropriate diagnosis and prompt conservative or surgical intervention is of paramount importance in any type of epidural hematoma. At present, surgical intervention is considered the most appropriate treatment if neurological compromise is evident; however, the literature illustrating improvement with conservative management raises additional questions. Thus, appropriate discussion with the patient, surgical team, and consideration of the degree of neurological deficit and progression, stability, or regression with shared decision-making is essential.

Multiple guidelines have been published with differing recommendations not only based on different regional practice approaches, but also on different specialties such as regional anesthesia versus interventional pain management (85,492-495,537-541). All these guidelines are prepared based on case reports and observational studies with inadequate sample sizes. Raj et al (86) have described specific protocols for interventional pain management with risk stratification. However, it seems that the interventional pain management community continues to focus on the

guidelines developed by ASRA (85). Due to the lack of guidelines prepared for interventional pain management with specific concerns, regional anesthesia guidelines are discussed herewith. The most commonly used guideline is the one prepared by ASRA. These guidelines are described as evidence-based guidelines with appropriate strength and grade of recommendations. However, these are based on observational studies and case reports. In fact, the process and validity of these guidelines has been questioned (405,491). It is universally accepted that warfarin has to be stopped 3 to 5 days prior to interventional techniques, unless the INR is at an acceptable level, antiplatelet therapy and bridging have been described with variable opinions in multiple guidelines (85,492-495,537-541). ASRA guidelines by Horlocker et al (85) recommend the following on perioperative management of patients on antiplatelet therapy:

- For patients with coronary stents, elective surgery is to be postponed for aspirin and clopidogrel therapy, therapy is continued for 4 to 6 weeks for bare-metal stents and 12 months for drug eluting stents (85,492,493).
- If surgery cannot be postponed, continue aspirin throughout perioperative period.
- Patients at highest risk for cardiac events exclusive of coronary stents.
- Continue aspirin throughout the perioperative period. Discontinue clopidogrel at least 5 days and preferably 10 days before surgery. Resume clopidogrel 24 hours postoperatively.
- Patients at low risk of cardiac events.
- Discontinue antiplatelet therapy 7 to 10 days before surgery. Resume antiplatelet therapy 24 hours postoperatively.

Horlocker (494) in a manuscript published in 2011 in reference to regional anesthesia and the patient receiving antithrombotic and antiplatelet therapy provided the same guidance as described in the guidelines (85).

- The concurrent use of medications that affect other components of clotting mechanisms, such as oral anticoagulants, standard heparin, and LMWH, increases the risk of bleeding complications for patients receiving antiplatelet agents.
- NSAIDS, by themselves, represent no significant risk for the development of spinal hematoma in patients having epidural or spinal injections.
- Allow platelet function to recover before neuraxial block after administration of ticlopidine, clopido-

grel, and platelet glycoprotein IIb/IIIa receptor antagonist.

- The time to normal platelet aggregation after discontinuation of therapy is 14 days for ticlopidine, 5 to 7 days for clopidogrel, and 7 to 10 days for Prasugrel (Effient).
- For the platelet glycoprotein IIb/IIIa inhibitors, the duration ranges from 8 hours for eptifibatide and tirofiban and 48 hours after abciximab administration.

Nordic guidelines for neuraxial blocks in disturbed hemostasis from the Scandinavian Society of Anesthesiology and Intensive Care Medicine were published in 2010 (538). These guidelines were developed by a task force of experts to establish consensus on recommendations for best clinical practice in providing effective and safe central neuraxial blocks in patients with an increased risk of bleeding. They performed a literature search and expert evaluation of the evidence which included risks of spinal bleeding from hereditary and acquired bleeding disorders and antihemostatic drugs used for thromboprophylaxis, risk evaluation in published case reports, and recommendations in published national guidelines. In reference to platelet inhibitors, they recommended the following.

1. Aspirin
- In patients on aspirin for secondary prevention after coronary event or stroke, aspirin is continued up to the day of central neuraxial block. (Recommendation grade C; evidence category III)
- In patients on aspirin for primary prevention of arterial thrombotic events, aspirin is interrupted 3 days before a planned central neuraxial block. (Recommendation grade D; evidence category IV)
- In patients on higher doses of aspirin treatment for its analgesic or anti-inflammatory effects (greater than 1 gm per day), 7 days should be allowed to elapse between the last aspirin dose and central neuraxial block. (Recommendation grade D; evidence category IV)

2. NSAIDs other than aspirin
- In patients treated with NSAIDs, they recommended that the treatment is discontinued before a central neuraxial block. The drug-free intervals should be no less than 12 hours for Diclofenac, ibuprofen, ketoprofen; 24 hours for indomethacin, Ketoralac, Lornoxicam; 48 hours for naproxen; and 2 weeks for piroxicam and tenoxicam. (Recommendation grade D; evidence category IV)
- In patients planned for central neuraxial blockade,

they recommended that a non-selective NSAID be replaced by another analgesic in the immediate perioperative period. (Recommendation grade D; evidence category IV)

3. Dipyridamole
- The consensus of these guidelines was that dipyridamole was a weak platelet inhibitor without any clinical important antihemostatic effect. Consequently, they recommended that there is no need for discontinuation before a central neuraxial blockade.

4. Thienopyridine-adenosine phosphate (ADP) blockers. These include clopidogrel, ticlopidine, prasugrel (Effient), and other novel antiplatelet drugs.
- In patients treated with clopidogrel or ticlopidine alone for primary prevention of thrombotic events, the treatment is discontinued no less than 5 days before an intended central neuraxial block. (Recommendation grade C; evidence category IV)
- In patients treated with dual antiplatelet medication with a thienopyridine and aspirin, after coronary stent implantation, the antiplatelet medication should not be interrupted and central neuraxial block is contraindicated. (Recommendation grade C; evidence category III)

Recommendations of the European Society of Anesthesiology (ESA) for regional anesthesia and antithrombotic agents (539) were published in 2010 by the ESA. They arrived at the guidelines by extensive review of the literature and consensus. Their results and conclusions included that in order to minimize bleeding complications during regional anesthetic techniques, care should be taken to avoid traumatic puncture. They also concluded:

- Regional anesthesia in patients receiving full anticoagulation treatment continues to be contraindicated.
- Aspirin and other NSAIDs may be continued.
- Clopidogrel be discontinued 7 days prior to central neuraxial block, ticlopidine 10 days, prasugrel (Effient) 10 days.

Green and Machin (540) in 2010 described the management of anticoagulant patients during neuraxial anesthesia. They summarized the results that performing a central neuraxial block in patients on anticoagulant therapy is a complex decision that should take into account the twin risks of bleeding and venous/arterial thrombosis if anticoagulation therapies were to be stopped. They felt that various guidelines issued to achieve normal hemostasis and thus allow safe admin-

istration of central neuraxial block are weak based on the evidence which is observational studies and mainly case reports. Thus, they recommended that it is crucial to fully assess individual risk factors and understand anticoagulant pharmacokinetics in order to appropriately provide central neuraxial blockade. They described multiple patient-related risk factors associated with spinal epidural hematoma which included patient related factors such as elderly, female gender, acquired coagulopathy (liver/renal failure, malignancy, HELLP syndrome, DIC, etc.), thrombocytopenia, spinal abnormalities such as spina bifida, spinal stenosis, spinal tumors, ankylosing spondylitis, and osteoporosis. They also described procedure-related risk factors including a traumatic procedure with multiple attempts, presence of blood in the needle or the catheter, indwelling epidural catheter compared to a single shot epidural, and catheter removal. Drug related factors included anticoagulant therapy, and dual anticoagulant and antiplatelet therapies. They reported 9 cases of epidural hematomas (98,175,189,190,283,386-389).

Vandermeulen (541) in a 2010 manuscript described various issues related to regional anesthesia and anticoagulation. He summarized the recommendations from various guidelines.

- Clopidogrel has to be stopped 7 days prior, ticlopidine 10 days, eptifibatide/tirofiban 8 to 10 hours, and prasugrel (Effient) for at least 7 days before intervention.
- Low-dose aspirin and dipyridamole may be continued except in cases with concomitant administration of other drugs.

Non-steroidal Antiinflammatory Drugs (NSAIDS)

NSAIDs inhibit cyclooxygenase and thus platelet aggregation in a reversible manner in proportion to the half-life of the agent used. For selective COX-2 inhibitors, there is no evidence of any relevant effects on platelet aggregation capacity or an increased bleeding tendency (542). The nonopioid analgesics, acetaminophen and dipyrone, have not been linked to spinal epidural hematomas. In contrast, aspirin, even after a single-dose, leads to irreversible inhibition of platelet function as a result of cyclooxygenase inhibition. Due to the lack of a nucleus, platelets are not able to synthesize new cyclooxygenase, so that the effect persists for the entire lifetime of the platelets, usually 7 to 10 days. However, healthy bone marrow will replace more than 30% of the irreversibly inhibited platelets within 3 to 4

days (543,544). Bleeding effects of aspirin appear to be dose dependent, with more adverse events observed in patients receiving more than 100 mg daily (545). Even though spontaneous bleeding in those taking aspirin is doubled, the risk remains generally very low, with a requirement of 800 patients annually to be treated for one additional bleeding event to occur (546). In a meta-analysis of noncardiac surgical procedures, 1.5-fold higher bleeding rates were reported in patients receiving aspirin (539). With the exception of intracranial procedures, prosthetic resections, and tonsillectomies, no severe cases of bleeding were observed (143). Multiple studies considered the safety of neuraxial interventions during aspirin administration (82-85,89,96,461,462). The Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) (557) included a total of 9,364 pregnant women, only 2,783 of the women underwent epidural analgesia. Overall, only 700 women were available for analysis. None of the women in this study experienced a problem related to aspirin. Pregnancy was associated with a general low grade activation of coagulation, and aspirin was taken alone rather than in combination with other thromboprophylaxis. These 2 factors would have reduced the risk of epidural hematoma in this cohort. Horlocker et al (83,84,96) included a number of patients not only for surgery, but also for interventional techniques with epidural steroids. A small proportion of patients received concurrent thromboprophylaxis with heparin, a significant proportion received multiple antiplatelet drugs, and no epidural hematomas were observed. Manchikanti et al (82,461,462) evaluated 12,000 encounters with 18,000 procedures which included over 1,500 patients on aspirin undergoing epidural injections with 1,050 of them continuing their aspirin therapy during the procedures and 500 discontinuing it, with no incidence of epidural hematoma or major bleeding episodes for any interventions.

Multiple adverse cardiovascular events have been described with discontinuation of aspirin. Aspirin is known to reduce the risk of a recurrent cardiovascular event by around 30%, and mortality by approximately 15%, in patients with a history of acute coronary syndrome, stroke, or peripheral arterial occlusive disease (547). The risk of discontinuing aspirin in patients with implanted coronary stents or unstable coronary syndromes has been described, along with a rebound phenomenon. Consequently, the preoperative withdrawal of aspirin is unnecessary in most cases and is associated with a high risk of acute thrombosis (539). However, it should be noted that concurrent intake of ibuprofen

may lead to a reduction in the efficacy of aspirin (542) and that NSAIDs increase the risk of adverse cardiovascular events. The American College of Chest Physicians (ACCP) does not currently recommend assessment of platelet function before invasive procedures because there is no apparent correlation with the bleeding (492).

Thus, based on the previous guidelines and comprehensive evaluation of the literature, NSAIDs, including low-dose aspirin, specifically when given in isolation, do not increase the risk of spinal epidural hematoma and are not a contraindication for interventional techniques.

Platelet Aggregation Inhibitors:

Ticlopidine and clopidogrel are the most commonly utilized platelet aggregation inhibitors belonging to the thienopyridine group (560-562). Prasugrel (or Effient) is also a platelet aggregation inhibitor (563-569). They act by antagonizing adenosine diphosphate (ADP) at the platelet's purine receptors. ADP-induced aggregation is noncompetitively and irreversibly inhibited whereas arachidonic acid metabolism is unaffected. They undergo hepatic conversion into active metabolites in vivo. Consequently, several days are required before full effect is reached, and the process is dose dependent. The active metabolites are eliminated by the kidneys (548). A reduction in ADP-dependent activation of the glycoprotein 2B/3A receptor takes place, causing a reduction in fibrinogen fixation and platelet cross-linking. On a 500 mg per day regimen, the maximum aggregation inhibiting effect is achieved after 8 to 11 days on ticlopidine. The elimination half-life is 24 to 32 hours, but because platelet function inhibition is irreversible, the effect is still in evidence more than 72 hours after its withdrawal (549). However, with long-term administration, the elimination half-life increases to over 90 hours, and following cessation, 10 days should be allowed before normalization can be expected (550). In contrast to clopidogrel, ticlopidine can lead to neutropenia in up to 1% of the patients, limiting widespread use of the drug and making regular blood count checks necessary in the initial weeks.

Prasugrel or Effient is a thienopyridine which is a prodrug that requires conversion to an active metabolite before binding to the platelet P2Y2 receptor to develop antiplatelet activity (563-569).

Prasugrel, or Effient, is given as a 60 mg loading dose producing at least 50% inhibition of platelet aggregation by one hour in 90% of patients. Mean steady-state inhibition of platelet aggregation was about 70% following 3 to 5 days of dosing at 10 mg daily after 60 mg loading dose of Effient (563-569). Platelet aggregation gradually returns to baseline values over 5 to 9 days after discontinuation of prasugrel, which is a reflection of new platelet production rather than the pharmacokinetics of prasugrel. However, the relationship between inhibition of platelet aggregation and clinical activity of Prasugrel has not been established (563). Prasugrel is a prodrug and is rapidly metabolized to a pharmacological active metabolite and inactive metabolites. The active metabolite has an elimination half-life of about 7 hours ranging from 2 to 15 hours. In addition, healthy subjects, patients with stable atherosclerosis, and patients undergoing percutaneous coronary intervention show similar pharmacokinetics. A large phase 3 study randomly assigned 13,608 patients with moderate to high risk acute coronary syndromes scheduled for percutaneous and coronary intervention to receive prasugrel (Effient) or clopidogrel for 6 to 15 months. Prasugrel (Effient) therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major hemorrhage that was occasionally fatal (570). Thus far, no data are available in reference to use of this drug prior to interventional techniques. The antiplatelet effects last for the platelet lifespan and pretreatment levels of platelet function are achieved 7 to 10 days after discontinuation.

Adverse events of prasugrel included hypertension, hypotension, atrial fibrillation, brachycardia, noncardiac chest pain, and peripheral edema in 3% to 8% of the patients; headache, dizziness, fatigue, fever, extremity pain in 3% to 6% of the patients; and hypercholesterolemia and hyperlipidemia in 7% of the patients. Epistaxis, dyspnea, and cough also have been reported. Surprisingly, back pain was reported in 5% of the patients (551-557).

The maximum platelet function inhibiting effect is observed after 3 to 7 days or approximately 12 to 24 hours following oral administration of clopidogrel 75 mg, 6 to 7 days after following oral administration of clopidogrel 75 mg, or in approximately 12 to 24 hours following initial bolus administration of 300 to 600 mg. Recovery of platelet function occurs only 6 to 7 days after clopidogrel administration (558).

Risk of bleeding with thienopyridines has been reported to be more frequent than with aspirin. The incidence of severe bleeding is increased by simultaneous treatment with vitamin K antagonists, dextrans,

or heparins (548). Clopidogrel treatment in patients undergoing cardiac surgery may cause severe surgical bleeding, with a 2.5-fold increase in the need for transfusion and a 5- to 10-fold increase in the risk of repeat surgery, as well as prolonged course of intensive therapy (559-561). Immediate improvement of hemostasis is only possible by administering platelets. There have been reports of spinal epidural hematoma following neuraxial blockade during clopidogrel administration. However, spinal epidural hematoma following discontinuation of clopidogrel administration also has been described (81,176,177). In the study by Manchikanti et al (82), with over 265 patients on clopidogrel and an additional 265 patients on combination of aspirin and clopidogrel, with continued therapy during interventional procedures in over 200 patients and discontinuation of at least 7 days in 330 patients, there were no differences noted in outcomes with no major bleeding or epidural hematoma.

In reference to the thromboembolic events, compared to aspirin, clopidogrel and ticlopidine are better at preventing ischemic cerebral infarction (562), MI, and vascular deaths in general (555,558,560,562). Prasugrel has been shown to be more effective than ticlopidine and clopidogrel in reducing the combined rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (552). However, an increased rate of serious bleedings and fatal bleedings was also observed (565-570). However, the overall mortality did not differ between the 2 treatment groups. Overall, it has been suggested that acute coronary syndrome patients can be safely switched from clopidogrel to prasugrel and that doing so results in a further reduction in platelet function after one week (567). Another study of high risk patients also produced similar results with clopidogrel and prasugrel (569).

Thus, patients with unstable coronary syndromes, previous percutaneous coronary interventions, and stent implantations, benefit from long-term dual platelet aggregation inhibitors with aspirin and clopidogrel (562,571). The premature withdrawal of this treatment following coronary interventions increases the risk of stent thrombosis and MI with high mortality (572). Patients with a drug eluting stent are at risk for a particularly long period, due to late and incomplete endothelialization (573). Consequently, the American Heart Association (AHA) currently recommends drug eluting stents are used only provided no surgery is planned within the following 12 months, and the patients show a high degree of compliance (574). Thus, with multiple

other risk factors in interventional pain management settings, a cardiologist should be consulted before an interruption of platelet aggregation inhibition, and clopidogrel with aspirin should be administered during the perioperative period. However, with bare-metal stents, dual platelet aggregation inhibition should be administered for at least 4 to 6 weeks and with both types of stents, the administration of aspirin should be continued on a lifelong basis and perioperative interruption should be avoided (574).

It is also important to consider that selective serotonin reuptake inhibitors (SSRIs) are often used to treat depression and also deplete serotonin in platelets by blocking reuptake and can produce a range of disorders through a decreased platelet binding affinity, blockade of platelet calcium mobilization, and reduced platelet secretion (575-577). A slight bleeding tendency may be evident during the perioperative period (578-580) and one study found blood transfusion requirements to be higher in patients on SSRIs (581). However, others have failed to find increased perioperative bleeding in patients undergoing coronary artery bypass grafting (582,583). Thus, the use of SSRIs with other drugs have an influence on coagulation, such as aspirin, thienopyridines, NSAIDs, vitamin K antagonists, or even LMWH which seem to increase the bleeding tendency (584-586). However, there are no reports of spinal hematoma following neuraxial block during the use of SSRIs.

Platelet function after cessation of therapy was assessed in some studies, and clopidogrel therapy showed variable results (401,587). Perakis et al (587) examined the change in platelet function after the common clinical scenario of discontinuing chronic clopidogrel therapy in those patients preparing to undergo an elective surgery and the time course of platelet function recovery after clopidogrel discontinuation. Platelet inhibition was evaluated at baseline before clopidogrel discontinuation, and subsequently every other day in the week before their scheduled procedure, utilizing a VerifyNow P2Y12 device (Accumetrics, San Diego, CA). Mean platelet inhibition was 32.1% on day 0 before clopidogrel discontinuation, decreasing to 3.7% on day 4. Platelet inhibition decreased significantly after discontinuation of clopidogrel in a time-dependent manner, even though a considerable interindividual variability was observed over the study period. Patients on concomitant proton pump inhibitors and clopidogrel demonstrated a decreased effect of clopidogrel. In another study, Benzon et al (401) determined residual antiplatelet activity of clopidogrel before neuraxial in-

jections. They assessed residual platelet activity in 13 patients at baseline and 3, 5, and 7 days after discontinuation of clopidogrel. On day 3 after clopidogrel discontinuation, 2 patients had greater than 30%, 7 patients had 11% to 29%, and 4 patients had less than 10% platelet inhibition. On day 5, none of the patients had greater than 30%, 3 patients had 11% to 29% and 10 patients had less than 10% platelet inhibition. There were no differences between the platelet inhibition groups between days 5 and 7. The authors concluded that their findings support the recommendation that discontinuation of clopidogrel for 5 days allows greater than 70% of platelet function and might be adequate before a neuraxial injection is performed. This is an extremely small study. Consequently, it is difficult to draw conclusions on which to base patient care decisions.

Glenn et al (588) also described safe removal of an epidural catheter 72 hours after clopidogrel and aspirin administrations guided by platelet function analysis and thromboelastography. In addition, the influence of proton pump inhibitors on the antiplatelet potency of clopidogrel was evaluated by 5 different platelet functions concluding that concomitant treatment with proton pump inhibitors did not attenuate the antiplatelet effect of clopidogrel in patients on dual antiplatelet therapy irrespective of the type of proton pump inhibitor and the used test system (589). In contrast, increased platelet inhibition by enhancement of CYP3A4 metabolic activity was demonstrated by St. John's wort (590). Similarly, the addition of polyunsaturated Omega-3 ethyl esters to the combination of aspirin and clopidogrel significantly potentiated platelet response to clopidogrel after percutaneous coronary intervention (591).

Based on previous guidelines and comprehensive literature review with the existent case reports of epidural hematomas and thromboembolic events, there is limited evidence either to continue or discontinue clopidogrel and ticlopidine prior to interventional techniques. The current recommendations are that they may be discontinued for 7 days with clopidogrel and prasugrel and/or 10 to 15 days with ticlopidine, based on the consideration of the individual patient, risk factors, and the planned procedure in consultation with the treating cardiologist.

Phosphodiesterase Inhibitors:

Cilostazol, or Pletal, and dipyridamole or Persantine, produces a selective inhibition of phosphodiesterase, thereby increasing the intracellular level or cyclic adenosine monophosphate and causing a weak revers-ible inhibition of platelet aggregation (592-605). However, dipyridamole is used for inhibition of thrombus formation for chronic use, whereas it is used for vasodilation in high doses over a short-term period (594). Cilostazol, or Pletal with similar profile, is used in the alleviation of the symptoms of intermittent claudication in individuals with peripheral vascular disease (600,601).

Dipyridamole blocks the thromboxane synthase as well as the thromboxane receptor. It inhibits the cellular reuptake of adenosine into platelets, red blood cells, and endothelial cells leading to increased extracellular concentration of adenosine. Dipyridamole has also been shown to lower pulmonary hypertension without significant drop of systemic blood pressure. Dipyridamole inhibits formation of proinflammatory cytokines in vitro and proliferation of smooth muscle cells in vivo. Dipyridamole has been shown to increase myocardial profusion and left ventricular function in patients with ischemic cardiomyopathy. It has been shown to inhibit the replication of Mengovirus RNA (606) and can be used for myocardial stress testing as an alternative to exercise-induced stress methods. In fact, modified release dipyridamole, or Aggrenox, is used in conjunction with aspirin in the secondary prevention of stroke and transient ischemic attack (596). Dipyridamole absorption is pH dependent and concomitant treatment with gastric acid suppressors such as proton pump inhibitors will inhibit the absorption of liquid and plain tablets (597,598). However, modified-release preparations are buffered and absorption may not be affected (596,597,607,608). However, it is not approved as monotherapy for stroke prophylaxis, even though a Cochrane review has suggested that dipyridamole may reduce the risk of a further vascular event in patients presenting after cerebral ischemia (599).

Vascular smooth muscle contains PDE3A (phosphodiesterase 3A), thus, cilostazol also produces direct arterial vasodilatation. Consequently it is most commonly used for peripheral vascular disease. It has been approved for treatment of chronic peripheral arterial disease and recently, the ACCP recommended it for intermittent claudication in patients who do not respond to exercise therapy and are not candidates for revascularization (595). In addition, investigators also found that adding cilostazol to a dual antiplatelet treatment with aspirin and clopidogrel was superior in the prevention of coronary artery stenosis and cardiac death after primary percutaneous coronary intervention with drug eluting stents, without increasing the incidence of bleeding (609,610). Cilostazol is used orally at a dose

of 100 mg twice daily reaching maximum plasma levels after 2.7 to 3.6 hours. The compound is eliminated predominantly by hepatic metabolism and subsequent urinary excretion of the metabolites (593). The total pharmacological activity of cilostazol and its metabolites in mild hepatic or mild to moderate renal impairment was similar to that of healthy individuals. However, due to renal excretion of metabolites, cilostazol is contraindicated in patients with severe renal insufficiency and also moderate to severe hepatic impairment.

Aggrenox is a combination antiplatelet agent in a gelatin capsule format containing 200 mg of dipyridamole in an extended-release form and 25 mg of aspirin, as an immediate-release sugar-coated tablet. Their combination has been used in prevention of stroke and transient ischemic attack.

There has been one case report of a hematoma following epidural catheter removal during treatment with cilostazol (400), but in general, any prospective data on the perioperative use of the drug are lacking and the effect on the incidence of bleeding is currently unknown. In fact, Vandermeulen (541) after reviewing various guidelines concluded that dipyridamole may be continued except in cases with concomitant administration of other drugs. The Nordic guidelines (538) also recommended not to stop dipyridamole.

Based on the available guidelines and comprehensive review of the literature, there is limited evidence in reference to discontinue or continue these drugs during interventional techniques. Thus, considering the individual patient, risk factors, the planned procedure, and in consultation with the treating physician, dipyridamole (Persantine), Aggrenox (aspirin and dipyridamole), and Cilostazol (Pletal) may be continued.

Glycoprotein Inhibitors:

Glycoprotein IIb/IIIa inhibitors block the glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation, which represents the most potent form of platelet inhibition, though it is reversible (539). Abciximab inhibits over 80% of ADP-induced platelet aggregation and reduces thrombin generation after intravenous administration. Additional antithrombotic properties that distinguish it from other agents in this group include binding to platelets very quickly with its presence observed 2 weeks after the last administration, with no significant renal elimination. If severe bleeding occurs, transfusion of platelet concentrates is required, although redistribution of abciximab among the freshly infused platelets can also partly inhibit these. There is

approximately 50% to 80% platelet aggregation capacity 4 hours after intravenous administration with eptifibatide and tirofiban (611).

The most frequent side effects are severe bleeding and thrombocytopenia (612), which after abciximab occurs in 0.3% to 1.0% (611). Thrombocytopenia is most likely to have an immunological cause and occurs within the first 24 hours, so platelet count is required at this time (539,613). In acute coronary intervention, glycoprotein IIb/IIIa inhibitors reduce the incidences of MI and mortality. Abciximab is more effective than tirofiban or eptifibatide (614). In contrast to the acute effects of intravenous glycoprotein IIb/IIIa inhibitors, long-term administration of oral preparations does not appear to reduce cardiovascular complications; instead, an increased tendency to bleed and an increased mortality rate were observed (611).

As glycoprotein IIb/IIIa inhibitors are used only in acute coronary syndromes, in combination with anticoagulants and aspirin, and as cardiac surgery procedures are usually conducted as emergencies with continuing anticoagulation, neuraxial blockade is contraindicated (Class III, level C) (539). If a catheter has to be removed after their administration, most guidelines recommend waiting at least 48 hours after abciximab, and 8 to 10 hours after tirofiban or eptifibatide (615). At this time, a platelet count should always be obtained to exclude thrombocytopenia. In addition, their use has been restricted significantly (611,616-620).

Heparins:

Patients on unfractionated heparin as well as LMWH for thromboprophylaxis may present for interventional techniques. Thromboprophylaxis with low dose heparin does not lead to an increased risk of bleeding after neuraxial blockade, provided that a time interval of 4 to 6 hours is observed between heparin administration and puncture or catheter manipulation and withdraw (539). However, additional administration of low dose heparin should be delayed for at least one hour after the block (Evidence Class IIb, Level C evidence) (539). Generally, doses of low dose heparin used for venous thromboprophylaxis are relatively safe, an increased risk of bleeding occurs at therapeutic doses when neuraxial techniques are performed. Thus, they are contraindicated at therapeutic doses. Thus, a neuraxial block should be considered only after interrupting heparin administration for at least 4 hours and a normal activated partial thromboplastin time (aPTT) and/or anti-Xa activity be assessed. (Evidence Class: IIa, Level C) (539). However, coagulation

studies are not required during prophylaxis with unfractionated heparin, except when treatment has lasted 5 days or more, when a platelet count is needed to exclude heparin induced thrombocytopenia.

LMWHs are used for both prophylaxis and treatment of venous thromboembolism (621). The anticoagulated effect of LMWH is assessed by measuring plasma antifactor Xa activity. (Evidence Class I, Level A) (539). The described advantages of LMWH are related to its high bioavailability (approximately 100% after subcutaneous administration) and their longer half-life of 4 to 7 hours, which together make once daily administration feasible. For thromboprophylaxis, LMWHs are considered superior to unfractionated heparins and are the treatment of choice (622,623). With subcutaneous administration of LMWH, maximum efficacy levels are observed in approximately 3 to 4 hours, and the terminal elimination half-life in patients with normal renal function is approximately 4 to 6 hours (624,625). However, in patients with severe renal insufficiency, anti-Xa activity reaches a higher maximum level and the elimination half-life can increase by up to 16 hours (626). Thus to avoid any bleeding complications, there should be a time interval of at least 12 hours between subcutaneous administration of LMWH at prophylactic doses and neuraxial blockade (262,619,627). (Evidence Class IIa, Level C). If LMWH is prescribed on a twice daily schedule (e.g., enoxaparin 30 mg per day), compared to a once daily regimen, the risk of epidural hematoma may be increased because the trough levels of anti-Xa activity are higher (628). Consequently, when patients are receiving a twice daily schedule, at least one dose of LMWH should be omitted creating a 24 hour time interval before an interventional procedure and the subsequent dose. (Evidence Class IIb, Level C). However, when the risk of thrombosis is high in settings such as mitral or double mechanical valve replacement, neuraxial blockade is contraindicated. In addition, epidural hematomas with surgical anesthesia or spontaneously have been reported with LMWH (629-633).

Based on the available literature and guidelines with the risk of epidural hematomas, bleeding events, and thromboembolic events, there is limited evidence either to continue or discontinue unfractionated heparin or LMWH prior to interventional techniques. The current recommendations are that they may be discontinued approximately 12 hours to providing interventional techniques based on consideration of the individual patient, risk factors, the planned procedure in consultation with the treating cardiologist.

Vitamin K Antagonists:

Vitamin K antagonists, specifically warfarin have been utilized for therapeutic anticoagulation which is considered an absolute contraindication to neuraxial blockade unless INR is below the considered safe limits for the specific interventional technique. It can take several days after these drugs have been withdrawn before coagulation returns to normal; however, the process can be accelerated by administering vitamin K, prothrombin complex concentrates (PCC), or if PCC is unavailable, fresh frozen plasma. However, it requires an appropriate indication and should follow an individual risk-benefit analysis. Further, new oral anticoagulants such as Xa inhibitors, rivaroxaban (634), and apixaban or the thrombin inhibitor dabigatran have been utilized and also have been described to lack some of the limitations of the well known vitamin K antagonists (634). Multiple instances of bleeding or epidural hematoma have been reported with warfarin administration.

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-life (405,635,636). The half-life of factor VII is 6 to 8 hours, factor IX is 24 hours, factor X is 25 to 60 hours, and factor II is 50 to 80 hours. The prothrombin time (PT) is the test used most commonly to monitor therapy with vitamin K antagonists (405). The PT response to reduction of 3 of the 4 vitamin K-dependent procoagulant clotting factors II, VII, and X (635). The lack of reliability of the PT led to the use of the INR, the ratio of patient's PT to that of a control sample (635). The INR represents the activities of several coagulation factors during the onset and steady-state of warfarin therapy. 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 (637). Bleeding may occur if the level of any clotting factor is decreased to 20% to 40% of baseline. During the first few days of therapy, the PT reflects primarily a reduction of factor VII, the half-life of which is approximately 6 hours (85,405,638). Prolongation of the INR greater than 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% (636).

Multiple factors affecting warfarin response include patient variables such as age, female sex, and

preexisting medical conditions (lower patient weight, hepatic, cardiac, and renal disease) that are associated with an enhanced response to warfarin and/or a lower dose requirement for maintenance anticoagulation (85), Asian patients requiring lower doses than white patients during long-term therapy (85,635,639), and concomitant administration of various drugs with anticoagulant effects. Warfarin is a drug with a narrow therapeutic range. Consequently, attention to the individual patient's response to warfarin therapy and maintenance of a consistent level of anticoagulation is of paramount importance. Multiple dietary ingredients may affect clotting levels. Patients are advised to avoid grapefruit and cranberry products, to eat a consistent amount a week to week of spinach, turnip greens, other leafy greens, broccoli, brussel sprouts, kale, parsley, natto, liver, or green tea; herbal supplements such as garlic, ginger, gingko biloba ginseng, fish oil, tumeric, St. John's wort, chondroitin sulfate; vitamin supplements including vitamin A, C, or E over the 100% of the recommended doses; and chronic heavy drinking of beverages containing alcohol. Further, patients are recommended to drink black tea, which is not high in vitamin K and also choose vegetables which are not high in vitamin K such as corn, squash, potatoes, onions, carrots, cucumbers, celery, peppers, pumpkin, and tomatoes.

There are no studies directly examining the risk of procedure-related bleeding and INR in patients recently discontinued from warfarin. Consequently, careful consideration should be given before performing neuraxial interventional techniques 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. ASRA limitations provide timing of neuraxial catheter removal during warfarin thromboprophylaxis.

Administration of PCC or fresh frozen plasma is associated with high risk and has been considered inappropriate to normalize coagulation before neuraxial procedures (640-656). Vitamin K supplementation may be considered in some patients (640-666). A literature review by Holbrook et al (640) found a weak recommendation for vitamin k supplementation along with a multitude of other factors. However, the anticoagulation management guidelines by Holbrook et al (640) provided a strong recommendation to target an INR ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy. Gebuis et al (659) showed variability in INR

with vitamin K1 supplementation resulting in an improvement of time that anticoagulation was within the therapeutic range. Vitamin K1 and K2 are capable of reversing the anticoagulant activity of warfarin. Supplemental vitamin K, for which oral dosing is often more active than injectable dosing in human adults, reverses the vitamin K deficiency caused by warfarin, and therefore modulates or totally reverses the intended anticoagulant action of warfarin and related drugs. Foods containing high amounts of vitamin K like green leafy vegetables may reverse anticoagulant action of warfarin; however, occasionally small amounts of vitamin K (1 mg per day) are given orally to patients taking warfarin to facilitate more predictable action of warfarin. However, similar to warfarin, oral administration of vitamin K requires 2 to 5 days after dosing to have maximum effect while there is minimum effect in the first 24 hours after they are given. Vitamin K injection is administered most commonly in newborns (667). Vitamin K is also administered as an antidote for poisoning by vitamin K antagonists. In fact, multiple benefits of vitamin K have been demonstrated in animal studies (668-670). Dentali et al (671), in a systematic review of treatment of coumarin-associated coagulopathy, showed that vitamin K therapy is an effective treatment for INR prolongation in patients with Coumadin-associated coagulopathy. However, they showed that clinical trials powered to detect differences in rates of bleeding and thrombosis are now required to determine if vitamin K reduces the risk of bleeding without causing thrombosis in non-bleeding patients. Others (672,673) have also shown that vitamin K therapy is an effective treatment in patients with vitamin K-associated therapy in patients who have been anticoagulated. However, it was shown that oral vitamin K lowers the INR more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy in a randomized trial (673). This study showed that 15 of 26 patients receiving oral vitamin K and 6 of 26 patients receiving subcutaneous vitamin K had therapeutic INRs on the day after study drug administration in patients with an INR between 4.5 and 10.0. In a systematic review, Ansell et al (635) also recommended oral vitamin K rather than subcutaneous administration to reverse a mildly elevated INR. In contrast, in a systematic review and meta-analysis, Dezee et al (674), with inclusion of 21 studies of which 10 were randomized and 10 were prospective, concluded that there was limited evidence to suggest that oral and intravenous vitamin K are equivalent and more effective for excessive anticoagulation than sim-

ply withholding warfarin sodium. They also concluded that subcutaneous vitamin K is inferior to oral and intravenous vitamin K for this indication and is similar to placebo. They were unable to establish if treatment with vitamin K decreases hemorrhagic events from the published literature. Thus, the literature is conflicting in reference to the efficacy of vitamin K to reverse the anticoagulant effect of warfarin (575-592). Vitamin K supplements may be used either intravenously or orally based on the emergence of the situation in low doses with caution and understanding of adverse effects and risk of thromboembolism.

Warfarin may be stopped 3 days or longer based on risk factors, the planned procedure, individual patient, in consultation with the treating cardiologist. If the INR is higher than the desired level or 1.4 for epidural injections and somewhat higher for facet joint nerve blocks, etc., individual consideration must be given.

Thrombin Inhibitors

Dabigatran, or Pradaxa®, is an oral anticoagulant, which has been used more frequently to reduce thromboembolic phenomenon in stroke, as well as non-valvular atrial fibrillation. Dabigatran etexilate is an inactive pro-drug, which is converted to dabigatran in plasma. It is a direct thrombin inhibitor. After an oral dose, the peak effect is reached within 2 to 4 hours and the plasma half-life ranges from 11 to 22 (mean 13) hours after multiple dose administration (675). The dose recommendations are 150 mg taken orally twice daily for patients with creatinine clearance of greater than 30 mL per minute. However, for patients with severe renal impairment, the recommended dose is 75 mg twice daily. Many of the patients are converted from warfarin to dabigatran. Since dabigatran is an oral direct thrombin inhibitor, anticoagulant effect is through direct clotting factor inhibition and not clotting factor depletion. Thus, the administration of clotting factors is not anticipated to be wholly effective in reversing the effects of dabigatran. However, dabigatran is not highly protein bound and is mostly cleared by the kidneys. Administration in the setting of renal failure will lead to a half-life in excess of 24 hours. Consequently, the primary means of reversing the effects of dabigatran is through natural renal elimination. Hemodialysis may be effective in removing approximately 60% of dabigatran.

There is no data correlating any lab tests of dabigatran levels to any clinical outcome. In the absence of such a test, measurements are very difficult. Essentially a normal thrombin time means that the drug is dissi-pated, which may take several days to occur even in patients with normal creatinine clearance. There have not been any major prospective studies.

Dabigatran or Pradaxa may be stopped for procedures with standard risk of bleeding for 24 hours in patients with creatinine function over 50 mL per minute or for 2 to 5 days for those with reduced renal function for interventional techniques with high risk of bleeding entering the epidural space or spinal canal for patients with normal renal function with creatinine clearance of 50 to 80 mL,. They may be stopped for 2 to 4 days. In patients undergoing spinal interventional techniques entering the epidural space, with low renal function below 50 mL creatinine clearance per minute, they should be stopped for at least 4 days or longer.

Anti-Xa Agents

Among the multiple factor Xa inhibitors, rivaroxaban, or Xarelto®, has been utilized commonly in the United States by oral administration. Its renal elimination and hepatic clearance is dabigatran 33% active drug with each route. The hepatic elimination make accumulation less likely than with other anticoagulants which are exclusively eliminated through the kidney. Rivaroxaban prolongs the PT time in a dose-dependent manner (680). Its half-life is 5.7 to 9.2 hours. Plasma protein binding of rivaroxaban is approximately 92% to 95% with albumin being the main binding component in humans. Following oral administration, approximately one-third of the absorbed dose is excreted and changed in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and feces. Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increases in subjects with renal impairment, with increased pharmacodynamic effects. Similarly, with hepatic impairment, compared to patients with normal liver function, significant increases in rivaroxaban exposure were observed, along with increased pharmacodynamic effects.

There have not been any major prospective studies in assessment of laboratory tests for dabigatran prior to surgery or interventional techniques. However, some laboratory coagulation tests can be used as qualitative assessment to determine if dabigatran is significantly contributing to bleeding event. Activated partial thromboplastin time, or aPTT, can be used but is relatively insensitive to the effects of direct thrombin inhibitors. The expected median peak aPTT level is approximately 2 times control values and median trough aPTT is approximately 1.5 times control values. The

utility of aPTT assessment is primarily for its negative predictive value. Consequently, aPTT indicates a little anticoagulant activity. However, even a mildly elevated aPTT can still be associated with clinically important levels of dabigatran and aPTT becomes increasingly insensitive at higher dabigatran levels as could be seen in an overdose (676). Thrombin time (TT) or aPTT is a sensitive test to assess the effects of therapeutic dabigatran levels and a normal TT excludes the presence of significant dabigatran levels. Further, TT is also subject to influence of concomitant administration of other coagulants.

Ecarin clotting time (ECT) is a test which shows strong linear relationship between dabigatran levels and ECT a normal ECT generally excludes the presence of significant dabigatran levels. Moreover, the ECT is not influenced by the concomitant administration of other anticoagulants. However, ECT is not an easily available test.

In most patients with normal kidney function, dabigatran is excreted within one to 2 days after the last dose has been taken. Since the half-life of dabigatran is considered as 13 hours, due to its renal excretion, 50% of dabigatran is excreted within 13 hours, with another 25% excreted in the next 13 hours and 87.5% in the next 13 hours. Thus, in patients with standard risk of bleeding, discontinuation for 24 hours and those with high risk of bleeding for 2 to 4 days with renal function with creatinine clearance above 50 mL per minute is advised. In patients with creatinine clearance of 30 to 50 mL, half-life is considered as 18 hours with discontinuation for 48 hours in patients with standard risk of bleeding and over 4 days for high risk bleeding is applicable. In patients with creatinine clearance of less than 30 mL where half-life is expected to be 27 hours with a range of 22 to 35 hours, in patients with standard risk of bleeding, it may be discontinued for 48 to 120 hours, whereas in patients with high risk of bleeding, it should be discontinued a minimum of 5 days. The examples of high risk of bleeding include surgical intervention such as heart surgery, neurosurgery, abdominal or major organ surgery. Further, patients with low blood platelets, bleeding disorders, and previous major bleeding, etc., are also considered as high risk. Finally, spinal anesthesia is considered as high risk. Consequently, spinal interventional techniques involving epidural or spinal modalities are considered as high risk. Extraspinal techniques such as facet joint nerve blocks may fall into standard risk of bleeding category (677-679).

The potential for drug interactions include CYP3A4 and P-glycoprotein inhibitors. It may be monitored by assessing PT and there are no antidotes available. Consequently, there is no absolute data correlating any lab tests of rivaroxaban levels to any clinical outcome, either thrombosis or bleeding. PT time goes up to 13 to 25 seconds, 2 to 4 hours after the dose, then returns to normal, before the drug is fully dissipated. There has not been INR correlation. Thus, an abnormal PT means rivaroxaban has been taken recently (680). There are various other tests in consideration. There is no specific antidote for rivaroxaban (680). In addition, because of high plasma protein binding, it is not expected to be dialyzable. Protamine sulfate and vitamin K are not expected to affect anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents in individuals receiving rivaroxaban.

Available experience with neuraxial blockade or interventional techniques is very limited, thus, extreme caution is recommended when performing interventional techniques in the presence of rivaroxaban. However, it is clearly noted that epidural or spinal hematomas have occurred in patients treated with rivaroxaban in patients undergoing either neuraxial anesthesia, spinal puncture, or spinal interventional techniques. Concomitant use of other drugs that affect hemostasis such as NSAIDs, platelet inhibitors, and other anticoagulants, a history of traumatic or repeated epidural or spinal puncture, a history of spinal deformity, or a spinal surgery are important correlates for increased levels of risk. A time interval of 22 to 26 between the last dose of rivaroxaban of 10 mg and catheter withdrawal has been required (539).Further, rivaroxaban dose is not to be administered earlier than 6 hours after the removal of a catheter and it may be delayed for 24 hours if traumatic puncture occurs.

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban may be stopped at least 24 hours before the procedure to reduce the risk of bleeding. Rivaroxaban may be restarted after the surgical or other procedures as soon as adequate hemostasis have been established noting that the onset of therapeutic effect is short. Based on the current literature, rivaroxaban may be discontinued 24 hours prior to performing interventional techniques based on risk factors, the planned procedure, individual patient, in consultation with the treating cardiologist.

Recommendations:

This comprehensive review with extensive literature search and analysis of various guidelines and the literature has provided recommendations specific for interventional techniques (Table 6). The recommenda-

Table 6. *Antithrombotic/antiplatelet therapy and interventional techniques guidelines.*

Medication	ASIPP Guidance		ASRA Guidelines (2317,2396)	Nordic Guidelines (2397)	European Guidelines (2398)	Belgium Guidelines (2399)
	Time to Wait After Last Dose of Medication Before High Risk Interventional Techniques Are Performed	Time to Wait After Last Dose of Medication Before Caudal or Paravertebral Interventional Techniques are Performed				
NSAIDS	Do not stop	Do not stop	Do not stop	12 hours to 2 weeks	Do not stop	Do not stop
Aspirin						
Low dose aspirin	Do not stop	Do not stop	Do not stop	None to 12 hours	Do not stop	Do not stop
High dose aspirin	May stop for 7 days	May stop for 7 days	7 days	3 days	Do not stop	NA
Antiplatelet Agents						
Phosphodiesterase Inhibitors						
Dipyridamole (Persantine)	Do not stop	Do not stop	Do not stop	Do not stop	NA	NA
Cilostazol (Pletal)	Do not stop	Do not stop	NA	NA	42 hrs	NA
Aggrenox (dipyridamole plus aspirin)	Do not stop	Do not stop	NA	NA	NA	NA
Platelet Aggregation Inhibitors						
Clopidogrel (Plavix)	May stop for 7 days	May stop for 7 days	5-10 days	5 days	7 days	7 days
Prasugrel (Effient)	May stop for 7 days	May stop for 7 days	7-10 days	5 days	7-10 days	7 days
Ticlopidine (Ticlid)	May stop for 14 days	May stop for 14 days	5-10 days	5 days	10 days	10 days
Vitamin K Antagonists						
Warfarin	When INR is 1.4 or less, both warfarin may be stopped for 1-5 days.	When INR is 2.0 or less, both warfarin may be stopped for 1-5 days.	When INR is 1.4 or less, stop for at least 5 days.	When INR is below 1.4-2.2 stop for 1-4 days	When INR is 1.4 or below	When INR is less than 1.4. Stop for 4-10 days
Thrombin Inhibitors						
Dabigatran (Pradaxa)*	Normal renal function 2-4 days Impaired renal function (creatinine clearance < 50 mL/min) at least 5 days	Normal renal function 24 hrs. Impaired renal function (creatinine clearance < 50 mL/min) at least 5 days	NA	NA	NA	NA
Anti-Xa Agents						
Rivaroxaban (Xarelto)	24 hrs	24 hrs	NA	NA	NA	NA
Heparins						
Heparin (treatment) -IV	6 hrs and a PTT within normal limits	6 hrs and a PTT within normal limits	10-12 hrs and a PTT within normal limits	4 hrs and a PTT within normal limits	4-6 hrs and a PTT within normal limits	6 hrs and a PTT within normal limits
Heparin (treatment) - SC	12 hrs and aPTT within norm al limits	12 hrs and aPTT within normal limits	10-12 hrs and a PTT within normal limits	4 hrs and a PTT within normal limits	4-6 hrs and a PTT within normal limits	12 hrs and a PTT within normal limits
LMWH	12 hrs	12 hrs	10 hrs	10-24 hrs	12 hrs	12-24 hrs

*These recommendations are dependant on multiple factors including the individual patient, risk factors, and cardiologist opinion.
LMWH = Low Molecular Weight Heparin; PTT = Partial Thromboplastin Time; NSAID = Nonsteroidal Anti-inflammatory Drugs; INR = International Normalized Ratio; hrs = Hours

tions for various agents are dependent on multiple factors including the individual patient, risk factors, and cardiologist's opinion. This must be a shared decision. The risks of thromboembolic phenomenon and bleeding with hematoma formation must be considered equally. The recommendations provided here are based on previous guidelines and comprehensive literature reviews.

- NSAIDS, including low dose aspirin, do not increase the risk of spinal epidural hematoma and are not a contraindication for interventional techniques (evidence –good).
- However, high dose aspirin and combination of multiple drugs should be taken into consideration and may or may not be discontinued based on clinical judgment of individual risk and benefits assessment. In this regard, the simultaneous use of multiple agents that possess anticoagulant properties (e.g. NSAIDs or aspirin along with SSRIs, fish oil, etc.) will increase the risk of morbidity and/or mortality.
- Phosphodiesterase inhibitors including dipyridamole (Persantine), Aggrenox (dipyridamole plus aspirin), and cilostazol (Pletal) do not appear to increase the risk of spinal epidural hematoma and are not a contraindication for interventional techniques (evidence – fair).
- They may or may not be discontinued prior to interventional techniques.
- Platelet aggregation inhibitors including ticlopidine (Ticlid), clopidogrel (Plavix), and prasugrel (Effient) may be continued or discontinued prior to interventional techniques (evidence – fair).
- Based on patient factors and managing cardiologist's opinion, if a decision is made to discontinue, the current recommendations are that they may be discontinued for 7 days with clopidogrel and prasugrel and/or 10 to 15 days with ticlopidine (evidence – fair).
- There is also emerging evidence that discontinuation of 3 days may be effective (evidence – limited).
- Warfarin may be continued or discontinued based on INR achieved during therapy (evidence – good).
- For high risk interventional techniques including interlaminar epidural injections, percutaneous adhesiolysis, disc decompression, sympathetic blocks, and placement of implantables, warfarin should be discontinued for an appropriate period of time and INR of 1.4 or less must be achieved (evidence – good).

- For intermediate risk procedures such as caudal epidural injection, paravertebral interventional techniques, and peripheral joint injections, warfarin should be continued for an appropriate period of time and INR of 2 or less may be considered (evidence – limited).
- Unfractionated heparin or LMWH may be discontinued approximately 12 hours prior to providing interventional techniques (evidence – limited).
- Dabigatran (Pradaxa) may be stopped 2 to 4 days for major interventional techniques with high risk of bleeding in patients with creatinine clearance greater than 50 mL per minute. For low risk or paravertebral interventional techniques and caudal, it may be stopped for one day in patients with normal renal function. May be stopped at least 4 to 5 days for those with creatinine less than 50 mL per minute. (evidence – limited)
- Rivaroxaban (Xarelto) may be stopped for one day or longer (evidence-limited).

4.0 Conclusion

Based on the available literature including guidelines, the recommendations in patients with antithrombotic therapy for therapy prior to interventional techniques are provided.

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Conflict of Interest:

Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc.

Dr. Benyamin is a consultant with Bioness and Nevro; serves on the advisory boards of Vertos Medical and Nuvo Pharma; teaches/lectures for Vertos Medical, Boston Scientific, Neurotherm, and Bioness; and receives research/grants from Alfred Mann Foundation, Teknon Foundation, Spinal Restoration, Inc., Bioness, Boston Scientific, Vertos Medical, Medtronic, Kimberly Clarke, Epimed, BioDelivery Sciences International, Inc., Theravance, Mundipharma Research, Cephalon/Teva, AstraZeneca, and Purdue Pharma, LP.

Dr. Caraway is a consultant for Medtronic, Inc., Spinal Modulation, Inc., and Vertos, Inc.

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Dr. Schultz is a paid consultant for Medtronic.

Dr. Hirsch has received fees from CareFusion in the past 12 months. He participated in an Aetrium focus group and received compensation.

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