

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

NON-VITAMIN K ORAL ANTICOAGULANT REVERSAL

SUMMARY

The advent of new oral anticoagulant agents (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) has required a re-evaluation of anticoagulant reversal. These agents utilize novel mechanisms of action that require less monitoring, have fewer food and drug interactions, and possess less inter-patient variability with regards to dosing. At present time, only dabigatran has an approved agent that is specifically indicated for reversal of its anticoagulant effects. The goal of this guideline is to provide recommendations for the emergent reversal of oral direct thrombin inhibitors and Factor Xa antagonists in patients experiencing acute emergent hemorrhage.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Patients that meet criteria for reversal of dabigatran (Pradaxa®), should receive idarucizumab (Praxbind®) as a one-time intravenous dose of 5 grams**
 - **Anti-Factor Xa levels may be used to determine the presence of Factor Xa inhibitors [rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Sayvaysa®)] and monitor effectiveness of reversal**
 - **aPTT levels may be used to determine the presence of dabigatran**
 - **Use of activated Prothrombin Complex Concentrate (aPCC) (such as FEIBA and KCentra) or activated Factor VII are not effective in the reversal of dabigatran-based therapeutic anticoagulation**
- **Level 3**
 - **General hemostatic measures should be utilized in patients with life-threatening hemorrhage due to oral anticoagulants**
 - **Criteria for reversal of dabigatran with idarucizumab include:**
 - **Patients with a known history of dabigatran use and an elevated aPTT AND**
 - **Patients with severe traumatic brain injury (TBI) or other life-threatening bleed or injury requiring emergent surgery**
 - **Due to the lack of supporting data, patients should not receive more than one dose of idarucizumab**
 - **aPCC, along with tranexamic acid, can be considered in patients known to be taking a Factor Xa-inhibitor (rivaroxaban, apixaban, edoxaban) with life-threatening bleeds**
 - **FEIBA NF 2000 units (~2 vials) IV piggyback over 15 minutes**
 - **Tranexamic acid 1 gram IV piggyback over 10 minutes**
 - **Hemodialysis may be an option for reducing dabigatran levels in non-life-threatening situations**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Alternatives to vitamin K antagonists have begun to emerge as options for patients with hypercoagulable states. The direct thrombin inhibitor (DTI) dabigatran etexilate is a prodrug which has gained FDA approval for the prevention of venous thromboembolism (VTE) after elective total knee or hip arthroplasty, stroke, or systemic embolism prevention in non-valvular atrial fibrillation (AF), treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE) following parenteral therapy, and for prophylaxis of recurrent DVT or PE in patients who have been previously treated (1). Dabigatran acts by preventing thrombin-induced platelet aggregation with a peak activity occurring within 2 hours after dose administration and a terminal elimination half-life of 12-17 hours (1). Concentrations of dabigatran have been shown to be prolonged in patients experiencing renal dysfunction (2). As a DTI, it has the ability to prolong thrombin clotting time (TT), prothrombin time (PT), activated partial thromboplastin time (aPTT), and ecarin clotting time (ECT) (1). Monitoring of anticoagulant activity can be performed using PT and aPTT levels, however, the relation is nonlinear making plasma drug concentration for determination of therapeutic drug levels not feasible (1).

Oral Factor Xa inhibitors, including rivaroxaban, apixaban, and edoxaban, have also emerged as options for therapeutic anticoagulation. They require less monitoring and have fewer food and drug interactions than vitamin K antagonists. These agents selectively and competitively inhibit Factor Xa in a reversible fashion (1,3,4). Factor Xa inhibitors are FDA approved for the prevention of VTE after elective total knee or hip arthroplasty, prevention of stroke or systemic embolism in non-valvular atrial fibrillation, and treatment of DVT or PE (1,3-5). Maximum factor inhibition occurs between 1 and 4 hours post-medication administration with a terminal half-life observed between 7 and 17 hours (1).

Challenges with these agents include undefined monitoring parameters for detection of therapeutic drug levels and no antidotes being currently available for the reversal of the Factor Xa inhibitors. Correlations between Factor Xa activity, PT prolongation, or aPTT are linear in relation to plasma drug concentrations, however, variability in the reagents used for assays limits applicability to clinical practice (1).

Traumatic brain injury (TBI) is a significant source of morbidity and mortality. Annually, it accounts for nearly 1.4 million emergency department visits, 275,000 hospital admissions, and 52,000 deaths in the US alone. There is a bimodal distribution, with incidence most frequently affecting individuals over the age of 65, and under the age of 14 (6). Many elderly patients are on anticoagulation regimens such as warfarin, dabigatran, and apixaban for treatment and/or prevention of a wide spectrum of hypercoagulable disease states. It is well-established that use of anticoagulant medications can lead to excessive bleeding and poor outcomes in of elderly individuals with traumatic intracranial hemorrhage, particularly if anticoagulation cannot be reversed in a timely manner.

LITERATURE REVIEW

Monitoring

Dabigatran

Prothrombin time (PT) can be affected by dabigatran resulting in false elevations in point-of-care INR monitoring. However, there is inconsistency and insensitivity in the PT assays preventing their utility in drug monitoring (7-9). Thrombin time has shown significant sensitivity to the effects of dabigatran making it an effective assay for establishing the presence of dabigatran. Variability in thrombin time results, however, prevent this test from being effective for quantifying drug levels (9). aPTT has more sensitivity with less variability than PT in monitoring the effects of dabigatran. When drug concentrations reached >200 ng/mL, aPTT leveled off indicating that supratherapeutic drug concentrations may cause insensitivity of assays. Monitoring aPTT may be effective in the initial assessment of hemorrhagic patients on dabigatran (9).

Rivaroxaban, Apixaban

PT has been shown to be prolonged in a concentration-dependent, incremental manner with greater variation in PT occurring at higher drug concentrations. Conversion of PT to INR for monitoring creates a wider range of variability preventing standardization of treatment guidance. PT may allow for identification of patients who have rivaroxaban or apixaban present, but does not allow for accurate guidance of reversal effectiveness (10-12). In animal studies, rivaroxaban and apixaban had no effect on thrombin time and should not be used for monitoring. aPTT has been shown to have variable magnitude of alteration with

different reagents used. PT appears to be more sensitive for assessing medication effects and therefore is preferred over aPTT (11). Anti-Factor Xa levels have been shown to be accurate and precise in monitoring both rivaroxaban and apixaban in laboratory studies. They are more sensitive than PT, INR, and aPTT and are the preferred monitoring for the Factor Xa inhibitors (12-14).

Specific Reversal Agents (Antidotes)

Dabigatran

Idarucizumab is a monoclonal antibody fragment that binds specifically to dabigatran at a much higher affinity than thrombin, thus neutralizing the anticoagulant effects of dabigatran.

Glund and colleagues performed the initial Phase I trial of idarucizumab (15). The study utilized 47 volunteers, aged 18 to 45 years old, who were all given oral dabigatran 220 mg twice daily for 3 days with a final dose on day 4. Patients were assigned to one of four different dose treatment arms (1, 2, 4 or 5 g). Within each arm, patients were randomized to either the dose within their group or placebo. Post-treatment anticoagulant effect was assessed via diluted thrombin time (dTT), ecarin clotting time (ECT), thrombin time (TT), and activated partial thrombin time (aPTT). Idarucizumab doses of 2 g or more resulted in immediate and sustained reversal of ECT, aPTT and TT.

Pollack and colleagues performed a multicenter prospective Phase III trial using idarucizumab in the reversal of patients taking dabigatran who required urgent/emergent surgery or had life threatening hemorrhage (16). This trial studied 503 patients (301 had serious hemorrhage, 202 required urgent/emergent surgery). dTT and ECT were utilized to measure the degree of anticoagulant effect of dabigatran before and after the use of idarucizumab. Maximum percentage reversal of dTT or ECT within 4 hours of idarucizumab administration was the primary end point. Patients were given 5 g of idarucizumab divided into two 2.5 g IV infusions within a 15-minute period. The authors found that the idarucizumab reversed 100% of dabigatran anticoagulation within minutes of administration. >90% of patients had cessation of clinical bleeding with a median time of 1.6 hours after idarucizumab treatment.

In 2015, Pollack et al. performed RE-VERSE AD, a multicenter, prospective cohort study to evaluate the safety and efficacy of idarucizumab for the reversal of dabigatran in patients with serious bleeding or required urgent surgery (17). Group A patients had overt, uncontrolled bleeding or life-threatening bleeding. Group B patients required surgery that could not be delayed for at least 8 hours where normal hemostasis was necessary. Patients were treated with a single dose of idarucizumab 5 grams. Coagulation laboratory studies were performed (dTT and ECT) at baseline and numerous time points following administration. The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran with either laboratory test. The study included 90 total patients (51 patients in Group A and 39 in Group B). The median maximum percentage reversal of patients with either an elevated dTT or ECT at baseline was 100% with reversal seen on the sample obtained after first infusion. At 12 and 24 hours, the dTT was below the upper limit of normal in 90% of Group A patients and 81% of Group B patients. Cessation of bleeding was reported at a median of 11.4 hours in Group A while normal intraoperative hemostasis was reported in 92% of the patients in Group B. There were a total of five patients with thrombotic events (either DVT, PE, or both) reported.

The recommended dosing of idarucizumab is 5 g total, which is delivered in two 2.5 g (50mL) vials. These two vials can be either infused or injected with a syringe. The drug does not need to be renally dosed. Data does not support delivering a second 5 g dose of idarucizumab if clinical hemostasis is not achieved, and it is recommended that fully coagulation panels be drawn both prior to and after administration of the drug. There is no data available for use in pregnant or breastfeeding women, patients with hepatic impairment, or pediatric patients (18). There are no known significant drug interactions with idarucizumab. The average wholesale price of the packaged two 2.5g vials of drug is \$4200 (19).

Fresh Frozen Plasma (FFP) Reversal

Dabigatran

Various practice guidelines discuss the use of fresh frozen plasma (FFP) to help control bleeding in the presence of dabigatran, but state that it seems unlikely to influence drug effects (1). Case reports discuss the administration of FFP with some improvement in laboratory values; however, the effectiveness of correction of coagulopathy and decreasing bleeding rates remain suspect.

Warkentin et al. described a case of a 79 year old male taking dabigatran 150 mg daily with mild INR prolongation, increased aPTT, prolonged TCT, and normal fibrinogen experienced severe post-operative bleeding despite tranexamic acid, protamine, cryoprecipitate, and platelet transfusions (20). Additionally, a total of 22 units of FFP were administered which resulted in a decrease in patient aPTT, but did not alter his bleeding rate.

Dumkow reported the case of an 85 year old male experiencing a coagulopathic upper gastrointestinal bleed caused by dabigatran (21). For treatment of his coagulopathy on day 1, he received 6 units of FFP and 5 mg IV phytonadione with no success at lowering his INR or aPTT. He subsequently received 6 units of FFP and 2000 units of Factor IX complex. Thirty minutes after Factor IX was administered, the patient's INR and aPTT values had decreased slightly. The following day his INR had again increased so 4 units of FFP were infused with no improvement.

Rivaroxaban, Apixaban, Edoxaban

No published data exist to support the use of FFP for reversal during acute hemorrhage.

Factor VII

Dabigatran

In 2012, Marlu et al. published an in-vitro crossover study measuring the anticoagulation reversal activity of 4-factor PCC, aPCC (FEIBA®), and rFVIIa at different doses in 10 healthy male volunteers receiving dabigatran and rivaroxaban (22). Thrombin generation tests were used to measure the reversal activity and included the endogenous thrombin potential (ETP-AUC), maximum concentration of thrombin (peak), lag time (LT), and time to reach the maximum concentration of thrombin (time to peak, TTP). rFVIIa had no effect on ETP-AUC or thrombin peak; however, the highest dose of rFVIIa (120 mcg/kg) reduced the LT.

In Warkentin's case report of a 79 year old male taking dabigatran 150 mg daily (see above), three doses of rFVIIa were administered at 2.4 mg/dose which did not control the patient's bleeding (20). Two additional doses of 7.2 mg/dose were administered and the bleeding rate decreased from 1500 mL/hr to 800 mL/hr.

Rivaroxaban, Apixaban, Edoxaban

In Marlu et al. (see study in *Dabigatran* for design), rFVIIa had no effect on ETP-AUC; however rFVIIa did correct the LT to near baseline level ($p=0.6$). rFVIIa also significantly decreased TTP by 44% (22).

Prothrombin Complex Concentrates

PCC are derived from human plasma and contain the vitamin K-dependent coagulation Factors II, VII, IX, and X at varying concentrations. PCC is commonly used for vitamin K antagonist reversal and there have been trials using this therapy for reversal of non-vitamin K antagonist agents as well. Although many countries have successfully utilized these products for years, the use of PCC in the United States is still not widespread, especially in the trauma population. The non-activated PCC products available in the US contain negligible amounts of Factor VII which is the key clotting factor in trauma. These two products, Bebulin® and Profilnine®, are referred to as 3-factor products. In addition to the non-activated 3-factor PCC products there is also an activated PCC preparation, Factor VIII inhibitor bypassing activity (FEIBA NF). The actual percentage of each factor present in FEIBA is unknown, however it contains Factors II, IX, and X in addition to activated Factor VII.

Dabigatran

In 2011, Eerenberg et al published a randomized, prospective, placebo-controlled, crossover study of 12 healthy, male volunteers examining the effect of 4-factor PCC (containing factors II, VII, IX, and X) on patients treated with dabigatran and rivaroxaban (23). Patients received 2.5 days of either dabigatran or rivaroxaban followed by either PCC at a dose of 50 units PCC/kg or similar volume of saline. After an 11 day washout period, subjects received the other anticoagulant following the same protocol. Dabigatran efficacy was measured using aPTT, endogenous thrombin potential lag time (ETP lag time), thrombin time (TT), and ECT. The aPTT was increased from 33.6 ± 3.3 to 59.4 ± 15.8 seconds after drug administration. PCC administration had no effect on aPTT prolongation (70.3 ± 15.1 seconds; $p=0.21$). Similarly, ETP lag time was prolonged from 2.9 ± 0.4 to 7.5 ± 2.5 minutes and remained unchanged after PCC (8.7 ± 2.6 minutes; $p=0.2$). TT was >120 seconds at baseline and remained immeasurably high after PCC ($p=0.36$). ECT was prolonged from 33 ± 1 seconds to 69 ± 26 seconds and increased after PCC administration to 86 ± 20 seconds ($p=0.08$).

Arrelano-Rodrego et al. obtained similar results with their single-blind clinical trial in 2015 (24). They evaluated both rivaroxaban (20 mg/day) as well as dabigatran (150 mg/12 h), and applied PCC, activated PCC, as well as recombinant activated Factor VII in an ex-vivo setting after treatment with the aforementioned direct oral anticoagulants for a five day period. They found that PCC was able to restore some fibrin forming capacity to the rivaroxaban treated patients, but the dabigatran patients experienced no restoration of fibrin forming capacity.

In Marlu et al. (see study in *Dabigatran* for design), both 4-Factor PCC and FEIBA[®] increased the ETP-AUC of dabigatran anticoagulated plasma (22). However, 4-Factor PCC did not result in LT or TTP returning to near baseline values (prior to dabigatran), while a return to baseline were observed in these parameters after administration of rFVIIa and FEIBA[®]. Of interest, doses of FEIBA[®] in lower ranges were observed to have lowering of LT and TTP to nearly baseline values.

Rivaroxaban

Eerenberg et al (see study in *Dabigatran* for design) reported rivaroxaban monitoring using prothrombin time (PT) and endogenous thrombin potential (ETP) (23). Rivaroxaban administration significantly prolonged PT (15.8 ± 1.3 vs. 12.3 ± 0.7 seconds at baseline), but after PCC administration PT completely normalized (12.8 ± 1.0 seconds; $p<0.001$). ETP was decreased from $92 \pm 22\%$ at baseline to $51 \pm 21\%$. After PCC administration, ETP normalized to $114 \pm 26\%$ ($p<0.001$).

In Marlu et al (see study in *Dabigatran* for design), PCC and FEIBA[®], but not rFVIIa, had dose dependent increases in ETP-AUC (22). Of note, only the lower doses of 4-Factor PCC and FEIBA[®] reversed the ETP-AUC to near baseline, while the higher doses resulted in over-correction. 4-Factor PCC was responsible for a slight reduction in LT (15%) compared to 47% for FEIBA[®] ($p<0.0001$). 4-Factor PCC did not affect TTP while FEIBA[®] and rFVIIa decreased TTP by 30% and 44%, respectively.

Apixaban, Edoxaban

Currently, no published studies or case reports are available regarding utilization of PCC for apixaban reversal. However, having the same mechanism of action as rivaroxaban, possible extrapolation of data may be possible.

Tranexamic Acid

Tranexamic acid (TXA) is an antifibrinolytic agent that has historically been shown to decrease the need for blood transfusions in patients undergoing elective surgery. Additionally, TXA has also been shown to decrease all-cause mortality and death due to bleeding in trauma patients presenting with significant hemorrhage (25,26). Due to TXA's proven efficacy along with its low side effect profile, administration of TXA 1 gram IV infused over 10 minutes appears to be a reasonable intervention in a patient on a non-vitamin K anticoagulant with a life-threatening bleed.

Hemodialysis

Dabigatran

Dabigatran has an estimated protein binding of 35% and is predominantly renally eliminated; therefore utilization of hemodialysis to assist with drug clearance is a possible option (1).

A group of six non-bleeding patients receiving dabigatran 50 mg requiring hemodialysis were examined to determine the clearance of dabigatran (2). Dialysis inlet levels were measured compared to outlet levels. Mean dabigatran levels were lower in the dialysis outlet line than the inlet line (4.4 ng/mL vs. 12.5 ng/mL at 2 hours and 3.4 ng/mL vs 8.9 ng/mL at 4 hours). Estimated drug removal by dialysis was 62% at 2 hours and 68% at 4 hours.

In Warkentin's case report, dabigatran concentration was 76 ng/mL prior to hemodialysis and 27 ng/mL after a six-hour dialysis session (20).

Rivaroxaban

Rivaroxaban is 92 to 95% protein bound and hemodialysis has not been observed to be effective in the management of acute hemorrhage (1,2).

Apixaban, Edoxaban

Currently there is no information regarding utilization of hemodialysis or hemofiltration for the removal of apixaban or edoxaban.

REFERENCES

1. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e44S-88S.
2. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49(4):259-68.
3. Apixaban. DRUGDEX® System. Klasco RK (Ed). Thompson Micromedex, Greenwood Village, Colorado; 2012. [Accessed 17-December-2012].
4. Rivaroxaban. DRUGDEX® System. Klasco RK (Ed). Thompson Micromedex, Greenwood Village, Colorado; 2012. [Accessed 17-December-2012].
5. Dabigatran. DRUGDEX® System. Klasco RK (Ed). Thompson Micromedex, Greenwood Village, Colorado; 2012. [Accessed 17-December-2012].
6. Gardner A.J., Zafonte R. Chapter 12 – Neuroepidemiology of traumatic brain injury. *Handb Clin Neurol*. 2016;138:207-23
7. Van ryn J, Baruch L, Clemens A. Interpretation of point-of-care INR results in patients treated with dabigatran. *Am J Med*. 2012;125(4):417-20.
8. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol*. 2007;64(3):292-303.
9. Lindahl TL, Baghaei F, Blixter IF, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost*. 2011;105(2):371-8.
10. Tripodi A, Chantarangkul V, Guinet C, Samama MM. The International Normalized Ratio calibrated for rivaroxaban has the potential to normalize prothrombin time results for rivaroxaban-treated patients: results of an in vitro study. *J Thromb Haemost*. 2011;9(1):226-8.
11. Samama MM, Martinoli JL, Leflem L, et al. Assessment of laboratory assays to measure rivaroxaban-an oral, direct factor Xa inhibitor. *Thromb Haemost*. 2010;103(4):815-25.
12. Barrett YC, Wang Z, Frost C et al. Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. *Thromb Haemost*. 2010; 104:1263-71.
13. Asmis LM, Alberio L, Angelillo-scherrer A, et al. Rivaroxaban: Quantification by anti-FXa assay and influence on coagulation tests: a study in 9 Swiss laboratories. *Thromb Res*. 2012;129(4):492

14. Becker RC, Yang H, Barrett Y, et al. Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban--an oral, direct and selective factor Xa inhibitor. *J Thromb Thrombolysis*. 2011;32(2):183-7.
15. Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo controlled, double-blind phase 1 trial. *Lancet* 2015; 386:680–690.
16. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med*. 2017;377: 431–41
17. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015; 373:511–20.
18. Praxbind (idarucizumab) prescribing information. Ridgefield, Connecticut: Boehringer Ingelheim Pharmaceuticals, Inc.; 2018
19. Hutcherson, TC, Cieri-Hutcherson, NE, et al. Evidence for Idarucizumab (Praxbind) in the Reversal Of the Direct Thrombin Inhibitor Dabigatran: Review Following the RE-VERSE AD Full Cohort Analysis. *P & T*. 2017;42(11):692-698
20. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood*. 2012; 119(9):2172-2174.
21. Dumkow LE, Voss JR, Peters M, Jennings DL. Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. *Am J Health Syst Pharm*. 2012; 69(19):1646-1650.
22. Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost*. 2012; 108(2):217-224.
23. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011; 124(14):1573-1579.
24. Arellano-Rodrigo E, Lopez-Vilchez I, Galan AM, et al. Coagulation factor concentrates fail to restore alterations in fibrin formation caused by rivaroxaban or dabigatran in studies with flowing blood from treated healthy volunteers. *Transfus Med Rev* 2015; 29:242–249.
25. CRASH-2 trial collaborators. Effect of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage: a randomized, placebo-controlled trial. *Lancet* 2010; 376: 23-32.
26. CRASH-2 trial collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; 377: 1096-1101.

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Authors: Matthew Bamber, PharmD, Brandon Hobbs, PharmD, Phillips Nagsuk, MD
Editor: Michael L. Cheatham, MD
Last revision date: July 25, 2018

Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net