Early anticoagulant reversal after trauma: A Western Trauma Association critical decisions algorithm

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This is a recommended evaluation and management algorithm from the Western Trauma Association (WTA) Algorithms Committee addressing the management of adult patients who are taking anticoagulant medications at the time of injury and potentially require reversal of anticoagulation. Given the paucity of published prospective randomized clinical trials that have generated class I data, these recommendations are based primarily on data from published prospective and retrospective cohort studies and the expert opinion of WTA members. The final algorithm is the result of an iterative process including an initial internal review and revision by the WTA Algorithms Committee members followed by revisions based on input during and after presentation of the algorithm to the full WTA membership.

Management of the severely injured or bleeding patient is complicated by use of anticoagulant medications including vitamin K antagonists (VKAs), direct oral anticoagulant medications (DOACs), and therapeutic low–molecular weight heparins (LMWHs), primarily enoxaparin. With more favorable risk-benefit profiles, DOACs have become the oral agents of choice over VKAs for the management of atrial fibrillation[1] and venous thromboembolism.[2] Direct oral anticoagulant medications produce a more predictable anticoagulant effect and can be given in fixed dosing without need for routine coagulation monitoring.[3] There are two classes of DOACs: direct thrombin inhibitors (DTIs; namely, dabigatran) and factor Xa inhibitors (FXa-Is; primarily rivaroxaban and apixaban). Despite the known complexity of trauma-related bleeding in anticoagulated patients, there remains a lack of consensus regarding the management strategy for reversal of anticoagulation in these patients.

The algorithm (Fig. 1) and accompanying comments represent a safe and sensible approach to the evaluation and management of the injured patient with known or suspected anticoagulant use. We recognize that there will be multiple factors that may warrant or require deviation from any single recommended algorithm and that no algorithm can completely replace expert bedside clinical judgment. We encourage clinicians to use this as a general framework in the approach to these patients and to customize and adapt the algorithm to better suit the specific circumstances of their program or location.

ALGORITHM

The following lettered sections correspond to the letters of specific sections in the algorithm in Figure 1. Each section contains a brief summary of the important aspects and options that should be considered at that point in the evaluation and management process.

Assess Degree of Injury/Bleeding

For injured patients with known or suspected anticoagulant use, rapid assessment will determine the severity of injury and/or extent of bleeding. Assessment includes the standard Advanced Trauma Life Support physical examination, baseline laboratory testing, and appropriate radiographic evaluation when feasible. Patients are initially categorized by a level of suspicion for severe injury or bleeding, defined as need for urgent/emergent operation or intervention, need for immediate transfusion, presence of hemorrhagic shock or hemorrhage into a critical organ or space including major intracranial, ocular, spine, cavitary, or extremity injuries.

When time allows, laboratory tests may be helpful in assessing the degree of anticoagulant activity of a given agent. Table 1 summarizes the expected effects of the different oral agents on the commonly used coagulation tests.[4,5] It is important to note the limitations regarding the application of these tests in this setting. For example, although prothrombin time (PT) and international normalized ratio (INR) are laboratory measurements used to follow the effect of warfarin, they are not specific to warfarin use

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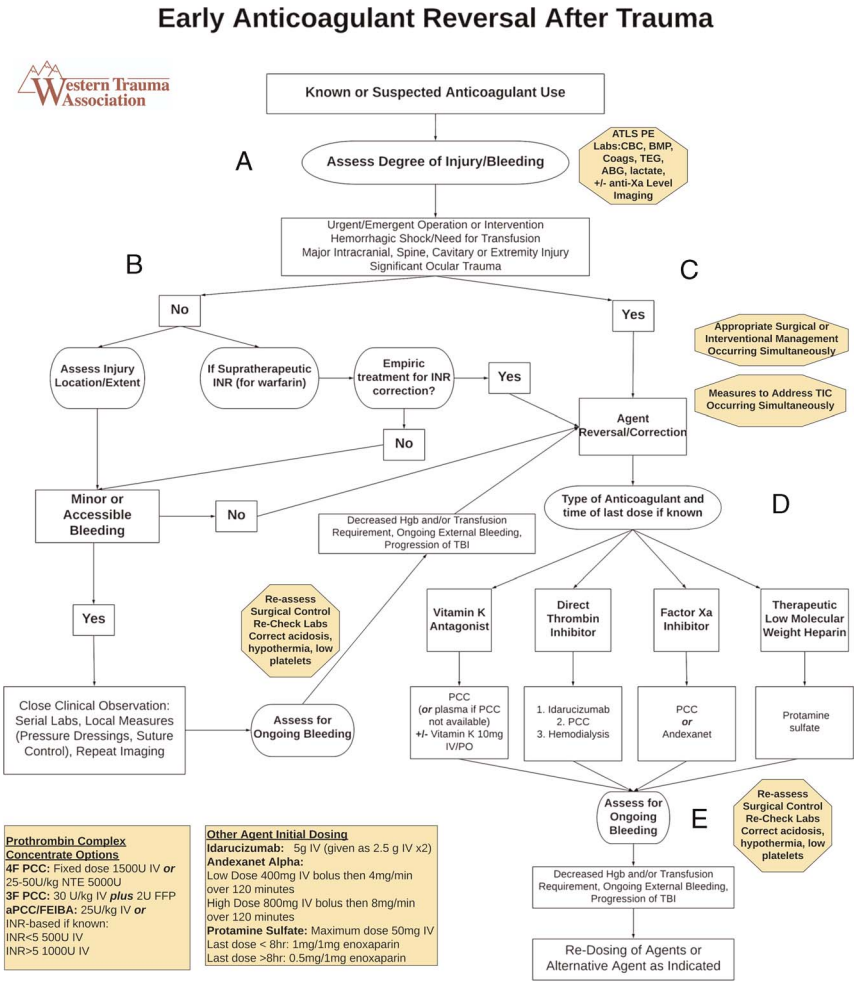

Figure 1. Western Trauma Association algorithm for early anticoagulant reversal after trauma. Letters correspond to sections in the associated article. ABG, arterial blood gas; ATLS PE, Advanced Trauma Life Support physical examination; BMP, basic metabolic panel; CBC, complete blood count; Coags, coagulation panel; FEIBA, factor eight inhibitor bypassing activity; FFP, fresh frozen plasma; Hgb, hemoglobin; MTP, massive transfusion protocol; NTE, not to exceed; PO, by mouth; TBI, traumatic brain injury; TIC, trauma-induced coagulopathy; TXA, tranexamic acid.

and may be elevated to varying degrees with other types of coagulopathy. Also, DOACs do not demonstrate a linear relationship with the most readily available coagulation tests.[4,5] Specific laboratory parameters that are relevant to each agent are discussed in the sections hereinafter addressing agent reversal or correction.

Management of Anticoagulated Patients Without Severe Injury or Bleeding

Patients with some degree of injury or bleeding not categorized as "severe" should be closely observed. Management may include simple, local hemostatic measures such as suture control or pressure/hemostatic dressings for bleeding that is easily accessible. Assessment for ongoing bleeding may include serial physical examination and laboratory testing as well as repeat imaging as indicated. Evidence of ongoing bleeding as manifested by continued external blood loss, decreased hemoglobin, transfusion requirement, and/or significant progression of injury on serial imaging (most notably traumatic brain injury) should prompt a change in management to agent reversal or correction.

TABLE 1. Comparison of Oral Anticoagulant Agents

Drug	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Mechanism	**VKA**	**DTI**	**FXa-I**	**FXa-I**
Renal Metabolism	No	80–85%	~35%	~25%
Peak effect, h	72–96	1–2	2–4	3–4
Half-life, h	40	12–14	6–13	10–14
PT/INR	↑	↑/–	↑/–	↑/–
aPTT	↑/–	↑	↑/–	↑/–
Anti-Xa level	—	—	↑*	↑*
Test for presence/ absence	PT/INR	Thrombin time*	Anti-Xa level*	Anti-Xa level*
Reversal agent	4F-PCC	Idarucizumab	Andexanet or 4F-PCC	Andexanet or 4F-PCC

*Thrombin time is best used to exclude the presence of dabigatran when normal; otherwise, it is very sensitive and so can be prolonged even with very small amounts of the drug present.

**Anti–factor Xa level of zero indicates no clinically relevant anti-Xa agent is present; otherwise, it must be calibrated for the specific anticoagulant to determine amount of drug present.

aPTT, activated partial thromboplastin time.

Management of Anticoagulated Patients With Severe Injury or Bleeding

Management strategies for anticoagulated patients with severe injury or bleeding will involve reversal or repletion of the anticoagulated state. None of the reversal agents discussed are hemostatic agents, meaning they do not stop bleeding. Rather, these agents serve to remove or reduce the antithrombotic/anticoagulant effect of the target medication and should be used in conjunction with standard management of hemorrhagic shock or severe injury. A standard multimodal approach is recommended, including balanced blood product transfusion and/or institution of massive transfusion protocol as needed. Appropriate surgical or interventional management should occur simultaneously as measures are taken to address specific coagulation abnormalities related to anticoagulant use. There is the potential for development of trauma-induced coagulopathy, which should also be addressed simultaneously, along with measures to correct acidosis, hypothermia, and thrombocytopenia if present. Specific management strategies depend upon the type of anticoagulant. Table 1 summarizes and compares the most common oral anticoagulants by mechanism of action, metabolism, peak onset, and effective therapeutic half-life.

Management of Specific Anticoagulant Medications

VKA: Warfarin

Warfarin, the most commonly used VKA, impairs vitamin K metabolism, thereby decreasing the hepatic synthesis of coagulation factors II, VII, IX, and X as well as proteins C and S.[6] The degree of anticoagulation with VKAs is measured with PT and INR. There is no "reversal" agent for VKAs; correction of anticoagulation related to warfarin is accomplished by repletion of deficient factors. This is most efficiently and safely accomplished with prothrombin complex concentrate (PCC).[7,8] The main types of PCCs available, the factors that each product contains, and their respective dosing options are listed in Table 2. All PCCs contain the vitamin K–dependent factors II, IX, and X along with variable levels of factor VII. When available, 4-factor (4F) PCC (Kcentra, CSL Behring GmbH, Marburg, Germany) is preferred.[8] It contains nonactive factors II, VII, IX, and X in concentrations approximately 25 times higher than in plasma.[9,10] In patients needing VKA reversal for urgent invasive or surgical procedures, 4F-PCC is superior to fresh frozen plasma in achieving rapid INR reversal and effective hemostasis.[11] It can be administered as a fixed dose of 1,500 U intravenous (IV) or as weight-based dose of 25 to 50 U/kg (maximum dose not to exceed 5,000 U).[12,13]

When 4F-PCC is not available, other PCC options may be used. Unlike 4F-PCC, 3F-PCC (Profilnine, Grifols Biologicals Inc., Los Angeles, CA) has low levels of factor VII and has been shown to be less effective than 4F-PCC with regard to INR reversal in patients taking warfarin.[14,15] To supplement factor VII when administering 3F-PCC, fresh frozen plasma can be added. Finally, activated prothrombin complex concentrate (aPCC; FEIBA, Baxter Healthcare Corporation, Westlake Village, CA) is the only commercially available PCC that contains activated factor VII in addition to inactive factors II, IX, and X. There are fixed dose and INR-based dosing options as listed in the algorithm and in Table 2. A retrospective study comparing low fixed-dose aPCC with standard 4F-PCC in warfarin-related hemorrhage showed equivalent correction of INR to <1.4 with no difference in thrombotic events in the two groups.[16]

Finally, if no PCC options are available or in a patient with a contraindication to PCC, plasma is a less preferred but valid alternative for INR correction. While relatively inexpensive and widely available, plasma transfusion requires significant time for cross-matching, thawing (if fresh frozen plasma is being used), and administration. Thawed plasma is available in some centers, allowing for expedited plasma transfusion.[17,18] Regardless of type of plasma, a large transfusion volume can be required for INR correction, which increases the risk of complications related to volume overload (particularly in elderly patients), allergic reactions, and risk of transfusion-related acute lung injury.[9] Plasma should therefore only be used when PCC is not available.[9,10] Plasma is initially administered at approximately 10 to 15 mL/kg, with further dosing based on the clinical response and laboratory parameters.[7,9,19]

In most cases, vitamin K, generally given as 5 to 10 mg IV or oral, may be added to repletion of factors with PCC or plasma.[8] Although vitamin K administration will restore hepatic synthesis of vitamin K–dependent factors, this process takes hours to days and may ultimately complicate the reinstitution of anticoagulation once bleeding is definitively controlled.[20] Administration of vitamin K for reversal of anticoagulation in patients with high-risk prosthetic valves must be approached with caution given the potential to delay the ability to reestablish therapeutic anticoagulation and the subsequent risk of valve thrombosis and embolism.[20] Use of low-dose vitamin K (1–2.5 mg) is a safe alternative,[20,21] or it may be omitted when it is anticipated that full anticoagulation will need to be rapidly reestablished.

TABLE 2. Prothrombin Complex Concentrate Products

Product	Factors	Dosing Options
4F-PCC (Kcentra)	Inactive factors II, VII, IX, and X	Fixed dose 1,500 U IV *or* 25–50 U/kg NTE 5,000 U
3F-PCC (Profilnine)	Inactive factors II, IX, and X (little to no factor VII)	30 U/g IV *plus* 2 U FFP
aPCC (FEIBA)	Inactive factors II, IX, and X; active factor VII	25 U/kg *or* INR based if known: INR < 5, 500 U IV INR > 5, 1,000 U IV

FEIBA, factor eight inhibitor bypassing activity; FFP, fresh frozen plasma; NTE, not to exceed.

DTI: Dabigatran

Dabigatran is the only oral DTI available for clinical use. It competitively binds to the active site of thrombin, which prevents subsequent thrombin-mediated conversion of fibrinogen to fibrin.[6,22] Dabigatran is primarily renally cleared and is therefore the only DOAC that can potentially be cleared by hemodialysis.[6] The most accurate tests to follow dabigatran effect, dilute thrombin time, and ecarin clotting time are not readily available in many centers.[9] Thrombin time and PTT may also be used to assess dabigatran effect.[6] However, because thrombin time is very sensitive to dabigatran and can be prolonged even with very small amounts of the drug, it is best used to exclude the presence of clinically relevant dabigatran levels when it is normal.[6]

Conversely, while the presence of dabigatran is suggested by a prolonged PTT, a normal PTT level does not exclude it.[4,5]

Dabigatran is reversed by idarucizumab (Praxbind, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT), which is a humanized monoclonal antibody fragment that binds dabigatran with strong affinity and specificity.[23] It is the only Food and Drug Administration-approved reversal agent for dabigatran and provides immediate and complete reversal.[6,24] The safety and efficacy of idarucizumab were demonstrated in the Reversal of Dabigatran Anticoagulant Effect with Idarucizumab (RE-VERSE AD) trial.[24] In this study of dabigatran-treated patients who had either uncontrolled bleeding or required an urgent procedure, patients were given 5 g of IV idarucizumab, administered as two successive doses of 2.5 g each. The median maximum percentage of anticoagulant reversal within 4 hours (based on dilute thrombin time and ecarin clotting time) was 100% and was achieved in more than 98% of patients. In evaluable patients undergoing invasive procedures or surgery, hemostasis was judged to be normal in 93% of patients. Overall, rates of thrombotic events in the study (4.8% at 30 days and 6.8% at 90 days) were reported as consistent with rates after major surgical procedures or hospitalization for bleeding. The mortality rate at 30 days and 90 days was 13% and 18%, respectively, which the authors attributed to a combination of patient comorbidities and severity of the index event.[24]

In the event idarucizumab is not available, either PCC or aPCC may be used, although the data for such use are limited to small in vitro studies and studies in healthy volunteers.[25–27] Neither PCC nor aPCC act as a specific reversal agent for dabigatran; rather, they raise the levels of vitamin K–dependent clotting factors with subsequent increase in thrombin generation.[28]

FXa-Is: Apixaban and Rivaroxaban

The common FXa-Is are rivaroxaban (Xarelto, Janssen Pharmaceuticals, Inc., Titusville, NJ), apixaban (Eliquis, Bristol-Myers Squibb Company, Princeton, NJ and Pfizer Inc., New York, NY), edoxaban (Savaysa, Daiichi-Sankyo, Inc., Basking Ridge, NJ), and betrixavan (Bevyxxa, Portola Pharmaceuticals, Inc., South San Francisco, CA). Most of the literature regarding FXa-Is is based on rivaroxaban and apixaban, so these two drugs are the focus of this class in the algorithm. As the name of their class implies, FXa-Is agents directly inhibit factor Xa, resulting in decreased conversion of prothrombin to thrombin.[22] The preferred test to measure anticoagulation with FXa-Is is an anti-Xa level.[4,5] If absent, anti-Xa is helpful in determining that a clinically relevant anti-Xa drug level is not present. Otherwise, the anti-Xa assay must be calibrated to each specific drug to reliably determine the amount of drug present. While PT and PTT may be elevated with FXa-I use, normal values do not exclude clinically relevant drug levels.[4,5]

For the management of life-threatening bleeding or injury in the setting of FXa-I use, we suggest either andexanet alfa or 4F-PCC. Thus far, these agents have not been compared directly in a randomized trial. There is insufficient evidence regarding risks and benefits of the agents to recommend one over the other. Andexanet alfa is nonetheless the only US Federal Drug Administration–approved reversal agent for FXa-Is. Andexanet alfa is a recombinant inactive protein with a similar structure to endogenous FXa that competitively binds and sequesters FXa-Is.[29] There are two dosing levels based on the specific FXa-I taken as well as the amount and timing of the patient's last dose, if known: (1) low dose, a bolus of 400 mg IV given as 30 mg/min followed by an infusion of 480 mg given at 4 mg/min for up to 120 minutes; and (2) high dose, a bolus of 800 mg given at 30 mg/min followed by an infusion of 960 mg given at 8 mg/min for up to 120 minutes.[29] When dose and timing of FXA-I are unknown, it is recommended to use the high dose regimen.

The Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors (ANNEXA-4) trial evaluated 352 patients with acute major bleeding on apixaban and rivaroxaban treated with andexanet alfa.[29] Median anti-Xa levels decreased by 92% in both groups, and hemostasis was judged to be excellent or good in 82% of evaluable patients. Mortality was 14%, and thrombotic events occurred in 10% of patients within 30 days. However, clinical hemostasis did not correlate with anti-Xa levels. There have been several major critiques of the ANNEXA-4 trial, specifically as it applies to the trauma population. There was no comparator arm, so it is unknown how andexanet performs compared with PCC or placebo. Furthermore, patients requiring emergency surgery and those with more severe intracranial hemorrhage were excluded, further limiting the generalizability.

Given the concerns regarding applicability of the ANNEXA-4 trial to trauma patients specifically, the other option for management of bleeding patients on FXa-Is is off-label use of 4F-PCC. The 2017 UPRATE (Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-Factor Ten Inhibitors) trial evaluated 4F-PCC for reversal of major bleeding with rivaroxaban and apixaban use.[30] In 84 bleeding patients treated with 4F-PCC, hemostasis rate (assessed clinically without use of anti-Xa levels) was 69%. Thrombosis rate was 3.6%, and mortality was 32% at 30 days. In a multisite prospective study of 66 bleeding patients who took rivaroxaban or apixaban and were treated with 4F-PCC, hemostasis was described as good in 68%.[31] At 30 days, the thromboembolic rate was 8%, and mortality was 14%. In an observational study of 31 patients on rivaroxaban or apixaban with major bleeding, effective hemostasis was achieved in 80% of patients treated with 4F-PCC.[32] Death due to active bleeding occurred in 16%, and no thrombotic events were observed. Piran et al.[33] reported a meta-analysis of 340 patients treated with PCC for bleeding associated with FXa-Is, largely following rivaroxaban or apixaban. Depending on criteria used, the pooled proportion of patients with effective bleeding management was 0.69 to 0.77 with a thrombosis rate of 0.04 and a mortality rate of 0.16. These studies, although small and not specific to trauma patients, support the administration of 4F-PCC as an option for management of bleeding patients using FXa-Is, although the mortality rate associated with this approach remains high.

Therapeutic LMWH: Enoxaparin

Low–molecular weight heparins bind and accelerate antithrombin (AT), which in turn inhibits the activity of factor Xa and, to a lesser extent, factor IIa. For the purpose of the algorithm, enoxaparin is the primary LMWH discussed. As with oral FXa-Is, an anti-Xa level of zero indicates the absence of a clinically relevant level of enoxaparin. Enoxaparin is partially neutralized by protamine sulfate (PS).[34] Ideal dosing of PS is based on both the amount and timing of last enoxaparin administration, with a maximum single dose of 50 mg IV.[19] This is the default dose that can be used when details of enoxaparin

administration are not known. The dosing in the algorithm is based on known amount and timing of enoxaparin administration: 1 mg of PS per 1 mg of enoxaparin given within 8 hours prior or 0.5 mg of PS per 1 mg of enoxaparin given more than 8 hours prior. Because rapid administration can cause hypotension and reactions similar to anaphylaxis, the manufacturer recommends that PS be given by slow IV injection in doses no greater than 50 mg in any 10-minute interval.[35]

Assess for Ongoing Bleeding

Patients are closely monitored clinically for evidence of ongoing bleeding with measures previously described: repeat physical examination, serial laboratory testing, and serial imaging if indicated. Factors that may contribute to ongoing bleeding (i.e., hypothermia, acidosis, and thrombocytopenia) should be corrected. Patients are also reassessed to ensure that adequate surgical control has been accomplished. For those patients with ongoing hemorrhage despite administration of reversal agents and appropriate surgical or interventional control, redosing the initial agent or changing to an alternative agent should be considered. This should be instituted with caution, however, given the lack of evidence regarding safety or efficacy of using more than one agent in parallel or sequentially for reversal of anticoagulation.

AREAS OF CONTROVERSY AND EXISTING KNOWLEDGE/RESEARCH GAPS

Many areas of this algorithm lack high-quality evidentiary support and require further focused research. Studies to date regarding anticoagulant reversal are in mixed patient populations, making applicability to trauma patients somewhat difficult. There is also considerable variation in the primary endpoints of the various trials (e.g., pharmacologic vs. clinical parameters), which makes comparisons between trials difficult. The ability of reversal agents to normalize coagulation tests and/or improve clinical indicators of bleeding does not necessarily translate into improved overall outcomes. In fact, a mortality benefit has yet to be definitively established for reversal of anticoagulation in trauma patients.

Thromboembolism is a source of morbidity and mortality in injured patients taking preinjury anticoagulants. Simply withholding anticoagulant medications in this patient population exposes the baseline thrombotic state for which that medication is taken, with subsequent additional risk imposed following severe injury and hemorrhage. Furthermore, although the intrinsic prothrombotic effects of reversal agents have not been clearly defined, each of the agents discussed in this algorithm have potential thrombotic risk.[36] Resumption of anticoagulation should therefore occur as soon as possible when indicated. Guidelines regarding the timing for reinstitution of anticoagulant therapy following cessation of bleeding or management of severe injury are beyond the scope of the algorithm. The timing of resumption must be guided by clinical judgment.

The potential use of andexanet alfa for the reversal of anticoagulant effects of LMWHs has not been fully evaluated. The ANNEXA-4 trial included only 20 patients (6% of total) receiving enoxaparin.[27] Of the 20, 16 had a 75% reduction in anti-factor Xa activity. However, the study had multiple major limitations including no clinical demonstration of reduced bleeding, lack of a control group, and a relatively high mortality and morbidity rate. Additional study is warranted to evaluate the safety and efficacy of andexanet for enoxaparin reversal before a specific recommendation can be made.

Patients taking warfarin with supratherapeutic INR levels warrant special consideration. The American College of Chest Physicians 2012 guidelines for management of supratherapeutic INR in nonbleeding patients recommend only oral vitamin K administration for INR levels of >10.[8] Guidelines for management with severe bleeding were discussed previously. There are no specific guidelines for managing patients who fall between the two extremes. Clinical judgment must be used to identify patients with what might otherwise be minor to moderate injury who also have a supratherapeutic INR. These patients may benefit from empiric correction of the anticoagulated state before bleeding or injury progresses.

Finally, use of viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) is an area of controversy for this algorithm. Whereas the utility of TEG and ROTEM for the resuscitation of acute traumatic hemorrhage has been fairly well delineated,[37] the data regarding the use of these parameters for patients taking DOACs are less clear. In a retrospective review comparing trauma patients on anticoagulant medications to those who were not, Ali et al.[38] observed no difference in the number of patients who were found to have coagulopathy on TEG. Similarly, in a multicenter study of trauma patients taking dabigatran, rivaroxaban or apixaban, the authors concluded that neither traditional measures of coagulation nor TEG reliably identified coagulopathy in this patient group.[39] Recent investigations using the newer generation TEG, TEG6s, have found a correlation between prolonged reaction (*R*) time and DOAC use.[40–43] Given the scant evidence on the utilization of TEG or ROTEM to guide the reversal of therapeutic anticoagulation specifically and the limited availability of these tests at many trauma centers, a specific recommendation regarding the use of viscoelastic studies to guide reversal of anticoagulation in trauma patients cannot be made until further data emerges.

SUMMARY AND CONCLUSIONS

This algorithm was designed to guide clinicians in the management of severely injured patients who are taking anticoagulant medications at the time of injury and have potentially life-threatening bleeding. Early identification of those patients with severe injury or bleeding will determine the need for urgent reversal of anticoagulation. Reversal or correction of the anticoagulated state can be quickly accomplished using the provided information. Further study is needed to more clearly define the risks and benefits of reversal, to develop evidence-based guidelines for reversal protocols, and to determine the optimal circumstances for re-initiating anticoagulation.

AUTHORSHIP

All authors contributed in the concept and design of the algorithm. K.A.P. performed the literature review and prepared the article. K.A.P., E.J.L., E.E.M., K.I., and M.J.M. contributed in the critical revisions of the article.

DISCLOSURE

The authors declare no conflicts of interest.
The results and opinions expressed in this article are those of the authors and do not reflect the opinions or official policy of any of the listed affiliated institutions, the United States Army, or the Department of Defense (if military coauthors).

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