Adverse drug events associated with disorders of coagulation

Jeffrey F. Barletta, PharmD, FCCM; Brad Cooper, PharmD, FCCM; Martin J. Ohlinger, PharmD, BCPS

Disorders of coagulation are common adverse drug events encountered in critically ill patients and present a serious concern for intensive care unit (ICU) clinicians. Dosing strategies for medications used in the ICU are typically developed for use in noncritically ill patients and, therefore, do not account for the altered pharmacokinetic and pharmacodynamic properties encountered in the critically ill as well as the increased potential for drug-drug interactions, given the far greater number of medications ordered. This substantially increases the risk for coagulation-related adverse reactions, such as a bleeding or prothrombotic events. Although many medications used in the ICU have the potential to cause coagulation disorders, the exact incidence will vary based on the specific medication, dose, concomitant drug therapy, ICU setting, and patient-specific comorbidities. Clinicians must strongly consider these factors when evaluating the risk/benefit ratio for a particular therapy. This review surveys recent literature documenting the risk for adverse drug reactions specific to bleeding and/or clotting with commonly used medications in the ICU. (Crit Care Med 2010; 38[Suppl.]:S198–S218)

Key Words: bleeding; clotting; adverse drug event; critical illness; anticoagulation; heparin; low-molecular-weight heparin; thrombolytic; reversal; prophylaxis

Coagulation-associated adverse drug events (ADEs) are a serious concern among intensive care unit (ICU) clinicians and a common cause of nonpreventable ADEs encountered in critically ill patients (1–4). Many dosing strategies used for coagulation-related medications, however, are extrapolated from clinical trials conducted in noncritically ill patients. They fail to account for the altered pharmacokinetic and pharmacodynamic variability seen in this patient population. This variability can lead to unpredictable drug effects, greater toxicity, and increased potential for ADEs. In addition, ICU patients can receive up to 30 different medications throughout their admission, far greater than that observed in a non-ICU setting (2). This increases the potential for drug interactions or a synergistic/enhanced response. One study (2) which evaluated ADEs in both ICU and general care units, reported nearly double the amount of ADEs in the ICU compared with the amount of ADEs in the general care setting. This was largely due to the number of drugs ordered.

In this article, we address disorders of coagulation (i.e., bleeding and clotting) caused by various medications commonly used in the ICU. In addition, we present strategies that can be considered to reverse anticoagulation caused by an altered pharmacodynamic response or supratherapeutic drug concentrations.

Medications with anticoagulant effects

Anticoagulants used for venous thromboembolism prophylaxis

Venous thromboembolism (VTE) ranks among the top ten adverse events reported in hospitalized patients and has been regarded as the most important strategy to improve patient safety (5). Nevertheless, a substantial number of patients fail to receive adequate VTE prophylaxis (6). One potential barrier for the provision of VTE prophylaxis is the perceived risk of bleeding. The prevalence of bleeding will vary widely based on the specific medication (e.g., low-dose unfractionated heparin [LDUH] vs. low-molecular weight heparin [LMWH]), the medication dose, concomitant drug therapy, the patient population evaluated (medical ICU, surgical ICU, neurosurgical ICU, etc.) and underlying comorbidities (e.g., end-organ function). The prevalence of bleeding will also vary based on the definition used in the individual trials. Although most studies will report "any bleeding event," it is typically major bleeding, intracranial bleeding, and fatal bleeding that are the focus of most concern to ICU clinicians.

Medical/Surgical ICU. There are several data evaluating anticoagulation for VTE prophylaxis in acutely ill medical and surgical patients, but few data are specific to the critically ill (7–9). In addition, of the studies conducted in critically ill patients, even fewer studies have reported the occurrence of "any bleeding," and the definition for "major bleeding" has varied (Table 1). Studies that have reported bleeding rates have primarily been conducted with LMWH and have noted the prevalence of any bleeding event (as opposed to major bleeding) to be between 10% and 25%. Of note, only one trial (10) was a comparative trial, which noted an occurrence rate of major bleeding of 5.5% in the study group (nadroparin) vs. 2.7% with placebo. This is comparable to a prospective study (11) designed to estimate the prevalence of bleeding during critical illness, in an attempt to establish a reference range for bleeding. In this study, 100 consecutive patients admitted to a medical-surgical ICU were enrolled, whereby 480 discrete bleeding events among 90 patients were identified; 5.2% were considered major. Interestingly, neither prophylactic heparin nor antiplatelet agents were significant risk factors for major or minor bleeding. These results are slightly higher than that reported in noncritically

From Spectrum Health (JFB), Grand Rapids, MI; Department of Pharmacy (BC), Hamot Medical Center, Erie, PA; and the University of Toledo College of Pharmacy (MJO), University of Toledo Medical Center, Toledo, OH.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: jeffrey.barletta@spectrum-health.org

DOI: 10.1097/CCM.0b013e3181de11f9

Table 1. Prevalence of bleeding in medical/surgical intensive care unit patients receiving venous thromboembolism prophylaxis

Study	Design	Setting	n	Study Drug	Population	Major Bleeding Definition	Any Bleeding	Major Bleeding
Fraisse et al (10)	P, DB, RCT	Medical ICU	223	Nadroparin adjusted dose (3800–5700 units) Q 24 vs. placebo	Acute decompensated COPD	Overt bleeding plus a decrease in hemoglobin of 2 g/dL, necessitating a transfusion of ≥2 units of packed red cells; retroperitoneal or intracranial bleeding, or bleeding warranting discontinuation of therapy	Nadroparin: 25 (23%) of 108 vs. placebo: 18 (16%) of 113, $p = .18$	Nadroparin: 6 (5.5%) of 108 vs. placebo: 3 (2.7%) of 113, $p = .28$
Rabbat et al (184)	P, cohort	Mixed med/surg ICU	19	Dalteparin 5000 units daily	Respiratory, cardiovascular, GI, sepsis, neurologic	Fatal bleeding; clinically overt bleeding associated with a decrease in the hemoglobin of >2 g/dL or leading to transfusion of ≥2 units of whole blood or packed red cells; critical bleeding (intracerebral, intraocular, intraspinal, pericardial, or retroperitoneal); bleeding warranting treatment cessation; bleeding located at the surgical site and leading to reoperation	2 (10.5%)	1 (5.3%)
Douketis, et al (185)	P, MC, cohort	Medical ICU	138	Dalteparin 5000 units daily	Renal insufficiency (CrCl, <30 mL/min)	Decrease in hemoglobin of >2 g/dL, transfusion of >2 units of red cells and no increase in hemoglobin, spontaneous decrease in SBP of >20 mm Hg or heart rate increase of >20 beats/min or decrease in SBP of >10 mm Hg; bleeding at a critical site or bleeding at a wound site that required an intervention	34 (24.6%)	10 (7.2%)

P, prospective; DB, double blind; RCT, randomized controlled trial; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; MC, multicentered; GI, gastrointestinal; CrCl, creatinine clearance; SBP, systolic blood pressure.

ill patients. In one systematic review (12) of acutely ill general medical patients, the prevalence of major bleeding with pharmacologic prophylaxis (i.e., LMWH or LDUH) was approximately 2%. A second review (13) conducted in general surgical patients noted the prevalence of gastrointestinal (GI) bleeding, retroperitoneal bleeding, bleeding that led to discontinuation of prophylaxis, and bleeding that led to an operation to be 0.2%, <0.1%, 2%, and 0.7%, respectively. A large multicenter, multinational, randomized controlled trial (PROTECT) (14) is currently underway to evaluate the safety and efficacy of LMWH (dalteparin) and LDUH in medical-surgical ICU patients.

Bleeding rates with LDUH dosed tid vs. bid have not been studied in critically ill patients but have been evaluated in noncritically ill patients (13, 15). One meta-analysis (15) of 12 studies in hospitalized medical patients reported a significantly higher occurrence rate of major bleeding (which was reported as a rate per 1000 patient-days) with tid versus bid dosing (0.96 vs. 0.35, $p < .001$). A second study (13), which was a systematic review of 33 studies in general surgery patients, noted a greater prevalence of bleeding that led to discontinuation of prophylaxis (3.3% vs. 1.9%, $p = .02$) and subsequent operation (1.8% vs. 1%, $p = .06$) with tid vs. bid dosing. Future studies are needed to validate these findings in the ICU population.

LMWHs are eliminated primarily by the kidneys; therefore, there is an increased risk of drug accumulation in patients with renal insufficiency. Pharmacodynamic studies with prophylactic doses of LMWH have reported accumulation only with enoxaparin in patients with a creatinine clearance (CrCl) of <30 mL/min (16). Accumulation has not been noted with either dalteparin or tinzaparin. Data correlating these findings with clinical outcomes (using prophylactic doses), however, are limited. Nevertheless, in patients with severe renal impairment (i.e., CrCl of <30 mL/

min), enoxparin doses should be adjusted accordingly. Dosing adjustments with dalteparin or tinzaparin are not required with short-term use. Anti-Xa monitoring may be useful in these scenarios.

Trauma patients. The high risk for VTE in the critically ill trauma patient typically warrants aggressive VTE prophylaxis, as soon as it is considered safe, despite a higher risk for bleeding (8). Several studies (17–27) have evaluated the role of pharmacologic prophylaxis in the setting of trauma. Earlier studies (19, 23, 26), conducted with LDUH, have documented bleeding rates of 0% to 8%. However, a landmark trial (20) comparing enoxaparin with LDUH (started within 36 hrs of injury) demonstrated a 30% reduction in VTE with enoxaparin. LDUH, therefore, is no longer considered an acceptable option in the trauma population (8). Studies evaluating LMWH are displayed in Table 2. Collectively, these studies have demonstrated a relatively low occurrence rate of major bleeding (approximately 2% to 3%) when pharmacologic prophylaxis was initiated soon after injury (i.e., within 24–36 hrs).

Neurosurgical patients. There is wide debate over the risk/benefit ratio with pharmacologic prophylaxis for VTE in the neurosurgical population, particularly in the setting of intracranial pathology (28). In a recent survey, the percentage of respondents (intensivists and neurosurgeons) who would start pharmacologic prophylaxis within 48 hrs after surgery was 64% for elective craniotomy, 58% for diffuse axonal injury after severe traumatic brain injury, 34% for intracranial hemorrhage after severe traumatic brain injury, and 55% for nontraumatic subarachnoid hemorrhage. Several studies have evaluated the safety of pharmacologic prophylaxis post neurosurgery (Table 3). One recent meta-analysis (29), which primarily included patients post craniotomy surgery (penetrating and closed-head injury was excluded), reported bleeding rates of 0.04 per 1,000 patients with nonpharmacologic prophylaxis, 0.35 per 1,000 patients with LDUH, and 1.52 per 1,000 patients with LMWH. Statistical significance was achieved only between LMWH and nonpharmacologic subgroups. Bleeding rates may be higher when pharmacologic prophylaxis is initiated preoperatively vs. the early postoperative period (i.e., within 24 hrs). One review (30) calculated bleeding rates of 3.9% when prophylaxis was started before surgery compared with 1.9% postoperatively.

Few data (31–35) address the safety of pharmacologic prophylaxis specific to patients with severe head injury. In most studies, pharmacologic prophylaxis was initiated soon after injury (i.e., within 24 hrs) following the results of a stable computed tomography scan (typically 24 hrs from admission). In a study by Kim et al (31), there was no increase in intracranial bleeding or neurologic deterioration in 64 patients with severe head injury as a result of LDUH (5000 units every 12 hrs) when initiated either within or after 72 hrs from injury. In a study by Norwood et al (35), 4% (6 of 150) of patients displayed computed tomography progression of intracranial hemorrhage with enoxaparin (30 mg every 12 hrs), but all survived to hospital discharge. The mean time to the first dose of enoxaparin was 26.5 ± 11.5 hrs. Kleindienst et al (33) described a cohort of 280 patients with head injury and 238 with spontaneous intracranial hemorrhage, who received certoparin (administered 24 hrs after admission post a control computed tomography scan). Intracranial bleeding was recorded in 3.5% of patients with head injury (2.8% requiring operative revision) and 0% of patients with spontaneous intracranial hemorrhage. Kurtoglu et al (34) prospectively studied patients randomized to receive either enoxaparin (40 mg daily) or mechanical prophylaxis. Total bleeding rates were 15% and 8.3% for the enoxaparin and mechanical prophylaxis groups, respectively, but major bleeding rates (i.e., exacerbation of epidural hematoma) were 1.6% in both groups. Finally, Kim and Brophy (32) reported bleeding rates in 46 patients admitted to a neurointensive care unit (subarachnoid hemorrhage, n = 12; intracerebral hemorrhage, n = 15; traumatic brain injury, n = 19), who were primarily prescribed LDUH (5000 units every 12 hrs). Prophylaxis was initiated in 68% of patients within 24 hrs of hospital admission. There was no evidence of intracranial bleeding associated with pharmacologic prophylaxis nor was there early discontinuation of therapy due to bleeding.

Although these reports have suggested that early administration of pharmacologic prophylaxis in patients with severe brain injury is safe, clinicians must consider the fact that bleeding in this population can be devastating and lead to complete neurologic demise. The pooled incidence of intracranial hemorrhage seems low (approximately 3%), but clinicians must consider that many of these studies had small sample sizes, lacked a control group, or were retrospective in nature. Caution must be exerted when interpreting retrospective studies, as the potential for bias exists in that patients who received pharmacologic prophylaxis may have been perceived to be at a lower risk for hemorrhage. Clinicians, therefore, must give careful consideration to the risk of a deleterious outcome from both a thromboembolic event and intracranial bleeding when the decision to implement early pharmacologic prophylaxis is made.

Anticoagulants used for therapeutic anticoagulation

Although bleeding with therapeutic anticoagulation has been well documented, there are minimal data specific to the ICU setting. The prevalence of bleeding has been estimated to be between 5% and 20% but will vary based on the definition of bleeding, concomitant drug therapy, and patient-specific factors (36–38). Factors that have associated with an increased risk of bleeding are surgery, trauma, renal failure, age, and the use of thrombolytic therapy, aspirin, and glycoprotein IIb/IIIa inhibitors (38).

Heparin has been the cornerstone of therapy for ICU patients for several decades (39). The half-life of heparin is relatively short (60–90 mins), which is an advantage in the setting of overanticoagulation and/or bleeding. Heparin has limitations in that it binds to acute-phase plasma proteins, proteins released from platelets and possibly endothelial cells, thereby resulting in a variable response (39). This variability can lead to supratherapeutic levels of anticoagulation and increase the risk for bleeding. In one study (40) of patients with acute coronary syndromes, the probability of major bleeding was increased by 7% for every 10-sec increase in activated partial thromboplastin time ($p = .0004$). Nevertheless, bleeding with intravenous (IV) heparin is estimated to occur in approximately 4% to 7% of patients (36, 38).

LMWHs have a more predictable dose response than heparin and have been extensively studied in the setting of VTE (36). Compared with unfractionated heparin, LMWH may offer a slight benefit with regard to bleeding. In one system-

Table 2. Prevalence of bleeding in trauma patients receiving low-molecular weight heparin for venous thromboembolism prophylaxis

Study	Design	n	Study Drug	Time to Initiation of Prophylaxis	Bleeding Definition	Any Bleeding[a]	Major Bleeding[a]
Knudson et al (24)	P, RCT	372	Enoxaparin 30 mg Q 12 vs. IPC	Within 24 hrs of injury	Not stated	Enoxaparin: 6 (5%) of 120 IPC: 0%	Enoxaparin: 1 (0.8%) of 120
Geerts et al (20)	P, DB, RCT	265	Enoxaparin 30 mg Q 12 vs. LDUH 5000 units Q 12	Within 36 hrs of injury	Major: Overt bleeding associated with a decrease in hemoglobin of 2 g/dL, transfusion of ≥2 units of pRBC, an intracranial or retroperitoneal site of bleeding or the need for surgical intervention	—	Enoxaparin: 5 (2.9%) of 129 Heparin: 1 (0.6%) of 136
Haentjens (22)	P, MC, RCT	283	Nadroparin: Fixed dose 3075 units Q 24 vs. individualized dose (5000–15,000 units Q 24)	Within 8 hrs of injury	Major: Wound hematoma necessitating surgical intervention, macrospcoic hematuria, GI bleeding, bleeding requiring a transfusion or interruption of the study medication	—	Fixed dose: 5 (3.5%) of 142 Individualized dose: 5 (3.5%) of 141
Cohn et al (17)	P, DB, RCT	66	Enoxaparin 30 mg Q 12 vs. LDUH 5000 units Q 12	Within 24 hrs of injury	Major: Overt bleeding associated with a decrease in hemoglobin of 2 g/dL, transfusion of ≥2 units of pRBC, retroperitoneal or intracranial bleeding Minor: Excessive bleeding from operative sites, GI bleeding or hematuria	Enoxaparin: 5 (14.7%) of 34 LDUH: 5 (15.6%) of 32	—
Norwood, et al (25)	P, Obs	118	Enoxaparin 30 mg Q 12	Within 24 hrs of admission	Not stated	0 (0%) of 118	—
Ginzburg et al (21)	P, RCT	442	Enoxaparin 30 mg Q 12 vs. IPC	Within 24 hrs of injury	Major: Overt bleeding associated with a decrease in hemoglobin of 2 g/dL, transfusion of ≥2 units of pRBC, intracranial or retroperitoneal bleeding or bleeding requiring surgical intervention Minor: Excessive bleeding from operative sites, GI bleeding or hematuria	Enoxaparin: 13 (3.7%) of 218 IPC: 8 (3.6%) of 224	Enoxaparin: 4 (1.8%) of 218 IPC: 4 (1.8%) of 224
Stannard et al (27)	P, RCT	200	Enoxaparin 30 mg Q 12 (Early administration vs. VFP + delayed administration)	Early enoxaparin: within 24–48 hrs injury Delayed enoxaparin: 5 days after admission	Not stated but bleeding events included incision site hematomas, other hematomas, intracranial bleeding	Early enoxaparin: 18 (19%) of 97 Delayed enoxaparin: 18 (17%) of 103	—
Cothren et al (18)	P, Obs	743	Dalteparin 5000 units Q 24	Mean, 3.28 days from admission	Wound complications and transfusions unexplained by injury or surgery	Wound complications: 18 (2.7%) of 743 Unexplained transfusion: 22 (3%) of 743	—

RCT, randomized controlled trial; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; MC, multicentered; DB, double-blind; GI, gastrointestinal; pRBC, packed red blood cells; P, prospective; Obs, observational; VFP, venous foot pump.

[a] $p > .05$ for pair-wise comparisons within each study.

atic review (41), the occurrence rate of major hemorrhage was 1.2% with LMWH vs. 2% with unfractionated heparin (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.39–0.83). This potential benefit, however, must be balanced against the risk of using a long-acting drug that is only minimally affected by reversal agents. In addition, the effects of LMWH may be unpredictable in special situations, such as renal failure and morbid obesity. Studies (16) have indicated that

Table 3. Prevalence of bleeding in neurosurgical patients receiving venous thromboembolism prophylaxis

Study	Design	n	Population	Study Drug	Initiation of Prophylaxis	Bleeding
Cerrato et al (188)	RCT	100	Elective intracranial surgery	LDUH 5000 units Q 8 vs. control	2 hr before surgery	LDUH: 2 (4%) of 50 Control: 1 (2%) of 50
Frim et al (191)	Ret	611	Mixed neurosurgical population	LDUH 5000 units Q 12 vs. control	Within 24 hrs after surgery	LDUH: 0 of 138 Control: 1 of 473
Nurmohamed et al (196)	MC, DB, RCT	485	Intracranial (98%) and spinal surgery	Nadroparin 3075 units Q 24 vs. control	Within 24 hrs after surgery	Nadroparin: 6 (2.5%) of 241 Control: 2 (0.8%) of 244
Wen et al (197)	Obs	872	Mixed neurosurgical population (17% intracranial)	LDUH 5000 units Q 12	Evening before surgery	Any bleeding: 6 (0.7%) of 872 Major bleeding: 3 (0.34%) of 872
Dickinson et al (190)	RCT	66	Intracranial surgery for tumor	Enoxaparin 30 mg Q 12	Before anesthesia	Enoxaparin: 5 (11%) of 46 Control: 0 (0%) of 22
Agnelli et al (186)	MC, DB, RCT	307	Intracranial (85%) and spinal surgery	Enoxaparin 40 mg Q 24	Within 24 hrs after surgery	Any bleeding Enoxaparin: 18 (12%) of 153 Control: 11 (7%) of 154 Major bleeding Enoxaparin: 4 (2.6%) of 153 Control: 4 (2.6%) of 154
Macdonald et al (195)	Obs	106	Intracranial surgery	LDUH 5000 units Q 12	Before anesthesia	4 (3.8%) of 106
Constantini et al (189)	DB, RCT	103	Intracranial surgery for tumor	LDUH 5000 units Q 12 vs. control	2 hr before surgery	Any bleeding LDUH: 3 (5.5%) of 55 Control: 3 (6.3%) of 48 Major bleeding LDUH: 1 (1.8%) of 55 Control: 2 (4.2%) of 48
Raabe et al (30)	Ret	1564	Intracranial surgery	LDUH 5000 units Q 8	Within 24 hrs after surgery	All patients: 28 (1.8%) of 1564 Major procedures: 28 (2.3%) of 1197
Goldhaber et al (193)	DB, RCT	150	Intracranial surgery for tumor	Enoxaparin 40 mg Q 24 vs. LDUH 5000 units Q 12	Within 24 hrs after surgery	Any bleeding Enoxaparin: 2 (2.6%) of 75 LDUH: 1 (1.3%) of 75 Major bleeding Enoxaparin: 1 (1.3%) of 75 LDUH: 0 (0%) of 75
Kim et al (31)	Ret	64	Severe traumatic brain injury	LDUH 5000 units Q 12 hrs	<72 hrs of admission (early) vs. ≥72 hrs of admission (late)	Early administration: 0 (0%) of 47 Late administration: 0 (0%) of 17
Norwood et al (35)	Obs	150	Severe TBI	Enoxaparin 30 mg Q 12	Approximately 24 hrs after initial evaluation	6 (4%) of 150
Kleindienst et al (33)	Ret	785	TBI, spontaneous ICH and elective neurosurgery	Certoparin 18 mg Q 24	ENS: evening before surgery TBI/ICH: approximately 24 hrs postadmission	ENS: 3 (1.1%) of 267 TBI: 9 (3.2%) of 280 SAH: 0 (0%) of 238
Macdonald et al (194)	RCT	97	Intracranial surgery	Dalteparin 2500 units Q 24 vs. LDUH 5000 units Q 12	Before anesthesia	Dalteparin: 2 (4%) of 51 LDUH: 1 (2%) of 49
Gerlach et al (192)	Obs	2823	Intracranial surgery	Nadroparin 2850 units Q 24	Within 24 hrs after surgery	All patients: 43 (1.5%) of 2823 Major procedures: 42 (3.2%) of 1319
Kurtoglu et al (34)	RCT	120	Severe TBI (91%) and spinal trauma	Enoxaparin 40 mg Q 24 vs. control	Approximately 24 hrs after admission	Any bleeding Enoxaparin: 9 (15%) of 60 Control: 5 (8.3%) of 60 Major bleeding Enoxaparin: 1 (1.6%) of 60 Control: (1.6%) 0 (0%) of 37
Kim et al (32)	Ret	37	Aneurysmal SAH, TBI, ICH	LDUH 5000 units Q 12 (95%) or enoxaparin 30 mg Q 12 (5%)	Variable	
Cage et al (187)	Ret	86	Intracranial surgery for tumor	Enoxaparin 40 mg Q 24 vs. control	Within 48 hrs after surgery	Any bleeding Enoxaparin: 3 (12.5%) of 24 Control: 8 (12.9%) of 62 Major bleeding Enoxaparin: 1 (4.2%) of 24 Control: 5 (8.1%) of 62

RCT, randomized controlled trial; Ret, retrospective; Obs, observational; LDUH, low-dose unfractionated heparin; MC, multicenter; DB, double-blind; ENS, elective neurosurgery; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage.

clearance of LMWH (as measured by anti-Xa levels) are strongly correlated with CrCl, specifically with enoxaparin. These results are consistent with clinical evaluations, whereby bleeding rates with enoxaparin were higher in patients with severe renal insufficiency (CrCl of <30 mL/min) (16). Therefore, recent clinical practice recommendations (16) have advised against LMWH use in patients with CrCl of <20 mL/min. Furthermore, enoxaparin doses should be adjusted in patients with CrCl of <30 mL/min. There are limited data with other LMWH, such as dalteparin or tinzaparin, but available

evidence does not suggest a substantial degree of accumulation.

The direct thrombin inhibitors (e.g., lepirudin, argatroban) are primarily used in critically ill patients when heparin-induced thrombocytopenia (HIT) is either suspected or confirmed. Direct thrombin inhibitors do not bind to plasma proteins; therefore, they have less variability and a more predictable response compared with unfractionated heparin (42). Nevertheless, bleeding rates with lepirudin have been relatively high. A combined analysis of three studies (43) in patients with HIT revealed bleeding rates of 17.6% with lepirudin vs. 5.8% with historical controls ($p = .0015$). Similarly, one study (44) of non-HIT patients (e.g., myocardial infarction [MI] or unstable angina) noted higher bleeding rates with lepirudin vs. unfractionated heparin (1.2% vs. 0.7%, $p = .01$). It has been suggested that the approved dosing regimen of lepirudin (0.4 mg/kg bolus, followed by 0.15 mg/kg/hr) is too high, which may have contributed to the increased bleeding rates observed (45). In addition, increased serum creatinine (>1.0 mg/dL) has also been associated with increased bleeding (43). Lower starting doses (i.e., 0.1 mg/kg/hr in patients with normal renal function and 0.05 mg/kg/hr in patients with compromised renal function) are, therefore, recommended (46). Other ADEs with lepirudin include rare anaphylaxis reactions, which can occur on reexposure. It has been suggested that this can be avoided by omitting the bolus dose (45).

Major bleeding has been noted in 0% to 10% of patients treated with argatroban in clinical practice (47). In a pooled analysis of 882 patients with HIT, there was no significant difference in major bleeding in patients treated with argatroban vs. historic control (6% vs. 7%, respectively; $p = .74$) (48). Similar to lepirudin, lower doses (than recommended in the package insert) may be required, particularly in ICU patients. Studies (49–51) in ICU patients have reported average therapeutic doses ranging from 0.6 μg/kg/min to 1.2 μg/kg/min, substantially lower than the recommended 2 μg/kg/min. This could be a result of decreased perfusion to the liver (the primary mechanism for clearance) encountered in many ICU patients. In lieu of these data, recent guidelines have recommended a lower initial dose (i.e., 0.5–1.2 μg/kg/min) for patients with multiple organ system failure, heart failure, severe anasarca, or those who are postcardiac surgery (46).

Fondaparinux is a synthetic inhibitor of factor Xa that produces a predictable anticoagulant response. The use of fondaparinux for therapeutic anticoagulation has been studied in the settings of deep vein thrombosis (DVT), pulmonary embolism (PE), and acute coronary syndromes, but none were specific to the ICU (52–54). The Matisse-PE trial compared fondaparinux with unfractionated heparin for the initial treatment of PE and noted no significant difference in the incidence of bleeding (1.3% vs. 1.1%, respectively) (53). Similarly, in the Matisse-DVT trial, fondaparinux was compared with enoxaparin for the initial treatment of DVT and found no significant difference in bleeding between groups (1.1% vs. 1.2%, respectively) (52). In a combined analysis of the OASIS 5 and 6 trials, fondaparinux was compared with a heparin-based strategy (either unfractionated heparin or enoxaparin) in patients with acute coronary syndromes (54). Bleeding rates were significantly lower with fondaparinux (3.4% vs. 2.1%, $p < .00001$). Despite these potential advantages, fondaparinux has a prolonged half-life (approximately 17 hrs) and does not have a reversal agent. This, along with the fact that fondaparinux is contraindicated in patients with renal insufficiency (CrCl of <30 mL/min), markedly limits its usefulness in the ICU.

Thrombolytics

Bleeding after the administration of thrombolytic agents can lead to a catastrophic outcome and is a major consideration when evaluating the appropriateness of their use. Thrombolytic therapy is a potential treatment option for patients with venous thrombosis (e.g., DVT and PE), arterial thrombosis (e.g., MI and peripheral artery occlusion) and neurologic syndromes (e.g., ischemic stroke and intraventricular hemorrhage). Risk factors for bleeding seem to vary, based on the underlying disorder that is treated (38). For example, in patients with MI, increased age, low body weight, prior cerebrovascular disease or hypertension, increased systolic/diastolic blood pressure and drug (randomization to tissue plasminogen activator) were independent predictors for intracranial hemorrhage (55). Risk factors for bleeding in patients with PE are similar to that observed in patients with MI (56). In patients with stroke, on the other hand, leukoaraiosis, pretreatment National Institutes of Health stroke scale score, degree of clinical deficit, brain edema, early signs of cerebral ischemia on computed tomography, mass effect before treatment and reduced pretreatment middle cerebral artery blood flow have been identified as independent risk factors for bleeding (38). Clinical pathways/checklists are available to aid with the decision to administer thrombolytics for the treatment of stroke (57). For further reading regarding thrombolytic therapy for the indication of stroke and MI, the reader is referred elsewhere (58–60).

The benefit of thrombolytic therapy for the treatment of stroke and MI has been well established, but their use for the treatment of PE remains a challenge. Clinical trials evaluating the efficacy of thrombolytic therapy have only shown marginal benefit; therefore, the risk/benefit ratio may weigh more favorably against their use when bleeding risk is considered. There have been several randomized trials evaluating thrombolytics for PE, but collectively these trials have only included <800 patients (Table 4). In a meta-analysis (61) of these trials, a nonsignificant increase in major bleeding was noted (9.1% vs. 6.1%) with a significant increase in nonmajor bleeding (22.7% vs. 10%). Clinicians must consider that the bleeding rates reported in clinical trials (which must abide by stringent inclusion/exclusion criteria) may differ from that observed in clinical practice. Registry data from the International Cooperative Pulmonary Embolism Registry, which included 2,454 patients, reported bleeding rates of 21.7% and 8.8% for patients who did and did not receive thrombolytics, respectively (62). The prevalence of intracranial bleeding was 3% (thrombolytics) and 0.3% (no thrombolytic). Clinical algorithms are available which weight the risk and benefit of thrombolytic therapy stratified by the degree of hemodynamic stability (e.g., massive PE vs. submassive PE) (63, 64).

Drotrecogin

Drotrecogin or activated protein C (APC) is a vitamin K-dependent protein, which has several mechanisms of action that may benefit patients with sepsis, including anticoagulant activity (inhibiting coagulation factors Va and VIIIa), inhibition of the production and release of inflammatory cytokines such as interleukin

Table 4. Bleeding rates in patients receiving thrombolytics for pulmonary embolism

Study	Design	n	Thrombolytic Drug	Major Bleeding Thrombolytic	Major Bleeding Control
UPET (198)	MC, RCT	160	UK 2000 units/lb bolus, followed by 2000 units/lb for 12 hrs	22 (26.8%) of 82	11 (14.1%) of 78
Tibbutt et al (208)	2 center, RCT	30	SK 600,000 units intrapulmonary followed by 100,000 units/hr for 72 hrs	1 (7.7%) of 13	1 (5.9%) of 17
Ly et al (206)	RCT	25	SK 250,000 units followed by 100,000 units/hr for 72 hrs	4 (28.6%) of 14	2 (18.2%) of 11
Dotter et al (207)	RCT	31	SK 250,000 units followed by 100,000 units/hr for 18–72 hrs	3 (20%) of 15	4 (25%) of 16
Marini et al (207)	RCT	30	UK 800,000 units over 12 hrs daily for 3 days or UK 3,300,000 units over 12 hrs	0 (0%) of 20	0 (0%) of 10
Levine et al (205)	MC, DB, RCT	58	tPA 0.6 mg/kg over 2 mins	0 (0%) of 33	0 (0%) of 25
PIOPED (199)	MC, DB, RCT	13	tPA 40–80 mg at 1 mg/min	1 (11.1%) of 9	0 (0%) of 4
Dalla-Volta et al (200)	MC, RCT	36	tPA 10 mg followed by 90 mg over 2 hrs	3 (15%) of 20	2 (12.5%) of 16
Goldhaber et al (202)	RCT	101	tPA 100 mg over 2 hrs	3 (6.5%) of 46	1 (1.8%) of 55
Jerjes-Sanchez et al (203)	RCT	8	SK 1,500,000 units over 1 hr	0 (0%) of 4	0 (0%) of 4
Konstantinides et al (204)	MC, DB, RCT	256	tPA 10 mg bolus followed by 90 mg over 2 hrs	1 (0.8%) of 118	5 (3.6%) of 138

MC, multicentered; RCT, randomized controlled trial; UK, urokinase; SK, streptokinase; DB, double-blind; tPA, tissue plasminogen activator.

and tumor necrosis factor, and restoration of fibrinolyis by inhibiting fibrinolytic inhibitors such as plasminogen activator inhibitor-1, and thrombin activatable fibrinolysis inhibitor. Because of its anticoagulant effects, the major adverse effect of APC is bleeding. Some of the major clinical trials with APC in severe sepsis and serious bleeding rates are summarized in Table 5.

Although the use of therapeutic anticoagulation was not allowed in clinical trials, prophylaxis doses of heparin was allowed. The PROWESS trial (65), which demonstrated a survival benefit of APC in patients with severe sepsis, did not report an increase in bleeding with prophylactic heparin. The XPRESS trial found a slight increase in bleeding risk in patients receiving heparin prophylaxis compared with placebo (10.8% vs. 8.1% in study days 0–6, $p = .049$) but also found a higher mortality rate in patients on heparin before randomization who received placebo (35.6% vs. 26.9%, $p = .005$), suggesting that it may be detrimental to discontinue prophylactic heparin when initiating drotrecogin (66).

Several observational trials have suggested that the rate of bleeding in clinical practice is much higher than that of the controlled trials and may be associated with increased mortality. These trials bring into question whether the benefit of APC exceeds the risk in general practice. As summarized by Gentry et al (67), several of the precautions of APC in the Food and Drug Administration-approved labeling were actually contraindications in the published controlled trials of APC. Therefore, the benefit/risk ratio is very difficult to determine in patients with these bleeding risks.

Bertolini et al (68) performed a prospective, multicenter, surveillance program with a parallel nonrandomized control group to monitor the use of APC in Italy and its effect on patient's health. A total of 668 patients received APC. Bleeding events during the infusion period occurred in 10.9% of patients (n = 73), which were much higher than that reported in controlled trials. The most common site of bleeding was GI (30.3%) followed by intrathoracic (17.9%), skin and soft tissue (12.5%), intracranial (10.7%), genitourinary (8.93%), intra-abdominal (1.79%), and the rest was undefined or missing. In a modified case report form which called for detailed evaluation of the severity of bleeding, 4.6% were classified as severe (defined as resulting in death, were life threatening, required prolonged hospitalization, or required >2 units of blood). In three patients, bleeding was life threatening, and in two others, it was fatal. Mortality was higher in patients with bleeding (57.5% vs. 44.9%; $p = .041$). Crude ICU mortality was lower in patients receiving APC, but multivariate analysis suggested that APC was associated with higher mortality in patients after scheduled surgery (OR, 2.79; 95% CI, 1.31–5.97). The authors concluded that: the target population for APC treatment is not clearly defined; the current definition of high-risk patients is questionable; treatment with APC may be harmful for patients who do not match currently provided indications; and further controlled trials are needed. As summarized by Gentry et al (67), several issues with this trial make it difficult to determine risk/benefit ratio, including the fact that the control group was from a different database, time period, and medical center; the serious bleeding rate was not determined for the majority of patients; platelet counts were available for a minority of treated patients; and several baseline characteristics were significantly different between the two groups.

Kanji et al (69) preformed a multicenter observational study evaluating the use of APC in adult severe sepsis. A total of 261 courses of APC were evaluated. Severe bleeding was defined as intracranial hemorrhage, any bleeding event classified as serious by the primary treating physician, or any bleeding event requiring 3 units of packed red blood cells for 2 consecutive days. Overall mortality was 45%, and the rate of serious bleeding was 10%, which is also higher than the PROWESS trial. The majority of bleeding events occurred during the infusion (76%). Of the 25 bleeding events, nine (36%) were GI or intra-abdominal, three (12%) were intrathoracic, one was intracranial, two (8%) were skin and soft tissue, three (12%) were genitourinary, two (8%) were other, and five (20%) had no identifiable source. One patient died of intracranial hemorrhage during the infusion. Logistic regression analysis revealed that having four or more failing organs (OR, 3.1; 95% CI, 1.2–7.8; $p = .016$) and having a relative

Table 5. Bleeding rates from clinical trials of drotrecogin in severe sepsis

Trial	Design	Serious Bleeding[a] During Infusion	Serious Bleeding During 28-Day Study Period	Identified Bleeding Risk Factors
PROWESS (65)	Multicenter, randomized, double-blind, placebo-controlled in 1690 patients with severe sepsis (SIRS with one or more organ failure)	NR	APC vs. placebo, 3.5% vs. 2%, $p = .06$	Gastrointestinal ulceration, APTT >120 secs, INR >3, platelet count decreased to <30,000, traumatic injury of blood vessel or traumatic injury of highly vascular organ
ADDRESS (209)	Multicenter, randomized, double-blind, placebo-controlled in 2640 patients with severe sepsis (SIRS with one organ failure or APACHE II score <25)	APC vs. placebo 2.4% vs. 1.2%, $p = .02$	APC vs. placebo 3.9% vs. 2.2%, $p = .01$	Not specifically reported but in surgical patients who had a bleeding event, more patients who received APC died of multisystem organ failure or of a hemorrhage
ENHANCE (210)	Open-label, multicenter in 2378 patients with severe sepsis receiving APC	3.6%	6.5%	Approximately 50% identified as being procedure related
XPRESS (66)	Multicenter, randomized, double-blind, phase 4, equivalence design in 1994 patients with severe sepsis receiving APC randomized to prophylactic heparin vs. placebo	5.7% APC plus heparin vs. 7.5% APC plus placebo, $p = .12$	3.9% APC plus heparin vs. 5.2% APC plus placebo, $p = .16$	NR

NR, not reported; APTT, activated partial thromboplastin time; INR, international normalized ratio; APC, activated protein C; SIRS, systemic inflammatory response syndrome; APACHE, Acute Physiology and Chronic Health Evaluation.

[a]Serious bleeding defined similarly in PROWESS, ADDRESS, and ENHANCE as serious intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding event requiring the administration of 3 units of packed red cells on 2 consecutive days. Serious bleeding defined in XPRESS as fatal bleeding and/or nonfatal serious bleeding (defined as intracranial hemorrhage or bleeding at a critical location).

contraindication to APC therapy (OR, 2.7; 95% CI, 1.1–6.5; $p = .028$) were predictive of a serious bleeding event.

Wheeler et al (70) performed an observational study of APC in 274 patients with severe sepsis from five teaching institutions in the United States. Severe bleeding was defined the same as in the PROWESS trial and in the trial by Kanji et al (69). Hospital mortality was 42% and the serious bleeding rate during the infusion was 4%. The prevalence of serious bleeding seemed to be higher among patients with thrombocytopenia (18.8% of patients with platelet count of <50,000) and in patients with recent surgery (6.6%). However, the investigators failed to find an increased risk of bleeding among patients who would have been excluded from the PROWESS trial, but the analysis is limited by the few patients who met these criteria.

Gentry et al (67) performed a retrospective study on 73 patients with severe sepsis treated with APC from two tertiary Veterans Affairs Medical Centers, and compared outcomes in patients with baseline bleeding precautions with those without bleeding precautions. Serious bleeding events occurred in seven (35%) of 20 patients with any bleeding precaution as opposed to only two (3.8%) of 53 patients without any bleeding precautions ($p < .0001$). Mortality was also higher in patients with bleeding precautions (65% vs. 24.5%, $p = .0015$). Multivariate analysis found that the presence of a baseline bleeding precaution, increased Acute Physiology and Chronic Health Evaluation II score, and the presence of bloodstream infection were independent variables associated with mortality.

Colloids

Excessive hemodilution after volume expansion may increase the risk of bleeding by decreasing the concentration of platelets and coagulation factors, and some colloids may have other properties that can increase the risk of bleeding.

Levi and Jonge (71) summarized the literature regarding known effects of various colloids on coagulation. Gelatins were initially felt to only influence coagulation by dilution, but some data suggested that they may decrease clot strength and decrease platelet aggregation through binding and decreasing von Willebrand factor (VWF). Dextrans are known to decrease VWF and factor VIII and increase fibrinolysis, and they have been shown to be effective in preventing thrombosis and PE. Therefore, the dextrans have become utilized more as an anticoagulant than as a plasma expander. Hydroxyethlystarch (HES)-based compounds have also been found to decrease VWF and factor VIII as well as increase fibrinolysis.

Westphal et al (72) recently reviewed differences in HESs. HESs are identified by three numbers: the first number is the concentration in percentage; the second number is the average molecular weight; and the third number is the molar substitution (MS). HES products with an MS of 0.7 are called hetastarches, MS of 0.6 are hexastarches, MS of 0.5 are pentastarches, and MS of 0.4 are tetrastarches. Older-generation HES with high MS are less prone to enzymatic breakdown and accumulate in the plasma more than newer-generation tetrastarches. The more rapidly degradable HES products have been found to have a greatly reduced effect on coagulation as

compared with hetastarches. In a pooled analysis of clinical trials in major surgery, Kozek-Langenecker et al (73) found that 6% HES 130/0.4 significantly reduced blood loss by 404 mL ($p = .006$) and transfusion volumes by 137 mL ($p = .004$) as compared with 6% HES 200/0.5. Hetastarch is available in normal saline or lactated Ringer's; however, several studies (74, 75) suggested that the diluent does not make a difference in the effect on coagulation.

There are very few trials in critically ill patients that compare various colloids in terms of their effects on bleeding. However, some recent large-scale trials have compared colloids with crystalloids in critically ill patients. Albumin is generally felt to have the least effect on coagulation. The SAFE trial (76) was a multicenter, randomized trial comparing albumin 4% with normal saline in the resuscitation of 6,997 patients in ICU. Overall, there were no significant differences in overall outcomes at 28 days. Patients receiving albumin did receive a higher volume of packed red cells on average than those receiving normal saline on day 1 (97.8 mL vs. 71.7 mL, respectively, $p < .001$) and on day 2 (106.5 mL vs. 61.1 mL, respectively, $p < .001$). During the first 4 days, this averaged to less than one quarter of a unit of packed red cells. Therefore, the authors did not feel this would have a clinically significant effect on outcomes.

Brunkhorst et al (77) conducted a multicenter randomized trial evaluating both intensive insulin therapy and conventional insulin therapy and a pentastarch (10% HES 200/0.5) or Ringer's lactate for fluid resuscitation in 537 patients with severe sepsis. The mortality rate at 28 days did not vary between the HES and Ringer's lactate group (26.7% vs. 24.1%, respectively, $p = .48$). There was a trend toward a higher mortality in the HES group at 90 days (41% vs. 33.9%, $p = .09$). The HES group had significantly higher rates of acute renal failure (34.9% vs. 22.8%, $p = .002$), a lower median platelet count (179,600/mm^3 vs. 224,000/mm^3, $p < .001$), and received more units of packed red cells (6 vs. 4, $p < .001$) compared with Ringer's lactate. Although the difference was not statistically significant, there were slightly more patients in the HES group who had bleeding (5% vs. 3.6%, $p = .45$) and serious bleeding (3.4% vs. 1.5%, $p = .14$) compared with Ringer's lactate. The authors concluded that HES solutions should be avoided until long-term studies with adequate numbers of patients show that HES solutions are safe in critically ill patients.

Medications with procoagulant effects

Although medications to prevent or manage severe and life-threatening bleeding in the critically ill are widely used, the potential for overcorrection or clotting exists. In addition, strategies to decrease blood transfusions are increasingly being considered, and ADEs relative to their use are becoming more recognized. Pharmacologic interventions (used to either manage bleeding or reduce transfusions) that have the potential to induce thrombosis are described below. ADEs that are encountered with medications used in the management of GI bleeding (e.g., vasopressin, octreotide, proton pump inhibitors) are covered in the portion of this supplement reviewing drug-induced GI complications.

Recombinant factor VIIa

Recombinant factor VIIa (rFVIIa) was originally developed and approved for use in patients with various types of hemophilia and patients with factor VII deficiency (78). Subsequent investigations probed its potential use for the control of bleeding in patients without hemophilia or other clotting deficiencies or disorders. Off-label use has focused on patients with multiple trauma, intracranial hemorrhage, transplantation, cardiac surgery, and bleeding due to warfarin or other anticoagulants.

The use of rFVIIa in nonhemophilia patients, in particular, its safety profile, has been reviewed previously (79–84). According to postmarketing surveillance data, adverse drug reactions are <1 per 1000 standard doses (78). Off-label use is widely published in the medical literature, although many of the publications are case reports or small uncontrolled studies (85, 86). Many of the studies, likely due to their small size, either did not observe or did not report adverse events. One of the more recent and largest reviews (81) of rFVIIa's safety profile evaluated serious thromboembolic events reported to the Food and Drug Administration's Adverse Event Reporting System. During a period of nearly 6 yrs, 431 adverse events reports were submitted, accounting for 185 thromboembolic events. Events included cerebrovascular accidents, MIs, other arterial thromboses, venous thromboses, PEs, and clotted devices. Probable cause of death in 36 of the 50 reported deaths was the thromboembolic event. Unfortunately, it is difficult to determine prevalence of ADEs from these data, as they were from voluntary reporting and total use (i.e., the denominator for this calculation) is unknown. Thomas et al (87) examined medical records of 285 patients, who received rFVIIa over a 5-yr period. Overall, 27 (9.4%) patients experienced a thromboembolic event with nine being highly related to rFVIIa. Interestingly, 18 (67%) of the events were observed in the anatomical vicinity of defined high-energy vascular trauma. There were ten deaths in the cohort thought to be caused, in part, by the thromboembolic complication.

Two studies that were performed simultaneously and reported in a single publication in blunt and penetrating trauma evaluated the efficacy and safety of rFVIIa vs. placebo (88). The primary outcome was red blood cell units transfused within 48 hrs of the first rFVIIa dose. Safety outcomes included adverse event frequency and timing, changes in coagulation-related laboratory values, and a composite end point of death and critical complications. Adverse events were similar between the treatment and control groups in both the blunt and penetrating trauma patients. Acute respiratory distress syndrome, multiple organ failure, and sepsis were the most frequently reported adverse events. Twelve thromboembolic events occurred during the study; six in each group, including PE, subclavian vein thrombosis, mesenteric vein thrombosis, cerebral infarction, and DVT in the placebo group; and jugular vein thrombosis, arterial limb thrombosis, cerebral infarction, intestinal infarction, phlebothrombosis, and DVT in the rFVIIa group. The authors reported no differences between rFVIIa and placebo for mortality, critical complications, or the composite end points.

Four separate studies (89–92) evaluated the safety and efficacy of rFVIIa in the management of intracerebral hemorrhage. The largest and most recent was a Phase III study comparing placebo to two dosages (20 μg/kg and 80 μg/kg) of rFVIIa given within 4 hrs after the onset of stroke (89). The primary outcome was death or disability at 90 days. Safety end points included occurrence of MI, ischemic stroke, DVT, and PE. The total prevalence of serious thromboembolic events was similar in each group (9% in patients

receiving 20 μg/kg, 10% in patients receiving 80 μg/kg, and 8% in the placebo group). There was no significant difference in MI, cerebral infarction, DVT, or PE between groups. However, there was a significant difference in the occurrence of arterial events (5% in patients receiving 20 μg/kg, 8% in patients receiving 80 μg/kg, and 4% in patients receiving placebo, $p = .04$ for 80 μg/kg vs. placebo). *Post hoc* analysis identified age and prior use of an antiplatelet agent as risk factors for thromboembolic events, but not rFVIIa. Survival and functional outcome were not different between groups. A more complete list off label rFVIIa studies is found in Table 6.

Prothrombin complex concentrates

Prothrombin complex concentrates (PCC) are heterogeneous mixtures of essential coagulation factors, including factors II, VII, IX, and X. Several products are available for use in the United States and Europe, each containing variable quantities of each factor. One major difference among the individual products is the amount or inclusion of factor VII. Earlier PCC products contained negligible amounts of factor VII and were referred to as "3-factor PCCs." Newer formulations, however, have added significant concentrations of factor VII and are deemed "4-factor PCCs." The thromboembolic potential between 3 and 4 factor PCCs has not been thoroughly described.

Early reports with PCCs have documented a high prevalence (11%) of thromboembolic events, but this has decreased markedly over the last 30 yrs, largely due to improvements in the quality of factors used in the formulation (93, 94). Furthermore, most formulations now contain one or more coagulation inhibitor, such as protein C, protein S, protein Z, antithrombin III, or heparin (95). The addition of small amounts of anticoagulant can potentially shift the balance of coagulation factors to a more physiologic state with the goal of preventing excessive clot formation (96). One recent review (97) of 14 studies, which included 460 patients with warfarin overdose, reported seven thrombotic complications.

Several risk factors for thrombosis post PCC have been proposed (94, 96, 98). First is the use of higher or repeated dosing of PCC. This is likely due to the differences in half-lives of factors II, VII, IX, X and proteins C and S and the potential for accumulation of factors II and X. Second is the composition of factors used in the individual formulation. Because there is no standardization of factor concentrations among the various products, the risk for thrombosis will vary within. Formulations that contain higher concentrations of factors II and X, active coagulation factors (e.g., factor VII), or phospholipids may increase thrombogenicity. An additional risk factor is the patient's underlying disease and current clinical condition. For example, patients with warfarin-related coagulopathy may have a higher tendency for thromboembolism as a result of the original indication for warfarin, and those with hepatic dysfunction can have antithrombin III deficiency. Finally, thrombus related to HIT should not be overlooked due to the presence of heparin in some formulations.

Antifibrinolytics

Aprotinin (a serine protease inhibitor), epsilon aminocaproic acid (EACA), and tranexamic acid (lysine analogs) have been widely used to facilitate hemostasis for many years (84, 99–103). The vast majority of use and research with these agents has been in cardiac surgery patients, although there are limited data in other patient populations. The Food and Drug Administration suspended aprotinin marketing in the United States in late 2007 due to acute renal failure and vascular safety concerns, and ultimately an increased risk of mortality associated with its use in cardiac surgery patients. Aminocaproic acid and tranexamic acid continue to be used. Adverse drug events associated with EACA and tranexamic acid use include minor side effects, such as transient hypotension (related to the rate of IV administration), nausea, vomiting, diarrhea (more common with oral tranexamic acid than IV lysine analogs), and rash, as well as more serious (e.g., thromboembolic) events.

The safety and efficacy of EACA and tranexamic in cardiac surgery patients are well described in the literature, with many large trials or meta-analyses published between 2007 and the first half of 2009 (104–109). Both of these medications are effective hemostatic agents, defined typically as decreased blood loss, decreased use of blood products, and/or a decreased need for reoperation due to excessive blood loss compared with placebo. Additionally, although ADEs associated with their use have been reported, neither the incidence nor severity of ADEs differs significantly from placebo. Thromboembolic events have been reported, including MI, stroke, PE, and DVT. Finally, EACA and tranexamic acid have not been shown to be associated with an increased risk of mortality in cardiac surgery patients. Although some literature has suggested a difference in efficacy between these two lysine analogs, this has not been observed consistently. The prevalence of ADEs associated with EACA and tranexamic acid seems to be similar (104–109).

Although the literature for EACA and tranexamic use in cardiac surgery is robust, the evidence for antifibrinolytic use beyond this patient population is less abundant and not convincing (110–123). Although one might expect ADEs in other patient populations to be similar to those reported in cardiac surgery patients, there is not enough evidence to support this conclusion. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage) is a large, randomized, placebo-controlled trial investigating the use of tranexamic acid in trauma patients with hemorrhage (124). This international multicenter trial is scheduled to complete enrollment of 20,000 patients by the end of 2009. Primary outcomes include death, transfusion requirements, and nonfatal vascular (hemorrhagic and occlusive) events. The authors plan to publish their results in 2010.

Desmopressin

Desmopressin is available in various dosage forms and is approved for use in the United States for a variety of uses, including hemophilia A (with factor VIII levels of >5%), von Willebrand disease type I (with factor VIII levels of >5%), diabetes insipidus, and primary nocturnal enuresis (125). Desmopressin stimulation of extrarenal V_2 receptors increases factor VIII and VWF, and has been used in an attempt to control bleeding in patients with and without normal coagulation physiology. Additionally, uremia is associated with decreased levels of VWF, leading to an interest in desmopressin use in uremic patients with bleeding (126, 127). Clinical trials (84, 99, 100, 103) in various surgical patient populations (e.g., general surgery, obstetrical/gynecology, orthopedic, cardiac surgery) have demonstrated limited and inconsistent success.

Reported ADEs thought to be related to desmopressin treatment for bleeding in the critically ill are relatively uncommon, although any procoagulant medication has the potential to increase throm-

Table 6. Adverse events associated with recombinant factor VIIa

Study	Design	n	Population	Safety/Adverse Drug Events
Diprose et al (212)	P, DB, RCT pilot study	20 (10 in each arm)	Cardiac surgery requiring CPB	Thromboembolic events Placebo: 1 stroke, 1 MI,1 death, rFVIIa: 1 stroke, 1 MI
Boffard et al (88)	P, DB, MC, RCT	143	Blunt trauma	Serious ADEs Placebo 66%, rFVIIa 64% Thromboembolic ADEs Placebo 4%, rFVIIa 3% Death or critical complications Placebo 42%, rFVIIa 29%
	P, DB, MC, RCT	134	Penetrating trauma	Serious ADEs Placebo 56%, rFVIIa 51% Thromboembolic ADEs Placebo 5%, rFVIIa 6% Death or critical complications Placebo 34%, rFVIIa 29%
Raobaikady et al (214)	P, DB, RCT	48	Pelvic trauma or major pelvic reconstruction	1 ADE reported in each group; both ADEs considered to be unrelated to treatment (rFVIIa or placebo)
Mayer et al (91)	P, DB, MC, RCT, dose escalation phase II trial	48 (12 placebo, 6 in each dosage)	Spontaneous ICH	Possible treatment-related ADEs (# patients) Placebo–DVT (1) 10 μg/kg–pruritic rash (1) 20 μg/kg–vomiting (1), fever (1), ECG changes, CK-MB negative (1), DVT (1) 40 μg/kg–ECG changes, troponin negative (1), USA 29 days after treatment (1) 80 μg/kg, 120 μg/kg, and 160 μg/kg–no ADEs reported
Mayer et al (90)	P, DB, MC, RCT	399 (randomized to placebo, 40 μg/kg, 80 μg/kg, or 160 μg/kg)	Spontaneous ICH	Serious thromboembolic ADEs (%) Placebo–2% 40 μg/kg–6% 80 μg/kg –4% 160 μg/kg –10% Mortality (%) Placebo –29% 40 μg/kg–18%[a] 80 μg/kg–18% 160 μg/kg–19%
Mayer et al (92)	P, DB, MC, RCT, dose escalation phase II trial	40 (8 in placebo and each of 4 dosage groups)	Spontaneous ICH	Serious ADEs possibly or probably related to treatment (n patients) Placebo–1 5 μg/kg–0 20 μg/kg–1 40 μg/kg–0 80 μg/kg–1 Mortality Placebo–1 5 μg/kg–2 20 μg/kg–2 40 μg/kg–3 80 μg/kg–0
Mayer et al (89)	P, DB, MC, RCT	841 (ITT) (randomized to placebo, 20 μg/kg or 80 μg/kg)	Spontaneous ICH	Thromboembolic ADEs (%)[b] Placebo–8% 20 μg/kg–9% 80 μg/kg–10% Mortality (%) Placebo–19% 20 μg/kg–18% 80 μg/kg–21%

Table 6.—*Continued*

Study	Design	n	Population	Safety/Adverse Drug Events
Lodge et al (213)	P, DB, MC, RCT	200 (randomized to placebo, 20 μg/kg or 80 μg/kg)	Noncirrhotic patients undergoing partial hepatectomy	Serious ADEs (% patients) Placebo–13% 20 μg/kg–17% 80 μg/kg–11% Thromboembolic ADEs (% patients) Placebo–4.4% 20 μg/kg–4.6% 80 μg/kg–4.6% Death (% patients) Placebo–4.4% 20 μg/kg–5.9% 80 μg/kg–0%
Shao et al (215)	P, DB, MC, RCT	232 (randomized to placebo, 50 μg/kg or 100 μg/kg)	Cirrhotic patients undergoing hepatectomy	Serious ADEs (% patients) Placebo–2.5% 50 μg/kg–2.7% 100 μg/kg–6.4% Thromboembolic events (n of events) Placebo–1 patient with pulmonary embolism 50 μg/kg–1 patient with suspected portal vein thrombosis 100 μg/kg–1 patient with suspected mesenteric vein thrombosis; 1 patient with ECG changes and increased cardiac enzymes
Alten et al (211)	Ret case series	135	Nonhemophiliac pediatric patients receiving at least 1 dose of rFVIIa	Authors reported 3 thromboembolic events: cerebral infarction, lower extremity arterial and venous thrombosis, and venous sinus thrombosis in the brain

P, prospective; DB, double blind; RCT, randomized controlled trial; ITT, intent to treat; CPB, cardiopulmonary bypass; MI, myocardial infarction; MC, multicentered; ADE, adverse drug event; DVT, deep vein thrombosis; ECG, electrocardiograph; USA, unstable angina; ICH, intracerebral hemorrhage; Ret, retrospective; rFVIIa, recombinant factor VIIa.

[a]$p = .05$ compared with placebo; [b]p = NS for total thromboembolic ADEs; $p = .04$ for arterial thromboembolic ADEs for placebo vs. 80 μg/kg.

boembolic risk. The most common side effect, flushing with or without decreased blood pressure, is usually mild. Reports of ADEs with desmopressin have mostly been limited to tachyphylaxis (and subsequent increase in bleeding time), free water retention with hyponatremia, and thromboembolic events. Tachyphylaxis is usually avoided by limiting desmopressin use to <24 hrs. Hyponatremia with seizure activity has been reported, but with long-term use of the drug in nocturnal enuresis (128). Much of the literature describing thromboembolic a associated with desmopressin consists of case reports (129–134).

The most recent review was a meta-analysis (155) of randomized controlled trials evaluating desmopressin use in surgery, its effect on blood loss and use of blood products, and adverse events. The authors analyzed 42 studies (from 38 publications). The 2,488 subjects included cardiac, vascular, orthopedic, plastic, and general surgery patients. Hypotension was the most common adverse event associated with desmopressin administration, but it was considered to be transient and not serious. The authors found no significant difference in ADEs between desmopressin and placebo. The prevalence of total thromboembolic adverse events was 5.7% in the DDAVP group vs. 4.6% in the placebo group (OR, 1.2; 95% CI, 0.68 –2.09); MI, 3.8% in the DDAVP group vs. 2.9% in the placebo group (OR, 1.27; 95% CI, 0.73–2.2; and death, 1.2% in the DDAVP group vs. 0.9% in the placebo group (OR, 1.25; 95% CI, 0.51–3.04).

Conjugated estrogens

Interest in the use of estrogens to treat bleeding began after reports of increased levels of estrogen and factor VIII in pregnant women with von Willebrand disease. This increase in factor VIII associated with increased estrogen levels led to studies (126, 136) demonstrating shortened bleeding times in uremic patients receiving conjugated estrogens. Further studies showed similar effects on bleeding time, as well as improved clinical outcomes. These studies (137–143) included patients with renal failure, patients with GI bleeding, patients undergoing renal or liver transplantation, and pediatric patients undergoing spinal surgery.

Due to the relatively small numbers of patients and studies (several of which are case reports, or small uncontrolled case series), ADEs due to estrogen use in critically ill patients are not well defined. Although there are no well-documented reports of thromboembolic ADEs in critically ill patients, estrogens are known to be potentially thrombogenic in the general population, particularly with long-term use. Whether or not the short-term regimens used in critically ill patients result in a lower risk of thromboembolic ADEs cannot be definitively answered. Additionally, it is not known if higher doses used in the management of bleeding increase the risk of ADEs. Doses ranging from 5 mg to 60 mg per dose, and up to a cumulative dose of 3 mg/kg have been used.

Finally, a small randomized, double-blind trial (144) compared blood loss (conjugated estrogens vs. placebo) in 16 patients undergoing coronary artery by-

pass graft surgery. Although no ADEs were observed, the investigators reported a nonsignificant trend toward an increased blood loss in the estrogen group (4-hr blood loss, 1449 ± 231 mL in the estrogen group vs. 1186 ± 187 mL in the control group). This is in contradiction to an earlier study (145), which found a benefit to estrogen therapy in cardiac surgery patients.

Topical hemostatic agents

Topical hemostatics are often used as adjunctive therapy in the management of bleeding. They are widely employed in the operative setting to help control surgical bleeding. Commonly used topical agents include various formulations of thrombin, fibrin sealants, and miscellaneous products, which can be applied as powders, sprays, foams, solutions, gels, granules, sponges, or bandages (84, 146–149). Although considered safe and effective, these agents, despite being applied locally, may cause clinically significant side effects. Many topical hemostatics are derived from bovine sources, which are potentially immunogenic, and carry a risk of transmitting diseases caused by blood-borne pathogens. Products derived from human plasma are less immunogenic, but they still carry a risk of disease transmission. Thrombin preparations are the most widely used topical hemostatics; they are used in >1 million cases/yr.

Bovine thrombin was introduced for clinical use in 1940 (147). Because it is a plasma-derived product, there is a risk of transmitting blood-borne pathogens, such as parvovirus, hepatitis A, and prions. Technology for purifying thrombin products and removing blood-borne pathogens has improved dramatically from the time they were first introduced, but these processes remain imperfect. Although there are no reports of infectious diseases caused by plasma-derived thrombin, the potential for transmission remains.

Exposure to bovine thrombin may induce the formation of antibodies to bovine and even human coagulation proteins (149–154). The incidence of reported antibody production varies widely, from 10% to >90% (150, 154–156). This variability seems to be dependent on factors such as the patient population, history of prior exposure, and the purity of the product (153, 155, 156). Because thrombin products contain contaminants, including other clotting factors, the immune response may not be limited to the production of antibodies to thrombin alone. In a study where 94% of patients had an immunologic response to a bovine thrombin product, 81% and 91% of patients demonstrated antibody production to bovine factors V and Va, respectively. Furthermore, 51% of individuals developed antibodies that cross-reacted with human coagulation proteins (154).

The ultimate concern with the immunologic response is if this translates into clinically significant ADEs. Numerous reports (154–162) established this link, citing increased clotting times, excessive oozing and bleeding, thrombosis, and anaphylactic reactions. Ortel et al (154) published their findings on 151 patients undergoing cardiac surgery who received bovine thrombin. Four to eight weeks after surgery, 36% of the evaluable patients had at least one abnormal coagulation test value. Although the authors did not find an association between thrombin use and postoperative ADEs, increased antibody levels to ≥2 coagulation proteins before surgery increased the risk of adverse postoperative outcomes, including hemorrhagic events (unadjusted OR, 5.40; 95% CI, 1.54 –18.8). There was also a significant difference in ADEs in patients with postoperative elevated antibodies to ≥2 bovine proteins (34.6% vs. 66.7%, $p = .0229$). A recent publication (149) provided a thorough safety review of bovine-derived topical hemostatics, including thrombin, fibrin sealants, and combination products. The authors reviewed data from randomized controlled trials, as well as case series and case reports.

A purer formulation of bovine thrombin (Thrombin-JMI) contains a higher percentage of thrombin and fewer contaminants, including factor V/Va. However, package inserts for this and other bovine thrombin products still have black-box warnings regarding antibody production, and the subsequent risk of immune-mediated coagulopathy and other ADEs.

In an effort to address safety concerns with bovine thrombin, two products were recently approved for use in the United States: A human pooled plasma thrombin (Evithrom) in 2007; and a recombinant human thrombin (Recothrom) in 2008 (147, 159, 163). Studies (151, 152) performed across a wide range of surgical disciplines indicated at least equivalent efficacy for the human pooled plasma and the recombinant human thrombins. As with bovine thrombin, there have been no reported cases of transmission of disease with human pooled plasma thrombin, but any blood-derived product has the potential for causing such infectious complications. Recombinant human thrombin is free from human and bovine proteins and, therefore, should carry no risk of blood-borne pathogen transmission.

In a multicenter, Phase III, prospective, randomized, double-blind trial (152), 305 surgery patients received either human pooled plasma thrombin or bovine thrombin. Efficacy (hemostasis) was similar between the two treatment groups; 12.2% of patients who received bovine thrombin developed antibodies to at least one anticoagulant protein vs. only 3.3% of patients who received human pooled plasma thrombin. A small number of patients (raw data not reported) who received bovine thrombin developed antibodies that cross-reacted with human thrombin; none of the patients in the human pooled plasma thrombin treatment group developed antibodies to any human coagulation protein. There were no differences in serious ADEs, and hemorrhagic complications were not observed in either group.

A multicenter, Phase III, prospective, randomized, double-blind trial by Chapman et al (151) compared the efficacy and safety of a bovine thrombin with recombinant human thrombin in 401 surgical patients. Efficacy (hemostasis at 10 mins) was similar between the two treatment groups. The investigators monitored clinical ADEs, as well as antibody production. There was a significantly higher prevalence of antibody development in patients receiving bovine thrombin as compared with recombinant human thrombin (21.5% vs. 1.5% respectively, $p < .0001$). However, there were no differences in total ADEs, or ADEs stratified by level of severity. A *post hoc* analysis showed that subjects who developed antibodies in the bovine thrombin group were more likely to manifest bleeding, thromboembolic events, hypersensitivity, and abnormal activated partial thromboplastin time values when compared with subjects (in the bovine thrombin group) who did not develop antibodies.

Finally, a Phase IIIb, open-label, single-group trial (164) evaluated the safety of recombinant human thrombin use in 209 vascular and spinal surgery patients with confirmed or highly likely prior history of bovine thrombin exposure; 15.6% of patients had preexisting antibodies to

bovine thrombin; 2% had antibodies to recombinant human thrombin (the authors were unable to explain these preexisting antibodies to the recombinant human product). After administration, no patients demonstrated seroconversion or a ≥10-fold increase in titers for antirecombinant human thrombin antibodies. Hypersensitivity reactions were minor and infrequent, with pruritis and rash reported in 7% and 2% of patients, respectively. Commonly occurring ADEs (≥10% of patients) were mild and transient. No serious ADEs occurred at an occurrence rate of >1%; and those serious ADEs observed were deemed to be consistent with the population studied. Two patients died during the study. Recombinant human thrombin treatment was not a contributory factor in either death, according to the principal investigator. The authors concluded that recombinant human thrombin can be safely administered to patients with a history of prior thrombin exposure, even those with preexisting antibodies to bovine thrombin.

Erythropoetin

Erythropoietin (EPO) has been studied in critically ill patients to reduce the need for blood transfusions. Thromboembolic complications have been documented with all of the EPOs, and have resulted in black-box warnings on product information. A meta-analysis of phase III trials in patients with cancer found that the use of darbepoetin or EPO was associated with an increased risk of venous thromboembolism compared with placebo or standard care (7.5% vs. 4.9%; relative risk, 1.57; 95% CI, 1.31–1.87) and increased mortality risk (hazard ratio, 1.1; 95% CI, 1.01–1.2) (165). In patients with chronic renal failure, a greater risk of arteriovenous access thrombosis and mortality was found when higher target hemoglobin concentrations were obtained as opposed to lower targets (thrombosis risk ratio, 1.34; 95% CI, 1.16 –1.54; mortality risk ratio, 1.17; 95% CI, 1.01–1.35) (166).

Anemia is common in the critically ill patient due to a variety of causes, and transfusions may result in many complications, including transfusion-related acute lung injury. EPO improves the red blood cell count by binding to receptors on erythroid progenor cells to stimulate the production of red blood cells. Although a comprehensive review of its efficacy in the prevention of transfusions in the critically ill patient is beyond the scope of this article, in two trials (EPO 1 and EPO 2) (167, 168), EPO showed a significant reduction in the need for blood transfusions in critically ill patients. A third trial (EPO 3) (169) conducted by the same EPO Critical Care Trials Group utilized a more conservative transfusion standard and did not show a reduction in the need for transfusions, but in a predefined subgroup analysis did find a significant reduction in mortality in trauma patients, suggesting that further study is warranted in this population.

EPO 1 and EPO 2 did not show an increase in thromboembolic events with EPO. However, EPO 3 did show an increased prevalence of thrombotic vascular events (defined as PE, DVT, cerebrovascular event, MI, or cardiac arrest) with EPO compared with placebo (16.5% vs. 11.5%, $p = .008$), predominately due to an increase in the occurrence of DVT (8.7% vs. 5.8%, $p = .04$) (169). This increased prevalence of thrombotic events was found despite exclusion of high-risk patients (acute ischemic heart disease, history of pulmonary embolus, DVT, ischemic stroke, other arterial or venous thrombotic events, or a hypercoagulable disorder). *Post hoc* analysis showed thrombotic events to be increased among patients who did not receive heparin at baseline (20.3% vs. 12.8%; hazard ratio, 1.58; 95% CI, 1.09 –2.28; $p = .008$) but not among those who received heparin at baseline (12.3% vs. 10.2%; hazard ratio, 1.16; 95% CI, 0.75–1.8; $p = .41$). If EPO is utilized in critically ill patients for prevention of transfusion, it should be in the same low-risk population as EPO 3, and prophylactic anticoagulation should be considered (170). Because evaluation for thrombotic events in the EPO trials was only done based on clinical suspicion and routine screenings were not performed, the actual occurrence of thrombotic complications from EPO remains unknown, and further study is needed. Investigators have suggested several different mechanisms of EPO that may cause thromboembolic phenomenon. Tobu et al (171) found increased levels of C-reactive protein, nitric oxide, and thrombin activatable fibrinolytic inhibitor in 106 hemodialysis patients with anemia being treated with EPO, and they suggested that a fibrinolytic deficit may cause thrombosis in these patients. In an *in vitro* study of cultured human endothelial cells, Fuste et al (172) demonstrated that EPO produced a dose-dependent activation of signaling pathways that result in an increased reactivity to platelets and expression of tissue factor that may cause thrombosis.

Reversal of antithrombotic agents

In certain situations, such as severe bleeding or the need for urgent surgery or invasive procedures, it may be necessary to reverse the effects of antithrombotic agents. Several options exist for reversal, which varies based on the causing drug, the speed of reversal, and prothrombotic risk. Therapeutic guidelines (84) are available, which address bleeding related to a variety of circumstances.

Heparin and LMWH

Protamine sulfate is a protein derived from fish sperm that binds to and neutralizes heparin. Protamine, 1 mg, will neutralize 100 units of heparin (39). Because the half-life of heparin is 60–90 mins, when neutralizing the effects of heparin, only the preceding several hours needs to be considered. LMWH is only partially reversed by protamine. It has been postulated that incomplete neutralization is due to incomplete binding. However, Crowther et al (173) demonstrated that variability in the reversal of LMWH correlated to the degree of sulfate charge. The total sulfate analysis and subsequent degree of neutralization of various LMWH by protamine are summarized in Table 7.

Hirsh et al (39) provided recommendations for reversing LMWH with protamine. If LMWH was given within 8 hrs, protamine should be administered at a dose of 1 mg per 100 anti-Xa units of LMWH (1 mg enoxaparin equals approximately 100 anti-Xa units). A second dose of 0.5 mg protamine per 100 anti-Xa units should be administered if bleeding continues. Smaller doses of protamine should be given if the time since LMWH administration is >8 hrs. Protamine should be administered slowly because of risk of histamine release and hypotension. Protamine has some intrinsic anticoagulant effect, and excessive dosing should be avoided. Noncardiogenic pulmonary edema has also been rarely reported with protamine.

Although there are little clinical data, Young et al (174) demonstrated that recombinant activated factor VII (rFVIIa)

Table 7. Protamine neutralization and total sulfate analysis of various low-molecular weight heparin

LMWH	% Anti-Factor Xa Activity Neutralized	Total Sulfate (%) ± SEM
Fraxiparine	57.7	34.7 ± 0.7
Tinazeparin	85.7	39 ± 0.1
Dalteparin	74	36.8 ± 0.1
Clivarin	51.4	34.8 ± 0.2
Enoxaparin	54.2	32.3 ± 0.2
SSLMWH	100	41.9 ± 1.1

LMWH, low-molecular weight heparin; SSLMWH, super sulphonated LMWH.

Data from reference 173.

effectively reversed the anticoagulant effects of heparin and enoxaparin *ex vivo* as measured using thromboelastography, although it did not reverse the anti-Xa activity of enoxaparin. The authors suggested that rFVIIa be considered for patients with excessive bleeding with heparin or LMWH.

Fondaparinux

Fondaparinux is an antithrombin-binding pentasaccharide. It does not bind to protamine; therefore, protamine is not effective in reversal of fondaparinux. The rFVIIa has been reported to reverse the anticoagulant effects of fondaparinux in human volunteers (175). Young et al (174) also found that rFVIIa reversed the anticoagulant effect of fondaparinux as measured, using thromboelastography. Fondaparinux has properties that would favor removal via hemodialysis (e.g., low molecular weight and low protein binding), but binding to antithrombin substantially decreases the degree of extracorporeal clearance and drug accumulation has been observed (176).

Direct thrombin inhibitors

There is no known reversal agent for the direct thrombin inhibitors (lepirudin, bivalrudin, argatroban). However, Young et al (174) also demonstrated that rFVIIa reversed the anticoagulant effects of argatroban. In addition, *in vitro* studies (177) with melagatran have reported improved clot formation using PCC, but clinical data are limited.

Vitamin K antagonists

Guidelines (178) for the management of bleeding from vitamin K antagonists, such as warfarin, have been extensively reviewed. Alternatives for managing bleeding from vitamin K antagonists include vitamin K1 or phytonidione, fresh frozen plasma (FFP), PCC, and rFVIIa. Recommendations from the American College of Chest Physicians are summarized in Table 8.

Table 8. Recommendations for the management of elevated international normalized ratios or bleeding in patients receiving vitamin K antagonists

Condition	Intervention
INR more than therapeutic but <5, no significant bleeding	Lower dose or omit dose, monitor more frequently and resume at lower dose when INR therapeutic. If only minimally above therapeutic range, no dose reduction may be required (grade 1C)
INR ≥5 but <9, no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit one dose and give vitamin K 1–2.5 mg orally particularly if at increased risk of bleeding (grade 1C). If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤5 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 hrs If the INR is still high, additional vitamin K (1–2 mg orally) may be given (grade 2C)
INR ≥9, no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg orally) with the expectation that the INR will be reduced substantially in 24–48 hrs (grade 1B). Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with FFP, PCC, or rFVIIa, depending on the urgency of the situation, vitamin K can be repeated every 12 hrs (grade 1C)
Life-threatening bleeding	Hold warfarin therapy and give FFP, PCC, or rFVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat if necessary, depending on INR (grade 1C)

INR, international normalized ratio; FFP, fresh-frozen plasma; PCC, prothrombin complex concentrates; rFVIIa, recombinant factor VIIa; IVM, intravenous.

Data from reference 178.

Vitamin K is not recommended to be given subcutaneously because its effect is variable and delayed by this route. Anaphylaxis is rare, but it can occur with IV administration. It may take up to 24 hrs to achieve the full effect of vitamin K (179). The recommended doses of vitamin K are summarized in Table 8. Excessive dosing of vitamin K in patients who are not bleeding should be avoided, as it will prolong the time to reach a therapeutic international normalized ratio (INR) when vitamin K antagonists are reinitiated.

FFP contains various amounts of clotting factors, and small volumes (10 mL/kg) will lower supratherapeutic doses, and larger volumes (30–40 mL/kg) are needed to normalize INR values (180). Concerns with FFP include volume overload, time for thawing, and transfusion-related immune reactions, including acute lung injury and transference of viruses.

PCC is primarily factor IX with smaller amounts of factors II, VII, and X (although some products do not contain factor VII). In addition, some contain protein C and/or S. PCC is about 25 times more concentrated than FFP, so the volume is substantially less (180). Furthermore, the time to administer PCC is markedly lower than FFP, which can be advantageous in select critically ill populations, such as those with traumatic brain injury (98). The optimal dose of PCC is not well established, but several dosing strategies exist. These can be classified as either a fixed (25–50 μg/kg) or an individualized (based on INR values and desired level of correction) dosing strategy.

There have been several small reports in the literature utilizing rFVIIa for reversing the INR of vitamin K antagonists, as well as treatment of severe bleeding. Similar to PCC, rFVIIa has the advantage of lower administration volumes and

shorter time to INR normalization when compared with FFP (181). Doses in reports have varied widely, but given the high expense of the product, it is prudent to use the lowest effective dose. In a report in 16 patients, Dager et al (182) found that 16 μg/kg effectively reversed the INR in 16 patients with bleeding on warfarin and achieved a desirable hemostatic effect in 14 patients. Thrombotic events are possible with both PCC and rFVIIa.

Thrombolytic agents

Thrombolytic agents convert plasminogen to plasmin, which then degrades fibrin, eventually breaking down fibrin clots. However, they also can break down circulating fibrinogen, factor V, factor VIII, and other proteins, and cause platelet dysfunction that can lead to bleeding complications. Treatments of thrombolytic-induced bleeding are outlined by Sane et al (183) and involve replacement of fibrinogen, clotting factors, and platelets. Cryoprecipitate is the best source of fibrinogen and may be given to maintain a fibrinogen level of >1 g/L, followed by FFP, if needed for additional replacement of clotting factors. If bleeding time is >9, platelet transfusions may also be considered. EACA and tranexamic acid are antifibrinolytic drugs that work by inhibiting the binding of plasmin to active sites, and may be considered if bleeding continues, despite cryoprecipitate and FFP. However, these may cause thrombotic complications, including reocclusion of the artery for which the thrombolytic was being administered. When intracerebral hemorrhage occurs after thrombolytics, the American Stroke Association Guidelines (79) recommended infusion of platelets (6–8 units) and cryoprecipitate to rapidly correct the thrombolytic state. Guidelines for surgical treatment of thrombolytic-induced intracerebral hemorrhage are the same as those followed for spontaneous intracerebral hemorrhage but should be initiated after a sufficient infusion of platelets and cryoprecipitate has stabilized the bleeding.

Conclusion

In conclusion, ADEs related to disorders of coagulation remain a serious concern among ICU practitioners. Clinicians must carefully evaluate both the expected occurrence of an ADE along with the potential consequences that could arise with their occurrence. Risk/benefit ratios, therefore, will likely vary for a particular therapy and must be considered on a case-by-case basis. Although agents do exist for the treatment of coagulation-related ADEs (e.g., reversal of anticoagulation in the setting of bleeding), the risk for overcorrection does exist, which could lead to further complications. Further randomized clinical trials are welcomed in this area.

References

1. Bates DW, Cullen DJ, Laird N, et al: Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274:29–34
2. Cullen DJ, Sweitzer BJ, Bates DW, et al: Preventable adverse drug events in hospitalized patients: A comparative study of intensive care and general care units. *Crit Care Med* 1997; 25:1289–1297
3. Kopp BJ, Erstad BL, Allen ME, et al: Medication errors and adverse drug events in an intensive care unit: Direct observation approach for detection. *Crit Care Med* 2006; 34:415–425
4. Leape LL, Brennan TA, Laird N, et al: The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324:377–384
5. Shojania KG, Duncan BW, McDonald KM, et al: Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology Assessment, No. 43. July 2001. Rockville, MD. Agency for Healthcare Research and Quality. Available at http://www.ahrq.gov/clinic/ptsafety. Accessed September 10, 2009
6. Cohn SL: Prophylaxis of venous thromboembolism in the US: Improving hospital performance. *J Thromb Haemost* 2009; 7:1437–1445
7. Cook DJ, Crowther MA, Douketis J, et al: Research agenda: venous thromboembolism in medical-surgical critically ill patients. *J Crit Care* 2005; 20:330–333
8. Geerts WH, Bergqvist D, Pineo GF, et al: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl): 381S–453S
9. Ribic C, Lim W, Cook D, et al: Low-molecular-weight heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review. *J Crit Care* 2009; 24:197–205
10. Fraisse F, Holzapfel L, Couland JM, et al: Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med* 2000; 161:1109–1114
11. Arnold DM, Donahoe L, Clarke FJ, et al: Bleeding during critical illness: A prospective cohort study using a new measurement tool. *Clin Invest Med* 2007; 30:E93–E102
12. Wein L, Wein S, Haas SJ, et al: Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: A meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167:1476–1486
13. Leonardi MJ, McGory ML, Ko CY: The rate of bleeding complications after pharmacologic deep venous thrombosis prophylaxis: A systematic review of 33 randomized controlled trials. *Arch Surg* 2006; 141:790–797; discussion, 797–799
14. Cook DJ, Rocker G, Meade M, et al: Prophylaxis of Thromboembolism in Critical Care (PROTECT) Trial: A pilot study. *J Crit Care* 2005; 20:364–372
15. King CS, Holley AB, Jackson JL, et al: Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis. *Chest* 2007; 131:507–516
16. Nutescu EA, Spinler SA, Wittkowsky A, et al: Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother* 2009; 43:1064–1083
17. Cohn SM, Moller BA, Feinstein AJ, et al: Prospective trial of low-molecular-weight heparin versus unfractionated heparin in moderately injured patients. *Vasc Surg* 1999; 33:219–223
18. Cothren CC, Smith WR, Moore EE, et al: Utility of once-daily dose of low-molecular-weight heparin to prevent venous thromboembolism in multisystem trauma patients. *World J Surg* 2007; 31:98–104
19. Dennis JW, Menawat S, Von Thron J, et al: Efficacy of deep venous thrombosis prophylaxis in trauma patients and identification of high-risk groups. *J Trauma* 1993; 35: 132–138; discussion, 138–139
20. Geerts WH, Jay RM, Code KI, et al: A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; 335: 701–707
21. Ginzburg E, Cohn SM, Lopez J, et al: Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg* 2003; 90:1338–1344
22. Haentjens P: Thromboembolic prophylaxis in orthopaedic trauma patients: A comparison between a fixed dose and an individually adjusted dose of a low molecular weight heparin (nadroparin calcium). *Injury* 1996; 27:385–390
23. Knudson MM, Collins JA, Goodman SB, et al: Thromboembolism following multiple trauma. *J Trauma* 1992; 32:2–11
24. Knudson MM, Morabito D, Paiement GD, et

al: Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *J Trauma* 1996; 41:446–459
25. Norwood SH, McAuley CE, Berne JD, et al: A potentially expanded role for enoxaparin in preventing venous thromboembolism in high risk blunt trauma patients. *J Am Coll Surg* 2001; 192:161–167
26. Shackford SR, Davis JW, Hollingsworth-Fridlund P, et al: Venous thromboembolism in patients with major trauma. *Am J Surg* 1990; 159:365–369
27. Stannard JP, Lopez-Ben RR, Volgas DA, et al: Prophylaxis against deep-vein thrombosis following trauma: A prospective, randomized comparison of mechanical and pharmacologic prophylaxis. *J Bone Joint Surg Am* 2006; 88:261–266
28. Scales DC, Riva-Cambrin J, Le TL, et al: Prophylaxis against venous thromboembolism in neurointensive care patients: Survey of Canadian practice. *J Crit Care* 2009; 24: 176–184
29. Collen JF, Jackson JL, Shorr AF, et al: Prevention of venous thromboembolism in neurosurgery: A metaanalysis. *Chest* 2008; 134:237–249
30. Raabe A, Gerlach R, Zimmermann M, et al: The risk of haemorrhage associated with early postoperative heparin administration after intracranial surgery. *Acta Neurochir (Wien)* 2001; 143:1–7
31. Kim J, Gearhart MM, Zurick A, et al: Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma* 2002; 53: 38–42; discussion, 43
32. Kim KS, Brophy GM: Symptomatic venous thromboembolism: Incidence and risk factors in patients with spontaneous or traumatic intracranial hemorrhage. *Neurocrit Care* 2009; 11:28–33
33. Kleindienst A, Harvey HB, Mater E, et al: Early antithrombotic prophylaxis with low molecular weight heparin in neurosurgery. *Acta Neurochir (Wien)* 2003; 145: 1085–1090; discussion, 1090–1081
34. Kurtoglu M, Yanar H, Bilsel Y, et al: Venous thromboembolism prophylaxis after head and spinal trauma: Intermittent pneumatic compression devices versus low molecular weight heparin. *World J Surg* 2004; 28: 807–811
35. Norwood SH, McAuley CE, Berne JD, et al: Prospective evaluation of the safety of enoxaparin prophylaxis for venous thromboembolism in patients with intracranial hemorrhagic injuries. *Arch Surg* 2002; 137: 696–701; discussion, 701–702
36. Bates SM, Ginsberg JS: Clinical practice. Treatment of deep-vein thrombosis. *N Engl J Med* 2004; 351:268–277
37. Pastores SM: Management of venous thromboembolism in the intensive care unit. *J Crit Care* 2009; 24:185–191
38. Schulman S, Beyth RJ, Kearon C, et al: Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):257S–298S
39. Hirsh J, Bauer KA, Donati MB, et al: Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):141S–159S
40. Anand SS, Yusuf S, Pogue J, et al: Relationship of activated partial thromboplastin time to coronary events and bleeding in patients with acute coronary syndromes who receive heparin. *Circulation* 2003; 107: 2884–2888
41. van Dongen CJ, van den Belt AG, Prins MH, et al: Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2004; 4:CD001100
42. Di Nisio M, Middeldorp S, Buller HR: Direct thrombin inhibitors. *N Engl J Med* 2005; 353:1028–1040
43. Lubenow N, Eichler P, Lietz T, et al: Lepirudin in patients with heparin-induced thrombocytopenia—Results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005; 3:2428–2436
44. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: A randomised trial. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. *Lancet* 1999; 353: 429–438
45. Selleng K, Warkentin TE, Greinacher A: Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med* 2007; 35: 1165–1176
46. Warkentin TE, Greinacher A, Koster A, et al: Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):340S–380S
47. Hursting MJ, Soffer J: Reducing harm associated with anticoagulation: practical considerations of argatroban therapy in heparin-induced thrombocytopenia. *Drug Saf* 2009; 32:203–218
48. Lewis BE, Wallis DE, Hursting MJ, et al: Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 2006; 129:1407–1416
49. Keegan SP, Gallagher EM, Ernst NE, et al: Effects of critical illness and organ failure on therapeutic argatroban dosage requirements in patients with suspected or confirmed heparin-induced thrombocytopenia. *Ann Pharmacother* 2009; 43:19–27
50. Kiser TH, Jung R, MacLaren R, et al: Evaluation of diagnostic tests and argatroban or lepirudin therapy in patients with suspected heparin-induced thrombocytopenia. *Pharmacotherapy* 2005; 25:1736–1745
51. Smythe MA, Koerber JM, Forsyth LL, et al: Argatroban dosage requirements and outcomes in intensive care versus non-intensive care patients. *Pharmacotherapy* 2009; 29:1073–1081
52. Buller HR, Davidson BL, Decousus H, et al: Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; 140:867–873
53. Buller HR, Davidson BL, Decousus H, et al: Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; 349:1695–1702
54. Mehta SR, Boden WE, Eikelboom JW, et al: Antithrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: An individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 and 6) randomized trials. *Circulation* 2008; 118: 2038–2046
55. Gore JM, Granger CB, Simoons ML, et al: Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global use of strategies to open occluded coronary arteries. *Circulation* 1995; 92: 2811–2818
56. Kearon C, Kahn SR, Agnelli G, et al: Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):454S–545S
57. ECC Committee S, Task Forces of the American Heart Association: 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005; 112(24 Suppl):IV1–IV203
58. Adams HP Jr, del Zoppo G, Alberts MJ, et al: Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/ American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007; 38:1655–1711
59. Albers GW, Amarenco P, Easton JD, et al: Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):630S–669S
60. Goodman SG, Menon V, Cannon CP, et al: Acute ST-segment elevation myocardial in-

farction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):708S–775S
61. Wan S, Quinlan DJ, Agnelli G, et al: Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: A meta-analysis of the randomized controlled trials. *Circulation* 2004; 110:744–749
62. Goldhaber SZ, Visani L, De Rosa M: Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353:1386–1389
63. Fengler BT, Brady WJ: Fibrinolytic therapy in pulmonary embolism: An evidence-based treatment algorithm. *Am J Emerg Med* 2009; 27:84–95
64. Todd JL, Tapson VF: Thrombolytic therapy for acute pulmonary embolism: A critical appraisal. *Chest* 2009; 135:1321–1329
65. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
66. Levi M, Levy M, Williams MD, et al: Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). *Am J Respir Crit Care Med* 2007; 176: 483–490
67. Gentry CA, Gross KB, Sud B, et al: Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precautions. *Crit Care Med* 2009; 37:19–25
68. Bertolini G, Rossi C, Anghileri A, et al: Use of Drotrecogin alfa (activated) in Italian intensive care units: The results of a nationwide survey. *Intensive Care Med* 2007; 33: 426–434
69. Kanji S, Perreault MM, Chant C, et al: Evaluating the use of Drotrecogin alfa (activated) in adult severe sepsis: A Canadian multicenter observational study. *Intensive Care Med* 2007; 33:517–523
70. Wheeler A, Steingrub J, Schmidt GA, et al: A retrospective observational study of drotrecogin alfa (activated) in adults with severe sepsis: Comparison with a controlled clinical trial. *Crit Care Med* 2008; 36:14–23
71. Levi M, Jonge E: Clinical relevance of the effects of plasma expanders on coagulation. *Semin Thromb Hemost* 2007; 33(8): 810–815
72. Westphal M, James MF, Kozek-Langenecker S, et al: Hydroxyethyl starches: Different products—Different effects. *Anesthesiology* 2009; 111:187–202
73. Kozek-Langenecker SA, Jungheinrich C, Sauermann W, et al: The effects of hydroxyethyl starch 130/0.4 (6%) on blood loss and use of blood products in major surgery: A pooled analysis of randomized clinical trials. *Anesth Analg* 2008; 107:382–390
74. Weeks DL, Jahr JS, Lim JC, et al: Does Hextend impair coagulation compared to 6% hetastarch? An ex vivo thromboelastography study. *Am J Ther* 2008; 15:225–230
75. Dailey SE, Dysart CB, Langan DR, et al: An in vitro study comparing the effects of Hextend, Hespan, normal saline, and lactated Ringer's solution on thrombelastography and the activated partial thromboplastin time. *J Cardiothorac Vasc Anesth* 2005; 19: 358–361
76. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
77. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139
78. NovoNordisk. NovoSeven Package Insert. Princeton, NJ, 2008
79. Broderick J, Connolly S, Feldmann E, et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 2007; 38: 2001–2023
80. Hedner U: Factor VIIa and its potential therapeutic use in bleeding-associated pathologies. *Thromb Haemost* 2008; 100:557–562
81. O'Connell KA, Wood JJ, Wise RP, et al: Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; 295:293–298
82. Patanwala AE: Factor VIIa (recombinant) for acute traumatic hemorrhage. *Am J Health Syst Pharm* 2008; 65:1616–1623
83. Roberts HR, Monroe DM 3rd, Hoffman M: Safety profile of recombinant factor VIIa. *Semin Hematol* 2004; 41(1 Suppl 1): 101–108
84. Voils S: Pharmacologic interventions for the management of critical bleeding. *Pharmacotherapy* 2007; 27:69S–84S
85. Barletta JF, Ahrens CL, Tyburski JG, et al: A review of recombinant factor VII for refractory bleeding in nonhemophilic trauma patients. *J Trauma* 2005; 58:646–651
86. DiDomenico RJ, Massad MG, Kpodonu J, et al: Use of recombinant activated factor VII for bleeding following operations requiring cardiopulmonary bypass. *Chest* 2005; 127: 1828–1835
87. Thomas GO, Dutton RP, Hemlock B, et al: Thromboembolic complications associated with factor VIIa administration. *J Trauma* 2007; 62:564–569
88. Boffard KD, Riou B, Warren B, et al: Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: Two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 2005; 59:8 –15; discussion, 15–18
89. Mayer SA, Brun NC, Begtrup K, et al: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; 358:2127–2137
90. Mayer SA, Brun NC, Begtrup K, et al: Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; 352:777–785
91. Mayer SA, Brun NC, Broderick J, et al: Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 2005; 36:74–79
92. Mayer SA, Brun NC, Broderick J, et al: Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocrit Care* 2006; 4:206–214
93. Aledort LM: Factor IX and thrombosis. *Scand J Haematol Suppl* 1977; 30:40–42
94. Kohler M: Thrombogenicity of prothrombin complex concentrates. *Thromb Res* 1999; 95(4 Suppl 1):S13–S17
95. Pindur G, Morsdorf S: The use of prothrombin complex concentrates in the treatment of hemorrhages induced by oral anticoagulation. *Thromb Res* 1999; 95(4 Suppl 1):S57–S61
96. Bershad EM, Suarez JI: Prothrombin complex concentrates for oral anticoagulant therapy-related intracranial hemorrhage: A review of the literature. *Neurocrit Care* 2009 Dec 5 [Epub ahead of print]
97. Leissinger CA, Blatt PM, Hoots WK, et al: Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature. *Am J Hematol* 2008; 83:137–143
98. Levy JH, Tanaka KA, Dietrich W: Perioperative hemostatic management of patients treated with vitamin K antagonists. *Anesthesiology* 2008; 109:918–926
99. Mannucci PM, Levi M: Prevention and treatment of major blood loss. *N Engl J Med* 2007; 356:2301–2311
100. Perkins JG, Cap AP, Weiss BM, et al: Massive transfusion and nonsurgical hemostatic agents. *Crit Care Med* 2008; 36(7 Suppl):S325–S339
101. Porte RJ, Leebeek FW: Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. *Drugs* 2002; 62:2193–2211
102. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, et al: Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007; 83(5 Suppl):S27–S86
103. Tinmouth AT, McIntyre LA, Fowler RA: Blood conservation strategies to reduce the need for red blood cell transfusion in critically ill patients. *CMAJ* 2008; 178:49–57
104. Brown JR, Birkmeyer NJ, O'Connor GT: Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; 115:2801–2813
105. Fergusson DA, Hebert PC, Mazer CD, et al: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; 358:2319–2331

106. Greilich PE, Jessen ME, Satyanarayana N, et al: The effect of epsilon-aminocaproic acid and aprotinin on fibrinolysis and blood loss in patients undergoing primary, isolated coronary artery bypass surgery: A randomized, double-blind, placebo-controlled, noninferiority trial. *Anesth Analg* 2009; 109:15–24
107. Henry D, Carless P, Fergusson D, et al: The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: A meta-analysis. *CMAJ* 2009; 180:183–193
108. Mangano DT, Miao Y, Vuylsteke A, et al: Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007; 297:471–479
109. McIlroy DR, Myles PS, Phillips LE, et al: Antifibrinolytics in cardiac surgical patients receiving aspirin: A systematic review and meta-analysis. *Br J Anaesth* 2009; 102:168–178
110. Benoni G, Fredin H, Knebel R, et al: Blood conservation with tranexamic acid in total hip arthroplasty: A randomized, double-blind study in 40 primary operations. *Acta Orthop Scand* 2001; 72:442–448
111. Coats T, Roberts I, Shakur H: Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev* 2004; 4:CD004896
112. Dalmau A, Sabate A, Acosta F, et al: Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg* 2000; 91:29–34
113. Ekback G, Axelsson K, Ryttberg L, et al: Tranexamic acid reduces blood loss in total hip replacement surgery. *Anesth Analg* 2000; 91:1124–1130
114. Hiippala ST, Strid LJ, Wennerstrand MI, et al: Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg* 1997; 84:839–844
115. Jansen AJ, Andreica S, Claeys M, et al: Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. *Br J Anaesth* 1999; 83:596–601
116. Kang Y, Lewis JH, Navalgund A, et al: Epsilon-aminocaproic acid for treatment of fibrinolysis during liver transplantation. *Anesthesiology* 1987; 66:766–773
117. Kaspar M, Ramsay MA, Nguyen AT, et al: Continuous small-dose tranexamic acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. *Anesth Analg* 1997; 85:281–285
118. McMichan JC, Rosengarten DS, Philipp E: Prophylaxis of post-traumatic pulmonary insufficiency by protease-inhibitor therapy with aprotinin: A clinical study. *Circ Shock* 1982; 9:107–116
119. Miller RA, May MW, Hendry WF, et al: The prevention of secondary haemorrhage after prostatectomy: The value of antifibrinolytic therapy. *Br J Urol* 1980; 52:26–28
120. Mutter WP, Stillman IE, Dahl NK: Thrombotic microangiopathy and renal failure exacerbated by epsilon-aminocaproic acid. *Am J Kidney Dis* 2009; 53:346–350
121. Piriyawat P, Morgenstern LB, Yawn DH, et al: Treatment of acute intracerebral hemorrhage with epsilon-aminocaproic acid: A pilot study. *Neurocrit Care* 2004; 1:47–51
122. Tanaka N, Sakahashi H, Sato E, et al: Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. *J Bone Joint Surg Br* 2001; 83:702–705
123. Veien M, Sorensen JV, Madsen F, et al: Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: A randomized, controlled study. *Acta Anaesthesiol Scand* 2002; 46:1206–1211
124. Clinical randomisation of an antifibrinolytic in significant haemorrhage. Available at : http://www.crash2.lshtm.ac.uk/MainFrame.htm. Accessed October 1, 2009
125. Sanofi-Aventis. DDAVP Package Insert. Bridgewater, NJ, 2007
126. Couch P, Stumpf JL: Management of uremic bleeding. *Clin Pharm* 1990; 9:673–681
127. Gralnick HR, McKeown LP, Williams SB, et al: Plasma and platelet von Willebrand factor defects in uremia. *Am J Med* 1988; 85:806–810
128. Donoghue MB, Latimer ME, Pillsbury HL, et al: Hyponatremic seizure in a child using desmopressin for nocturnal enuresis. *Arch Pediatr Adolesc Med* 1998; 152:290–292
129. Bond L, Bevan D: Myocardial infarction in a patient with hemophilia treated with DDAVP. *N Engl J Med* 1988; 318:121
130. Byrnes JJ, Larcada A, Moake JL: Thrombosis following desmopressin for uremic bleeding. *Am J Hematol* 1988; 28:63–65
131. Levi M, Cromheecke ME, de Jonge E, et al: Pharmacological strategies to decrease excessive blood loss in cardiac surgery: A meta-analysis of clinically relevant endpoints. *Lancet* 1999; 354:1940–1947
132. Mannucci PM, Carlsson S, Harris AS: Desmopressin, surgery and thrombosis. *Thromb Haemost* 1994; 71:154–155
133. McLeod BC: Myocardial infarction in a blood donor after administration of desmopressin. *Lancet* 1990; 336:1137–1138
134. O'Brien JR, Green PJ, Salmon G, et al: Desmopressin and myocardial infarction. *Lancet* 1989; 333:664–665
135. Crescenzi G, Landoni G, Biondi-Zoccai G, et al: Desmopressin reduces transfusion needs after surgery: A meta-analysis of randomized clinical trials. *Anesthesiology* 2008; 109:1063–1076
136. Liu YK, Kosfeld RE, Marcum SG: Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 1984; 2:887–890
137. Boyd GL, Diethelm AG, Gelman S, et al: Correcting prolonged bleeding during renal transplantation with estrogen or plasma. *Arch Surg* 1996; 131:160–165
138. Bronner MH, Pate MB, Cunningham JT, et al: Estrogen-progesterone therapy for bleeding gastrointestinal telangiectasias in chronic renal failure. An uncontrolled trial. *Ann Intern Med* 1986; 105:371–374
139. Frenette L, Cox J, McArdle P, et al: Conjugated estrogen reduces transfusion and coagulation factor requirements in orthotopic liver transplantation. *Anesth Analg* 1998; 86:1183–1186
140. Heunisch C, Resnick DJ, Vitello JM, et al: Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998; 18:210–217
141. Livio M, Mannucci PM, Vigano G, et al: Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986; 315:731–735
142. McCall RE, Bilderback KK: Use of intravenous Premarin to decrease postoperative blood loss after pediatric scoliosis surgery. *Spine (Phila Pa 1976)* 1997; 22:1394–1397
143. Shemin D, Elnour M, Amarantes B, et al: Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med* 1990; 89:436–440
144. Hull RW, Hasbargen JA, Fall S, et al: Conjugated estrogens reduce endothelial prostacyclin production and fail to reduce postbypass blood loss. *Chest* 1991; 99:1116–1119
145. Ambrus JL, Schimert G, Lajos TZ, et al: Effect of antifibrinolytic agents and estrogens on blood loss and blood coagulation factors during open heart surgery. *J Med* 1971; 2:65–81
146. Boucher BA, Traub O: Achieving hemostasis in the surgical field. *Pharmacotherapy* 2009; 29:2S–7S
147. Kessler CM, Ortel TL: Recent developments in topical thrombins. *Thromb Haemost* 2009; 102:15–24
148. Lomax C, Traub O: Topical thrombins: Benefits and risks. *Pharmacotherapy* 2009; 29:8S–12S
149. Ofosu FA, Crean S, Reynolds MW: A safety review of topical bovine thrombin-induced generation of antibodies to bovine proteins. *Clin Ther* 2009; 31:679–691
150. Carroll JF, Moskowitz KA, Edwards NM, et al: Immunologic assessment of patients treated with bovine fibrin as a hemostatic agent. *Thromb Haemost* 1996; 76:925–931
151. Chapman WC, Singla N, Genyk Y, et al: A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis. *J Am Coll Surg* 2007; 205:256–265
152. Doria C, Fischer CP, Wood CG, et al: Phase 3, randomized, double-blind study of plasma-derived human thrombin versus bovine thrombin in achieving hemostasis in patients undergoing surgery. *Curr Med Res Opin* 2008; 24:785–794
153. Nelson PA, Powers JN, Estridge TD, et al: Serological analysis of patients treated with a new surgical hemostat containing bovine proteins and autologous plasma. *J Biomed Mater Res* 2001; 58:710–719

154. Ortel TL, Mercer MC, Thames EH, et al: Immunologic impact and clinical outcomes after surgical exposure to bovine thrombin. *Ann Surg* 2001; 233:88–96
155. Dorion RP, Hamati HF, Landis B, et al: Risk and clinical significance of developing antibodies induced by topical thrombin preparations. *Arch Pathol Lab Med* 1998; 122: 887–894
156. Streiff MB, Ness PM: Acquired FV inhibitors: A needless iatrogenic complication of bovine thrombin exposure. *Transfusion* 2002; 42:18–26
157. Chouhan VD, De La Cadena RA, Nagaswami C, et al: Simultaneous occurrence of human antibodies directed against fibrinogen, thrombin, and factor V following exposure to bovine thrombin: Effects on blood coagulation, protein C activation and platelet function. *Thromb Haemost* 1997; 77:343–349
158. Christie RJ, Carrington L, Alving B: Postoperative bleeding induced by topical bovine thrombin: Report of two cases. *Surgery* 1997; 121:708–710
159. Ethicon Inc. Evithrom Package Insert. Somerville, NJ, 2007
160. Ortel TL, Charles LA, Keller FG, et al: Topical thrombin and acquired coagulation factor inhibitors: Clinical spectrum and laboratory diagnosis. *Am J Hematol* 1994; 45:128–135
161. Rapaport SI, Zivelin A, Minow RA, et al: Clinical significance of antibodies to bovine and human thrombin and factor V after surgical use of bovine thrombin. *Am J Clin Pathol* 1992; 97:84–91
162. Zehnder JL, Leung LL: Development of antibodies to thrombin and factor V with recurrent bleeding in a patient exposed to topical bovine thrombin. *Blood* 1990; 76:2011–2016
163. Zymo Genetics. Recothrom Package Insert. Seattle, WA, 2009
164. Singla NK, Ballard JL, Moneta G, et al: A phase 3b, open-label, single-group immunogenicity and safety study of topical re combinant thrombin in surgical hemostasis. *J Am Coll Surg* 2009; 209:68–74
165. Bennett CL, Silver SM, Djulbegovic B, et al: Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA* 2008; 299:914–924
166. Phrommintikul A, Haas SJ, Elsik M, et al: Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: A meta-analysis. *Lancet* 2007; 369:381–388
167. Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients: A randomized controlled trial. *JAMA* 2002; 288:2827–2835
168. Corwin HL, Gettinger A, Rodriguez RM, et al: Efficacy of recombinant human erythropoietin in the critically ill patient: A randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999; 27:2346–2350
169. Corwin HL, Gettinger A, Fabian TC, et al: Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007; 357:965–976
170. Corwin HL: Erythropoietin use in critically ill patients: Forest and trees. *CMAJ* 2007; 177:747–749
171. Tobu M, Iqbal O, Fareed D, et al: Erythropoietin-induced thrombosis as a result of increased inflammation and thrombin activatable fibrinolytic inhibitor. *Clin Appl Thromb Hemost* 2004; 10:225–232
172. Fuste B, Serradell M, Escolar G, et al: Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. *Thromb Haemost* 2002; 88:678–685
173. Crowther MA, Berry LR, Monagle PT, et al: Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. *Br J Haematol* 2002; 116:178–186
174. Young G, Yonekawa KE, Nakagawa PA, et al: Recombinant activated factor VII effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin ex vivo as measured using thromboelastography. *Blood Coagul Fibrinolysis* 2007; 18:547–553
175. Bijsterveld NR, Moons AH, Boekholdt SM, et al: Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; 106:2550–2554
176. Sharathkumar AA, Crandall C, Lin JJ, et al: Treatment of thrombosis with fondaparinux (Arixtra) in a patient with end-stage renal disease receiving hemodialysis therapy. *J Pediatr Hematol Oncol* 2007; 29:581–584
177. Sorensen B, Ingerslev J: A direct thrombin inhibitor studied by dynamic whole blood clot formation. Haemostatic response to ex vivo addition of recombinant factor VIIa or activated prothrombin complex concentrate. *Thromb Haemost* 2006; 96:446–453
178. Ansell J, Hirsh J, Hylek E, et al: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6Suppl):160S–198S
179. Schulman S, Bijsterveld NR: Anticoagulants and their reversal. *Transfus Med Rev* 2007; 21:37–48
180. MacLaren R: Key concepts in the management of difficult hemorrhagic cases. *Pharmacotherapy* 2007; 27:93S–102S
181. Stein DM, Dutton RP, Kramer ME, et al: Recombinant factor VIIa: Decreasing time to intervention in coagulopathic patients with severe traumatic brain injury. *J Trauma* 2008; 64:620–627; discussion, 627–628
182. Dager WE, King JH, Regalia RC, et al: Reversal of elevated international normalized ratios and bleeding with low-dose recombinant activated factor VII in patients receiving warfarin. *Pharmacotherapy* 2006; 26:1091–1098
183. Sane DC, Califf RM, Topol EJ, et al: Bleeding during thrombolytic therapy for acute myocardial infarction: Mechanisms and management. *Ann Intern Med* 1989; 111:1010–1022
184. Rabbat CG, Cook DJ, Crowther MA, et al: Dalteparin thromboprophylaxis for critically ill medical-surgical patients with renal insufficiency. *J Crit Care* 2005; 20:357–363
185. Douketis J, Cook D, Meade M, et al: Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: An assessment of safety and pharmacodynamics: The DIRECT study. *Arch Intern Med* 2008; 168:1805–1812
186. Agnelli G, Piovella F, Buoncristiani P, et al: Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med* 1998; 339:80–85
187. Cage TA, Lamborn KR, Ware ML, et al: Adjuvant enoxaparin therapy may decrease the incidence of postoperative thrombotic events though does not increase the incidence of postoperative intracranial hemorrhage in patients with meningiomas. *J Neurooncol* 2009; 93:151–156
188. Cerrato D, Ariano C, Fiacchino F: Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. *J Neurosurg* 1978; 49:378–381
189. Constantini S, Kanner A, Friedman A, et al: Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: A prospective, randomized, double-blind study. *J Neurosurg* 2001; 94:918–921
190. Dickinson LD, Miller LD, Patel CP, et al: Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* 1998; 43:1074–1081
191. Frim DM, Barker FG 2nd, Poletti CE, et al: Postoperative low-dose heparin decreases thromboembolic complications in neurosurgical patients. *Neurosurgery* 1992; 30: 830–832; discussion, 832–833
192. Gerlach R, Scheuer T, Beck J, et al: Risk of postoperative hemorrhage after intracranial surgery after early nadroparin administration: Results of a prospective study. *Neurosurgery* 2003; 53:1028–1034; discussion, 1034–1035
193. Goldhaber SZ, Dunn K, Gerhard-Herman M, et al: Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest* 2002; 122:1933–1937
194. Macdonald RL, Amidei C, Baron J, et al: Randomized, pilot study of intermittent

pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. *Surg Neurol* 2003; 59:363–372; discussion, 372–364
195. Macdonald RL, Amidei C, Lin G, et al: Safety of perioperative subcutaneous heparin for prophylaxis of venous thromboembolism in patients undergoing craniotomy. *Neurosurgery* 1999; 45:245–251; discussion, 251–242
196. Nurmohamed MT, van Riel AM, Henkens CM, et al: Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thromb Haemost* 1996; 75:233–238
197. Wen DY, Hall WA: Complications of subcutaneous low-dose heparin therapy in nonsurgical patients. *Surg Neurol* 1998; 50:521–525
198. The Urokinase Pulmonary Embolism Trial. A national cooperative study. *Circulation* 1973; 47(2 Suppl):II1–II108
199. Tissue plasminogen activator for the treatment of acute pulmonary embolism. A collaborative study by the PIOPED Investigators. *Chest* 1990; 97:528–533
200. Dalla-Volta S, Palla A, Santolicandro A, et al: PAIMS 2: Alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. *J Am Coll Cardiol* 1992; 20:520–526
201. Dotter CT, Seamon AJ, Rosch J, et al: Streptokinase and heparin in the treatment of pulmonary embolism: A randomized comparison. *Vasc Surg* 1979; 13:42–52
202. Goldhaber SZ, Haire WD, Feldstein ML, et al: Alteplase versus heparin in acute pulmonary embolism: Randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet* 1993; 341:507–511
203. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al: Streptokinase and heparin versus heparin alone in massive pulmonary embolism: A randomized controlled trial. *J Thromb Thrombolysis* 1995; 2:227–229
204. Konstantinides S, Geibel A, Heusel G, et al: Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002; 347:1143–1150
205. Levine M, Hirsh J, Weitz J, et al: A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest* 1990; 98:1473–1479
206. Ly B, Arnesen H, Eie H, et al: A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. *Acta Med Scand* 1978; 203:465–470
207. Marini C, DiRicco G, Rossi G, et al: Fibrinolytic effects of urokinase and heparin in acute pulmonary embolism: A randomized clinical trial. *Respiration* 1988; 54:162–173
208. Tibbutt DA, Davies JA, Anderson JA, et al: Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonay embolism. *Br Med J* 1974; 1:343–347
209. Abraham E, Laterre PF, Garg R, et al: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; 353:1332–1341
210. Vincent JL, Bernard GR, Beale R, et al: Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; 33:2266–2277
211. Alten JA, Benner K, Green K, et al: Pediatric off-label use of recombinant factor VIIa. *Pediatrics* 2009; 123:1066–1072
212. Diprose P, Herbertson MJ, O'Shaughnessy D, et al: Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: Randomized double-blind placebo-controlled pilot study. *Br J Anaesth* 2005; 95:596–602
213. Lodge JP, Jonas S, Oussoultzoglou E, et al: Recombinant coagulation factor VIIa in major liver resection: A randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology* 2005; 102:269–275
214. Raobaikady R, Redman J, Ball JA, et al: Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis or pelvis and acetabulum: A double-blind, randomized, placebo-controlled trial. *Br J Anaesth* 2005; 94:586–591
215. Shao YF, Yang JM, Chau GY, et al: Safety and hemostatic effect of recombinant activated factor VII in cirrhotic patients undergoing partial hepatectomy: A multicenter, randomized, double-blind, placebo-controlled trial. *Am J Surg* 2006; 191:245–249.