Pain Physician 2011; 14:317-329 • ISSN 1533-3159

Prospective Evaluation

A Prospective Evaluation of Bleeding Risk of Interventional Techniques in Chronic Pain

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Disclaimer and Conflict of interest: Please see page 326.

Manuscript received: 03/12/2011
Accepted for publication: 07/06/2011

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Background: The role of antithrombotic therapy is well known for primary and secondary prevention of cardiovascular disease to decrease the incidence of acute cerebral and cardiovascular events. Data shows that the risk of coronary thrombosis after antiplatelet drug withdrawal is much higher than that of surgical bleeding if the antiplatelet drug therapy were continued. However, it has been a common practice to discontinue antiplatelet therapy prior to performing interventional techniques, which may potentially increase the risk of acute cerebral and cardiovascular events.

Study Design: A prospective study of 3,179 patients undergoing interventional techniques with 12,000 encounters and 18,472 procedures from May 2008 to December 2009.

Study Setting: An interventional pain management practice, a specialty referral center, a private practice setting in the United States.

Objective: To assess the rates of adverse events in patients undergoing interventional techniques on antithrombotic therapy with cessation or without cessation and compare them to a group of patients without antithrombotic therapy.

Methods: Measurable outcomes employed were intravascular entry of the needle, bruising, local bleeding, profuse bleeding, local hematoma, oozing, and postoperative soreness.

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.

Results: 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 1376 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.

Limitations: Limitations include the nonrandomized observational nature of the study and that antiplatelet therapy was limited to aspirin and clopidogrel (Plavix).

Conclusion: No significant prevalence of adverse events was observed in those who continued with or ceased antithrombotic therapy.

Key words: Interventional pain management, interventional techniques, bleeding disorders, hemorrhagic complications, aspirin, nonsteroidal anti-inflammatory agents, clopidogrel (Plavix), warfarin (Coumadin), regional anesthesia, hemostasis, anticoagulants, antithrombotic agents.

Cardiovascular disease is among the leading causes of morbidity and mortality, whereas chronic persistent pain is the leading cause of disability and functional impairment around the world (1-4). 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 (1-4). Antithrombotic therapy has been established with a favorable risk-benefit ratio for prevention of cardiovascular disease and limits the present and future burden of coronary artery disease (1,5-11). Interventional techniques are performed with increasing frequency to manage chronic persistent pain, even though debate continues about their effectiveness and safety (12-39). 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 (5), noncompliance or withdrawal of aspirin treatment was illustrated with ominous prognostic implications in those with or 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 myocardial infarction (MI) associated with discontinuation of clopidogrel (Plavix) after acute coronary syndrome (10), 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 (40). However, the patients undergoing other invasive procedures such as interventional techniques may be even higher (13-21). 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. Even though data suggests that the traditional attitude of discontinuing the medication 10 days before interventions poses considerable danger (40-42), multiple guidelines recommend it and it has been a general practice to discontinue these drugs (43). Despite the lack of evidence of significant risk of bleeding during interventional techniques in patients with antithrombotic therapy (43-46), they are routinely discontinued. However, continuation and discontinuation of antithrombotic therapy are both not without risk (43,47-55). While most of the reports are related to regional anesthesia for surgical procedures, there have been multiple reports of epidural hematoma in patients undergoing interventional techniques for chronic pain with or without antithrombotic therapy – continued or discontinued (46,47,50-71).

Due to the lack of available evidence, direction, and continued debate, this prospective, nonrandomized evaluation was undertaken to assess the bleeding risk in patients with or without antithrombotic therapy and continuation or discontinuation of antithrombotic therapy.

Methods

The study was conducted in the United States in a private interventional pain practice and specialty referral center based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (72-74). The Institutional Review Board (IRB) approved the study protocol. The study is registered with the U.S. Clinical Trial Registry NCT00625248.

Participants

A total of 3,179 participants undergoing interventional techniques were assigned for evaluation from May 2008 to December 2009.

Interventions

This study was performed prospectively on patients without change in their normal course of treatment. Thus, the IRB waived the requirements for specific consent for inclusion in the study. However, all the patients were informed about the nature of the study with adherence to all confidentiality and Health Insurance Portability and Accountability Act (HIPAA) requirements.

Pre-Enrollment Evaluation

The patients provided the history of their antithrombotic therapy or lack thereof, the type of antiplatelet agents or warfarin (Coumadin), the status on the day of the procedure whether it had been discontinued or not, if discontinued, the duration prior to the

procedure was collected. Further the data with regards to previous bleeding history, unusual bruising, their response to previous treatments, if any were performed, were collected along with demographic data.

Inclusion and Exclusion Criteria

All the patients receiving interventional techniques during the time period were included, except those undergoing disc decompression procedures and intrathecal implantables.

Description of Interventions

Either diagnostic or therapeutic interventional techniques of various types were performed on all participants. The procedures were performed by 3 physicians in sterile operating rooms located in an ambulatory surgery center, using fluoroscopy except for intraarticular injections and peripheral nerve blocks.

Objectives

The study investigated the bleeding risk in participants undergoing various types of interventional techniques in managing chronic pain in patients with or without antithrombotic therapy, and in those patients who discontinued antithrombotic therapy or those who had not.

Outcomes

Measurable outcomes employed were intravascular entry of the needle, profuse bleeding, local bleeding, local hematoma, oozing, bruising, and postoperative soreness.

Eight nurses were trained to evaluate the above outcomes. Each participant was contacted postoperatively within 48 hours.

Statistical Analysis

Data were recorded in a database using Microsoft Access (Microsoft Corporation, Redmond, WA) by a person not participating in the study. The SPSS 9.0 statistical package (IBM Corporation, Armok, NY) was used to generate the frequency tables. Pearson chi-square test was carried out in the comparisons of proportion between antithrombotic with no antithrombotic. Results were considered statistically significant if the *P* value was less than 0.05.

Results

Participant Flow

Table 1 illustrates the baseline characteristics. The study period lasted from May 2008 to December 2009 (20 months) with a total number of participants of 3,179

Table 1. *Participant demographics based on encounter.*

Gender	Male	36.1% (4,336)
	Female	63.9% (7,664)
Age	Mean + SD (standard deviation)	50.5 + 13.00
Height	Mean + SD	65.8 + 7.95
Weight	Mean + SD	184.2 + 54.94
Smoker	Yes	59.4% (7,124)
	Quit	4.3% (518)
	No	36.3% (4,358)
Antithrombotic	Total	25.7% (3,087)
	• Aspirin	17.2% (2,070)
	• Plavix (Clopidogrel)	3.1% (370)
	• Warfarin (Coumadin)	2.2% (268)
	• Aspirin + Coumadin or Plavix	3.2% (379)
Antithrombotic status	Discontinued	44.6% (1,376)
	Continued	55.4% (1,711)

with 12,000 encounters and 18,472 procedures with an average encounter per participant of 3.7 and number of procedures per encounter of 1.5. Participants in the discontinued group stopped their antithrombotics 3 to 5 days prior for warfarin and 5 to 7 days for aspirin and clopidogrel.

Procedural Characteristics

The procedural characteristics are illustrated in Table 2. Total number of epidural procedures was 10,261, facet joint interventions were 7,482 (multiple levels and/or bilateral), and other procedures were 729 of which 199 were sacroiliac joint interventions, 114 were lumbar sympathetic blocks, 150 were stellate ganglion blocks, and the remaining were intercostal nerve blocks, occipital nerve blocks, intraarticular injections, and peripheral nerve blocks.

Outcomes

Table 3 illustrates the results of various outcomes observed in this study by type of procedure. Facet joint interventions had significantly higher intravascular entry, local bleeding, and oozing.

Table 4 illustrates the analysis of intraoperative complications based on the status of antithrombotic administration. These results illustrate significant differences with intravascular entry, local bleeding, oozing, and bruising with participants receiving antithrombotic agents compared to those not receiving antithrombotic agents.

Intravascular entry and oozing were higher in participants with continued antithrombotic therapy and local bleeding and bruising were higher in those who discontinued antithrombotic therapy.

Table 2. *Therapeutic procedural characteristics.*

	None	Aspirin			Warafin			Clopidogrel			Aspirin + Others			
		D	C	T	D	C	T	D	C	T	D	C	T	Total
EPIDURALS														
Cervical Epidural	1,824	161	249	410	12	1	13	67	10	77	34	18	52	2,376
Thoracic Epidural	237	19	30	49	1	1	2	7	1	8		5	5	301
Lumbar Epidural	1,169	63	128	191	23		23	16	14	30	28	9	37	1,450
Caudal Epidural	2,855	242	528	770	97	8	105	99	44	143	62	50	112	3985
Lumbar Transforaminal Epidural	1,019	51	144	195	25	2	27	21	10	31	24	14	38	1,310
Percutaneous Adhesiolysis	493	68	148	216	24		24	16	21	37	37	32	69	839
EPIDURALS - TOTAL	7,597	604	1,227	1,831	182	10	194	226	100	326	151	128	313	10,261
FACET JOINT INTERVENTIONS														
Cervical Facet Joint Interventions	2,459	194	397	591	93	2	95	54	58	112	65	48	113	3,370
Thoracic Facet Joint Interventions	631	57	125	182	41	1	42	20	22	42	29	24	53	950
Lumbar Facet Joint Interventions	2,324	178	363	541	104	4	108	50	36	86	67	36	103	3,162
FACETS - TOTAL	5,414	429	885	1,314	238	7	245	124	116	240	161	108	269	7,482
Others	546	51	55	106	22	2	24	19	16	35	11	7	18	729
GRAND TOTAL	13,557	1,084	2,167	3,251	442	19	463	369	232	601	323	243	600	18,472

None = Not on antithrombotic drugs; D = discontinued; C = continued; T = total
Others: Sacroiliac joint interventions, occipital nerve blocks, intercostal nerve blocks, stellate ganglion block, or lumbar sympathetic blocks

Table 3. *Intraoperative complications by treatment and antithrombotic status.*

		No Antithrombotics	Aspirin		Coumadin		Plavix		Aspirin + Others		Antithrombotics		Antithrombotics (Total)
			D	C	D	C	D	C	D	C	D	C	
Number	Epidurals	6386	502	1050	167	11	171	95	161	109	1001	1265	2266
	Facet	4181	320	673	160	4	93	92	115	79	688	848	1536
	Others	546	51	55	22	2	19	16	11	7	103	80	183
Intravascular	Epidurals	4.5%	6.0%	5.8%	13.2%	9.1%	5.8%	5.3%	3.7%	16.5%	6.8%	6.7%	6.8%#
	Facet	14.0%	11.6%	15.0%	14.4%	25.0%	16.1%	29.3%*	12.2%	16.5%	12.9%	16.7%	15.0%
	Others	4.2%	0.0%	1.8%	13.6%	0.0%	0.0%	12.5%	0.0%	0.0%	2.9%	3.8%	3.3%
Profuse Bleeding	Epidurals	0.4%	0.8%	1.0%	1.8%	0.0%	0.6%	0.0%	1.2%	0.9%	1.0%	0.9%	0.9%
	Facet	0.7%	0.6%	0.9%	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.7%	0.7%
	Others	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	6.3%	0.0%	0.0%	0.0%	1.3%	0.5%
Local Bleeding	Epidurals	66.5%	70.1%	61.4%*	63.5%	27.3%*	73.7%	57.9%*	62.1%	54.1%	68.3%	60.2%*	63.8%#
	Facet	75.7%	79.4%	73.1%*	78.1%	100.0%	78.5%	76.1%	78.3%	68.4%	78.8%	73.1%*	75.7%
	Others	57.3%	74.5%	60.0%	63.6%	0.0%	42.1%	62.5%	36.4%	28.6%	62.1%	56.3%	59.6%
Local Hematoma	Epidurals	0.2%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%
	Facet	1.5%	2.8%	1.6%	0.6%	0.0%	2.2%	3.3%	1.7%	2.5%	2.0%	1.9%	2.0%
	Others	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%
Oozing	Epidurals	13.2%	13.7%	15.8%	19.2%	18.2%	7.6%	11.6%	14.3%	18.3%	13.7%	15.7%	14.8%
	Facet	22.4%	24.7%	27.9%	26.9%	0.0%	20.4%	20.7%	27.0%	36.7%	25.0%	27.8%	26.6%#
	Others	4.6%	3.9%	10.9%	13.6%	0.0%	0.0%	12.5%	0.0%	14.3%	4.9%	11.3%	7.7%
Bruising	Epidurals	0.2%	0.4%	0.3%	0.0%	0.0%	0.6%	0.0%	1.2%	0.9%	0.5%	0.3%	0.4%
	Facet	0.3%	1.3%	0.4%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.7%	0.4%	0.5%
	Others	0.5%	0.0%	0.0%	4.5%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.5%

D = discontinued C = Continued
Others: Sacroiliac joint interventions or occipital nerve blocks or intercostal nerve blocks or stellate ganglion block or lumbar sympathetic block
- indicates significant difference with no antithrombotics
* - indicates significant difference discontinued within the same category

Table 4. *Analysis of intraoperative complications based on the status of antithrombotic administration.*

	No Antithrombotic (8,913)	**Antithrombotic**		
		Continued (1,711)	**Discontinued (1,376)**	**Total (3,087)**
Intravascular	9.7% (865)	13.0% (223)	10.9%# (150)	12.1%* (373)
Profuse Bleeding	0.7% (58)	1.1% (18)	1.0% (14)	1.0%* (32)
Local Bleeding	73.8% (6,579)	69.5% (1,190)	75.4%# (1,038)	72.2% (2,228)
Local Hematoma	0.8% (74)	1.0% (17)	1.0% (14)	1.0% (31)
Oozing	18.8% (1,672)	24.3% (415)	21.0%# (289)	22.8%* (704)
Bruising	0.3% (30)	0.4% (7)	0.8% (11)	0.6% (28)
No Notable Observations	14.7% (1,314)	15.4% (264)	12.4%# (170)	14.1% (434)

* indicates significant difference ($P < 0.05$) with no antithrombotic group vs antithrombotic group
# indicates significant difference ($P < 0.05$) with continued antithrombotic group vs discontinued antithrombotic group.

An overall significant difference was noted between the continued and discontinued groups for intravascular penetration, local bleeding, and oozing.

Table 5 illustrates the analysis of complications in the recovery room based on antithrombotic therapy.

Table 6 illustrates the analysis of postoperative complications based on antithrombotic therapy. There was no significant difference noted among the groups with any of the noted events.

Discussion

To our knowledge, this is the first study to evaluate patterns of adverse events in a large group of patients undergoing all types of interventional techniques with or without and continuation or discontinuation of antithrombotic therapy. 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, antithrom-

Table 5. *Analysis of complications based on antithrombotic therapy in the recovery room.*

	No Antithrombotics (8,913)	Antithrombotics		
		Continued (1,711)	Discontinued (1,376)	Total (3,087)
Local Bleeding	4.7% (421)	8.1% (138)	7.1% (98)	7.6%* (236)
Oozing	2.5% (219)	3.1% (53)	3.5% (48)	3.3%* (101)
Soreness	12.7% (1,136)	8.5% (146)	9.7% (133)	9.0%* (229)
No Complication	80.6% (1,733)	80.6% (1,379)	80.5% (1,107)	80.5% (2,486)

* indicates significant difference ($P < 0.05$) with no antithrombotic group vs antithrombotic group

Table 6. *Analysis of postoperative complications based on antithrombotic therapy.*

	No Antithrombotic (7,029)	Antithrombotic		
		Continued (1,376)	Discontinued (1,149)	Total (3,087)
Profuse Bleeding	0.2% (14)	0.3% (4)	0.4% (5)	0.3% (9)
Local Bleeding	0.9% (63)	0.9% (12)	1.0% (12)	0.8% (24)
Bruising	1.4% (101)	0.9% (12)	1.0% (12)	0.8% (24)
Soreness	16.6% (1,164)	14.3% (197)	13.1% (150)	11.2%* (347)

* indicates significant difference ($P < 0.05$) with no antithrombotic group vs antithrombotic group
There is no significant difference between continued antithrombotic group vs discontinued antithrombotic

botic therapy was continued during the interventional techniques, whereas, for 45%, or 1,376 encounters, antithrombotic therapy was discontinued at least 5 days prior to the procedure for aspirin and 7 days for clopidogrel (Plavix). The type of antiplatelet therapy included clopidogrel and aspirin only. Warfarin was discontinued 3-5 days earlier as per primary physician. A few were treated if coagulation was acceptable with continued therapy. Vitamin E therapy and herbal therapy were not included due to the extremely small number and were continued in all the groups. The results also showed 10,261 epidural interventions, 7,482 facet joint interventions, and 729 other interventions including sacroiliac joint injections, lumbar sympathetic blocks, stellate ganglion blocks, and other blocks. Even though the results showed variations in the group which discontinued compared to the ones which continued and also those not receiving any antithrombotics, clinical differences appear to be minor. There was a significantly higher proportion of participants with intravascular entry and oozing in the group without discontinuation of antithrombotic therapy compared to either no antithrombotic therapy or the group where antithrombotic therapy was discontinued. However, bruising and local bleeding were significantly higher in the group of patients where antithrombotic therapy was discontinued, thus providing a mixed picture. Further, the differences in the proportions for non-antithrombotic therapy versus discontinued thrombotic therapy versus continued thrombotic therapy was 9.7% vs. 13% vs. 10.9% for intravascular penetration, 73.8% vs. 75.4% vs. 69.5% for local bleeding, and 18.8% vs. 21% vs. 24.3% for oozing with the maximum differences noted for local bleeding which was lowest in the group with continued antithrombotic therapy compared to the other 2 groups. However, in the recovery room, local bleeding was higher in all antithrombotic group participants even though there were no differences between discontinued or continued antithrombotic groups for local bleeding, whereas for soreness, it was observed in 12.7% of those in the non-antithrombotic group compared to 8.5% of those in the continued therapy group and 9.7% in the discontinued group. There were no differences in postoperative complications within 48 to 72 hours later with any of the aspects including bruising, local bleeding, profuse bleeding, and soreness. Overall, these results illustrate that while intravascular penetration and oozing may be higher in those who continued antithrombotic therapy, bruising and local bleeding are higher in those who discontinued antithrombotic therapy without any difference, either statistical or clinical in any of the other aspects, either in the intraoperative, postprocedure in the recovery room, or postoperative period.

In a previous study (44), of 1,000 orthopedic procedures in 924 patients given spinal or epidural anesthesia, it was concluded 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. In an earlier retrospective review of 805 patients given 1,013 spinal or epidural anesthetics (45), they concluded that aspiration of blood through the spinal or epidural needle may not imply an increased risk of serious hemorrhagic complications. In another study, they reported no spinal hematomas or major hemorrhagic complications, even though blood was noted during needle or catheter placement in 63 of 1,032 or 5.2% of the patients. Further, among the multiple case reports, there were a number of cases with development of spinal hematoma and major neurological damage including paralysis after appropriate discontinuation in patients without any type of antithrombotic therapy and also atraumatic injection or without injection (43-47,59-71).

Overall, the incidence of spontaneous spinal hematoma is extremely rare with an estimate of one patient, per one million patients per year or less than one of 150,000 epidural anesthetics and less than one of 220,000 spinal anesthetics for surgical cases (75). It is well known that most surgical procedures involving the spine will develop a small, clinically insignificant epidural hematoma. However, postoperative epidural hematoma is extremely rare and no estimations are available with bleeding either for interventional techniques or anesthetic techniques. Consequently, the risk of stopping antithrombotic therapy, especially for all types of interventional techniques including epidural injections and facet joint nerve blocks, may be much higher. Further, acute coronary syndrome is linked with proinflammatory and prothrombotic conditions that involve an increase in fibrinogen, C-reactive protein, and plasminogen activator inhibitor (76). In addition, the risk of acute coronary syndrome is aggravated by the augmented release of endogenous catecholamines, increased platelet adhesiveness, and decreased fibrinolysis, in the perioperative setting, which are characteristic of acute phase reaction (77-79). Thus, antiplatelet agent therapy is crucial when the thrombogenic risk is the highest (80-82).

In a manuscript on perioperative antiplatelet therapy (83), the authors described that because of the hypercoagulable state induced by surgery, early withdrawal of antiplatelet therapy for secondary prevention of cardiovascular disease increases the risk of postoperative MI and death 5- to 10-fold in stented patients who are on continuous dual antiplatelet therapy. They added that the risk of surgical hemorrhage was increased approximately 20% by aspirin or clopidogrel alone, and 50% by dual antiplatelet therapy. They concluded that based on the clinical data as of 2010, the risk of a cardiovascular event when antiplatelet agents were discontinued preoperatively were higher than the risk of surgical bleeding when continuing these drugs, except during surgery in a closed space such as intracranial, posterior eye chamber, or surgeries associated with massive bleeding and difficult hemostasis. In another manuscript on perioperative handling of patients on antiplatelet therapy with need for surgery (84), the authors recommended that except for low-risk settings, the practice of withdrawing antiplatelet drugs 5-10 days prior to surgical procedures should be changed. As early as 1992 (85), the authors found that phacoemulsification and posterior chamber intraarticular lens implantation can be performed without serious complications. Further, in a systematic review of perioperative management of patients receiving oral anticoagulants (86), the authors concluded that most patients can undergo dental procedures, arthrocentesis, cataract surgery, and diagnostic endoscopy without alteration of their regimen.

In a 2007 review of perioperative antiplatelet therapy where the authors made the case for continuing therapy in patients at risk of MI (80), the authors proposed an algorithm for management of patients, based on the risk of myocardial ischemia and death compared with that of bleeding for different types of surgery. They also showed that even if large prospective studies with a high degree of evidence are still lacking on different antiplatelet regimens during non-cardiac surgery, they proposed that 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. Further, they also advised that a therapeutic bridge with shorter-acting antiplatelet drugs may be considered.

The risks of withdrawing the antiplatelet agents appear to be significant because of the rebound effect with increased platelet adhesiveness (87) and simultaneous systemic inflammatory syndrome and the acute phase reaction to surgery, including increased platelet adhesiveness and decreased fibrinolysis (76,79,88). Also, some pathologies, such as carcinoma and diabetes, are accompanied by hypercoagulability. This may double the infarction and death rates in acute coronary syndrome (89). Thus, it appears that the risks of withdrawing patients from antiplatelet agents in the perioperative period are generally higher than those of maintaining the vital medication (89). However, it has been cautioned that each case must be managed on an individual basis by the physician together with the cardiologist, and it is necessary to modify the approach of withdrawing agents from all antiplatelet agents 7 to 10 days before surgery, except when bleeding might occur in a closed cavity (89). Our study results show that there is no significant difference with the outcomes we have evaluated utilizing any interventional techniques.

Based on the previous literature, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are not contraindicated in neuraxial or non-neuraxial procedures (43). Our results echo the previous reports and recommendations. However, the recommendations on other agents are not clear. These include thienopyridine derivatives (ticlopidine and clopidogrel) and platelet glycoprotein (GP) IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) which exert diverse effects on platelet function. The pharmacologic differences make it impossible to extrapolate between the groups of drugs regarding the practice of neuraxial techniques (43). Further, there is no wholly accepted test, including the bleeding time, which will guide antiplatelet therapy. Since the actual risk of spinal hematoma with ticlopidine and clopidogrel and the GP IIb/IIIa antagonists is unknown, the American Society of Regional Anesthesia and Pain Medicine (ASRAPM) recommendations are based on labeling precautions and the surgical, interventional cardiology/radiology experience, and they therefore recommend that the suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine (Ticlid) and 7 days for clopidogrel (Plavix). With reference to platelet GP IIb/IIIa inhibitors which exert a profound effect on platelet aggregation, the time to normal platelet aggregation is 24 to 48 hours for abciximab (ReoPro) and 4 to 8 hours for eptifibatide (Integrilin) and tirofiban (Aggrastat). It has also been recommended by ASRAPM that neuraxial techniques should be avoided until platelet function has recovered. Further, GP IIb/IIIa antagonists are contraindicated within 4 weeks of surgery. Thienopyridine agents have been implicated in

bleeding following lumbar sympathetic blocks and cervical epidural steroid injections (44,47,48).

Oral anticoagulation is considered as a contraindication to neuraxial anesthesia. Atraumatic epidural catheterization in an anticoagulated patient has led to paraplegia (49). ASRAPM recommends that warfarin should be discontinued approximately 4 to 5 days before the planned procedure and international normalized ratio (INR) should be less than 1.5. They have developed guidelines for removal of the epidural catheters with an INR of greater than 1.5; however, no such guidelines are available for performing neuraxial or non-neuraxial interventional techniques. However, there is no significant evidence with regards to period of discontinuation before the planned procedure. Multiple risk factors need to be taken into consideration. Further, the INR of 1.5 was derived from studies correlating hemostasis with clotting factor activity levels greater than 40%. Warfarin has a very narrow therapeutic window. Even modest differences in body temperature between 35°C and 37°C affect coagulation factor activation and platelet function, which is not reflected in the prothrombin time (PT) and partial thromboplastin time (PTT) testing performed at 37°C in the laboratory (90). Thus, for patients on warfarin, multiple risk factors must be taken into consideration including the risk of hypercoagulability.

Raj et al (47) have devised a bleeding risk score estimation based on the potential hazards of bleeding associated with specific anticoagulants and bleeding disorders, which include proximity to significant vascular structures; proximity to significant neurological structures; target in a confined space; use of a sharp, rather than blunt needle to each target; multiple passages; contrast agent not used, if applicable; fluoroscopy not used, if applicable; aspiration not performed or presence of blood at needle hub; needle size larger than 20 gauge; and continuous procedure with each category providing one point. Thus, a score of 6 to 10 is associated with increased risk.

There are important considerations in interpreting the results of this study. The medication history of all drugs in current use by the participant was based on the information provided by them and as documented in the chart. Second, our study population had chronic pain, predominantly spinal pain. However, this was a real-world sample for a large pain management clinic. Third, we have not analyzed cause-specific mortality or adverse events for various techniques. Due to the paucity of literature, the data results of this study, considering that it is a large study involving various types of participants, supports the conclusion that there is a lack of adverse effects in patients who continue antiplatelet therapy. However, the sample may be too small for calculation of adverse effects, as well as rebound effects. Finally, we excluded patients undergoing intradiscal procedures, as well as implantables; however, these were a very small proportion.

There are several potential clinical implications of this study. Over 25% of the participants were on antithrombotic therapy. Even though major hemorrhagic complications were not observed, the relative prevalence of adverse events with minor hemorrhagic complications are significant in all groups. Further, there were no indicators of increased risk in patients either receiving antithrombotic therapy or with cessation or continuation of antithrombotic therapy compared to patients without antithrombotic therapy.

These findings, however, do not necessarily show adverse consequences or lack thereof when comparing cessation or continuation of antithrombotic therapy. This needs to be determined in a larger population; however, these have been reported in other settings. With respect to the lack of significant adverse effects with continuation of therapy, it may be beneficial for patients without increasing the risk. Even though additional studies may be needed to confirm our findings, based on the previous reports and recommendations, it appears that the therapy must be continued, at least in patients with high risk. At the same time, there do not seem to be any significant advantages of discontinuation.

Conclusion

No significant prevalence of adverse events was observed in patients ceasing or continuing antithrombotic therapy. The findings of this study, coupled with prior studies and guidelines, support the hypothesis that none of the NSAIDs, including aspirin, should be discontinued prior to interventional techniques. With regards to antiplatelet therapy, patients may be considered on an individual basis. Further, with regards to warfarin therapy, risk/benefit ratio must be assessed, including a risk assessment score in establishing the level of INR acceptable to do the procedure with consideration of the potential risk of cerebrocardiac events.

Disclaimer

Author Contributions: Dr. Manchikanti had full access to all the data in the study and takes responsibility

for the integrity of the data and the accuracy of the data analysis. Drs. Manchikanti, Malla, and Wargo designed the study protocol. Dr. Manchikanti managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. All other authors provided revision for intellectual content and final approval of the manuscript.

Conflict of Interest Disclosures: All authors have no conflicts of interest to report. None of the authors of the manuscript received any remuneration. Further, the authors have not received any reimbursement or honorarium in any other manner. However, all the authors are members of the American Society of Interventional Pain Physicians (ASIPP) and the first 3 authors are practicing interventional pain physicians. Dr. Manchikanti is the Chairman of the Board and founder of ASIPP. Vidyasagar Pampati, MSc, Statistician, is an employee of the Ambulatory Surgery Center. Kimberly A. Cash, RT, is a Research Coordinator at the Pain Management Center of Paducah; Carla D. McManus, RN, BSN, and Kim S. Damron, RN, are Nursing Administrators at the Pain Management Center of Paducah; and Sheila D. Jackson, RN, is a Clinical Coordinator at the Pain Management Center of Paducah, Paducah, KY. Bert Fellows, MA, is Director Emeritus of Psychological Services at the Pain Management Center of Paducah.

Funding/Support: The study was conducted by the Pain Management Center of Paducah and the Ambulatory Surgery Center without external support.

The authors also wish to thank Renee Barnhill, RN, and Chad Ames, RN, for collecting the data, Tom Prigge, MA, for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. We also would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

References

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. Heart Disease and Stroke Statistics—2006 Update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006; 113:E85-E151.
2. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician* 2009; 12:E35-E70.
3. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenaventura RM, Conn A, Datta S, Derby R, Falco FJE, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
4. Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W, Sullivan SD. Expenditures and health status among adults with back and neck problems. *JAMA* 2008; 299:656-664. Erratum in: *JAMA* 2008; 299:2630.
5. Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, Testa L, Sheiban I, Sangiorgi G. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006; 27:2667-2674.
6. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003; 107:2908-2913.
7. Geurts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW; American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133:381S-453S.
8. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293:2126-2130.
9. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillablower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: The GRAVITAS randomized trial. *JAMA* 2011; 305:1097-1105.
10. Ho PM, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, Jesse RA, Rumsfeld JS. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; 299:532-539. Erratum in: *JAMA* 2008; 299:2390.
11. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: A meta-analysis of randomized trials. *JAMA* 2009; 301:1909-1919.
12. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: Time to

back off? *J Am Board Fam Med* 2009; 22:62-68.

13. Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA. Analysis of growth of interventional techniques in managing chronic pain in Medicare population: A 10-year evaluation from 1997 to 2006. *Pain Physician* 2009; 12:9-34.
14. Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: A comparative evaluation of 1997, 2002, and 2006 data. *Pain Physician* 2010; 13:199-212.
15. Manchikanti L, Boswell MV, Singh V, Derby R, Fellows B, Falco FJE, Datta S, Smith HS, Hirsch JA. Comprehensive review of neurophysiologic basis and diagnostic interventions in managing chronic spinal pain. *Pain Physician* 2009; 12:E71-E120.
16. Chou R, Huffman L. *Guideline for the Evaluation and Management of Low Back Pain: Evidence Review*. American Pain Society, Glenview, IL, 2009.
    www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf
17. Manchikanti L, Datta S, Derby R, Wolfer LR, Benyamin RM, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 1. Diagnostic interventions. *Pain Physician* 2010; 13:E141-E174.
18. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm II S, Fellows B, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 2. Therapeutic interventions. *Pain Physician* 2010; 13:E215-E264.
19. Manchikanti L, Boswell MV, Datta S, Fellows B, Abdi S, Singh V, Benyamin RM, Falco FJE, Helm S, Hayek S, Smith HS. Comprehensive review of therapeutic interventions in managing chronic spinal pain. *Pain Physician* 2009; 12:E123-E198.
20. Manchikanti L, Singh V, Boswell MV. Interventional pain management at crossroads: The perfect storm brewing for a new decade of challenges. *Pain Physician* 2010; 13:E111-E140.
21. Benyamin RM, Datta S, Falco FJE. A perfect storm in interventional pain management: Regulated, but unbalanced. *Pain Physician* 2010; 13:109-116.
22. Conn A, Buenaventura R, Datta S, Abdi S, Diwan S. Systematic review of caudal epidural injections in the management of chronic low back pain. *Pain Physician* 2009; 12:109-135.
23. Parr AT, Diwan S, Abdi S. Lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain: A systematic review. *Pain Physician* 2009; 12:163-188.
24. Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009; 12:137-157.
25. Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician* 2009; 12:233-251.
26. Falco FJE, Erhart S, Wargo BW, Bryce DA, Atluri S, Datta S, Hayek SM. Systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions. *Pain Physician* 2009; 12:323-344.
27. Datta S, Lee M, Falco FJE, Bryce DA, Hayek SM. Systematic assessment of diagnostic accuracy and therapeutic utility of lumbar facet joint interventions. *Pain Physician* 2009; 12:437-460.
28. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. One year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections with or without steroids in managing chronic discogenic low back pain without disc herniation or radiculitis. *Pain Physician* 2011; 14:25-36.
29. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A preliminary report of a randomized double-blind, active controlled trial of fluoroscopic thoracic interlaminar epidural injections in managing chronic thoracic pain. *Pain Physician* 2010; 13:E357-E369.
30. Manchikanti L, Singh V, Cash KA, Datta S. Management of pain of post lumbar surgery syndrome: One-year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections. *Pain Physician* 2010; 13:509-521.
31. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:343-355.
32. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. Cervical epidural injections in chronic discogenic neck pain without disc herniation or radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:E265-E278.
33. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
34. Manchikanti L, Falco FJE, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: Part 1. Basic considerations. *Pain Physician* 2010; 13:E23-E54.
35. Manchikanti L, Falco FJE, Boswell MV, Hirsch JA. Facts, fallacies, and politics of comparative effectiveness research: Part 2. Implications for interventional pain management. *Pain Physician* 2010; 13:E55-E79.
36. Manchikanti L, Cash KA, McManus CD, Pampati V, Singh V, Benyamin RM. The preliminary results of a comparative effectiveness evaluation of adhesiolysis and caudal epidural injections in managing chronic low back pain secondary to spinal stenosis: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E341-E354.
37. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E355-E368.
38. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of lumbar facet joint nerve blocks in managing chronic low back pain: A randomized, double-blind, controlled trial with a 2-year follow-up. *Int J Med Sci* 2010; 7:124-135.
39. Manchikanti L, Singh V, Falco FJE, Cash KA, Fellows B. Comparative outcomes of a 2-year follow-up of cervical medial branch blocks in management of chronic neck pain: A randomized, double-blind controlled trial. *Pain Physician* 2010; 13:437-450.
40. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzier H. Coronary artery stenting and non-cardiac surgery—a prospective outcome study. *Br J Anaesth* 2006; 96:686-693.
41. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath

WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; 364:1519-1521.

42. Murphy JT, Brenda GF. Thrombosis of sirolimus-eluting coronary stent in the postanesthesia care unit. *Anesth Analg* 2005; 101:971-973.
43. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (third edition). *Reg Anesth Pain Med* 2010; 35:64-101.
44. Horlocker TT, Wedel DJ, Schroeder DR, Rose SH, Elliott BA, McGregor DG, Wong GY. Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg* 1995; 80:303-309.
45. Horlocker TT, Wedel DJ, Offord KP. Does preoperative antiplatelet therapy increase the risk of hemorrhagic complications associated with regional anesthesia? *Anesth Analg* 1990; 70:631-634.
46. Horlocker TT, Bajwa ZH, Ashraf Z, Khan S, Wilson JL, Sami N, Peeters-Asdourian C, Powers CA, Schroeder DR, Decker PA, Warfield CA. Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg* 2002; 95:1691-1697.
47. Raj PP, Shah RV, Kaye AD, Denaro S, Hoover JM. Bleeding risk in interventional pain practice: Assessment, management, and review of the literature. *Pain Physician* 2004; 7:3-51.
48. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. *Anesthesiology* 2004; 101:950-959.
49. Stafford-Smith M. Impaired haemostasis and regional anaesthesia. *Can J Anaesth* 1996; 43:R129-R141.
50. Lee LA, Posner KL, Kent CD, Domino KB. Complications associated with peripheral nerve blocks: Lessons from the ASA Closed Claims Project. *Int Anesthesiol Clin* 2011; 49:56-67.
51. Lee LA, Posner KL, Domino KB, Caplan RA, Cheney FW. Injuries associated with regional anesthesia in the 1980s and 1990s: A closed claims analysis. *Anesthesiology* 2004; 101:143-152.
52. Cook TM, Counsell D, Wildsmith JA; Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: Report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009; 102:179-190.
53. Tam NL, Pac-Soo C, Pretorius PM. Epidural haematoma after a combined spinal-epidural anaesthetic in a patient treated with clopidogrel and dalteparin. *Br J Anaesth* 2006; 96:262-265.
54. Maier C, Gleim M, Weiss T, Stachetzki U, Nicolas V, Zenz M. Severe bleeding following lumbar sympathetic blockade in two patients under medication with irreversible platelet aggregation inhibitors. *Anesthesiology* 2002; 97:740-743.
55. Benzon HT, Wong HY, Siddiqui T, Ondra S. Caution in performing epidural injections in patients on several antiplatelet drugs. *Anesthesiology* 1999; 91:1558-1559.
56. Williams KN, Jackowski A, Evans PJ. Epidural haematoma requiring surgical decompression following repeated cervical epidural steroid injections for chronic pain. *Pain* 1990; 42:197-199.
57. Weller RS, Gerancher JC, Crews JC, Wade KL. Extensive retroperitoneal hematoma without neurologic deficit in two patients who underwent lumbar plexus block and were later anticoagulated. *Anesthesiology* 2003; 98:581-585.
58. Stoll A, Sanchez M. Epidural hematoma after epidural block: Implications for its use in pain management. *Surg Neurol* 2002; 57:235-240.
59. Anderson TJ, Donaldson IM. Spontaneous resolution of cervical spine epidural haematoma. *Postgrad Med J* 1989; 65:488-490.
60. Lord, GM, Mendoza N. Spontaneous spinal epidural haematoma: A cautionary tale. *Arch Emerg Med* 1993; 10:339-342.
61. Shioya H, Kikuchi K, Suda Y, Shindo K. Spontaneous spinal epidural hematoma with spontaneous remission, diagnosed in MRI on superacute stage. *No To Shinkei* 1998; 50:447-452.
62. Ruelle A, Datti R, Pisani R. Thoracic epidural hematoma after spinal manipulation therapy. *J Spinal Disord* 1999; 12:534-536.
63. Van de Straete S, Demaerel P, Stockx L, Nuttin B. Spinal epidural hematoma and ankylosing spondylitis. *J Belge Radiol* 1997; 80:109-110.
64. Lobitz B, Grate I. Acute epidural hematoma of the cervical spine: An unusual cause of neck pain. *South Med J* 1995; 88:580-582.
65. Yagi S, Hida K, Iwasaki Y, Abe H, Akino M, Saito H. Cervical epidural hematoma caused by cervical twisting after epidural anesthesia: A case report. *No Shinkei Geka* 1998; 26:627-632.
66. Agnetti V, Monaco F, Mutani R. Postconvulsive spinal epidural haematoma in ankylosing spondylitis. *Eur Neurol* 1979; 18:230-233.
67. Xu R, Bydon M, Gokaslan ZL Wolinsky JP, Witham TF, Bydon A. Epidural steroid injection resulting in epidural hematoma in a patient despite strict adherence to anticoagulation guidelines. *J Neurosurg Spine* 2009; 11:358-364.
68. Ain RJ, Vance MB. Epidural hematoma after epidural steroid injection in a patient withholding enoxaparin per guidelines. *Anesthesiology* 2005; 102:701-703.
69. Marcou TA, Mignon A, Ozier Y. Could an epidural hematoma after neuraxial blockade really be idiopathic? *Anesth Analg* 2006; 102:332-333.
70. Hussenbocus SM, Wilby MJ, Cain C, Hall D. Spontaneous spinal epidural hematoma: A case report and literature review. *J Emerg Med* 2009 Jan 5. [Epub ahead of print].
71. Lee JH, Lee H, Jo DJ. An acute cervical epidural hematoma as a complication of dry needling. *Spine (Phila Pa 1976)* 2011; 36:E891-E893.
72. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *Ann Intern Med* 2007; 147:W163-W194.
73. Manchikanti L, Singh V, Smith HS, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 4: Observational studies. *Pain Physician* 2009; 12:73-108.
74. Manchikanti L, Datta S, Smith HS, Hirsch JA. Evidence-based medicine, systematic reviews, and guidelines in interventional pain management: Part 6. Systematic reviews and meta-analyses of observational studies. *Pain Physician* 2009; 12:819-850.
75. Tryba M. Epidural regional anesthe-

sia and low molecular heparin: Pro [in German]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1993; 28:179-181.

76. Hoffmeister HM, Heller W, Seipel L. Activation markers of coagulation and fibrinolysis: Alterations and predictive value in acute coronary syndrome. *Thromb Haemostasis* 1999; 82:76-79.
77. Blake GJ, Ridker PM. Inflammatory biomarkers and cardiovascular risk prediction. *J Intern Med* 2002; 252:283-294.
78. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery. *Anesthesiology* 2002; 97:215-252.
79. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. *Br J Anaesth* 2004; 93:9-20.
80. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: The case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; 99:316-328.
81. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: Results from the PREMIER registry. *Circulation* 2006; 113:2803-2809.
82. Eagle KA, Kline-Rogers E, Goodman SG, Gurfinkel EP, Avezum A, Flather MD, Granger CB, Erickson S, White K, Steg PG. Adherence to evidence-based therapies after discharge for acute coronary syndromes: An ongoing prospective, observational study. *Am J Med* 2004; 117:73-81.
83. Chassot PG, Marcucci C, Delabays A, Spahn DR. Perioperative antiplatelet therapy. *Am Fam Physician* 2010; 82:1484-1489.
84. Di Minno MN, Prisco D, Ruocco AL, Mastronardi P, Massa S, Di Minno G. Perioperative handling of patients on antiplatelet therapy with need for surgery. *Intern Emerg Med* 2009; 4:279-288.
85. Shuler JD, Paschal JF, Holland GN. Antiplatelet therapy and cataract surgery. *J Cataract Refract Surg* 1992; 18:567-571.
86. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: A systematic review. *Arch Intern Med* 2003; 163:901-908.
87. Vial JH, McLeod LJ, Roberts MS. Rebound elevation in urinary thromboxane B2 and 6-keto-PFF1 alpha exacerbation after aspirin withdrawal. *Adv Prostaglandin Thromboxane Leukot Res* 1991; 21A:157-160.
88. Levy JH, Dutton RP, Hemphill JC 3rd, Shander A, Cooper D, Paidas MJ, Kessler CM, Holcomb JB, Lawson JH; Hemostasis Summit Participants. Multidisciplinary approach to the challenge of hemostasis. *Anesth Analg* 2010; 110:354-364.
89. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndrome. *Circulation* 2004; 110:2361-2367.
90. Hoffman M, Monroe DM. Coagulation 2006: A modern view of hemostasis. *Hematol Oncol Clin North Am* 2007; 21:1-11.