EMERGENCY MEDICINE PRACTICE
EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE

Emergency Department Management of Patients Taking Direct Oral Anticoagulant Agents

August 2019
Volume 21, Number 8

Authors

Patrick Maher, MD
Assistant Professor, Emergency Medicine and Critical Care, Icahn School of Medicine at Mount Sinai, New York, NY

Emily Taub, MD
Department of Emergency Medicine and Critical Care, Icahn School of Medicine at Mount Sinai, New York, NY

Peer Reviewers

Dowin Boatright, MD, MBA, MHS
Assistant Professor, Department of Emergency Medicine, Yale School of Medicine, New Haven, CT

Natalie Kreitzer, MD, MS
Assistant Professor of Emergency Medicine, Neurocritical Care, and Stroke, University of Cincinnati, Cincinnati, OH

Isaac Tawil, MD, FCCM
Associate Professor, Critical Care and Emergency Medicine, University of New Mexico School of Medicine, Albuquerque, NM

Prior to beginning this activity, see "CME Information" on the back page.

This issue is eligible for 4 Pharmacology CME credits.

Abstract

Direct oral anticoagulant (DOAC) agents have become commonly used over the last 9 years for treatment and prophylaxis for thromboembolic conditions, following approvals by the United States Food and Drug Administration. These anticoagulant agents, which include a direct thrombin inhibitor and factor Xa inhibitors, offer potential advantages for patients over warfarin; however, bleeding emergencies with DOACs can present diagnostic and therapeutic challenges because, unlike traditional anticoagulants, their therapeutic effect cannot be easily monitored directly with common clotting assays. This review examines the growing body of evidence on the uses and risks of DOACs in the emergency department, including initiation of therapy and reversal strategies.

Case Presentations

As you begin your shift, the first patient is a 70-year-old man brought in for a ground-level fall with isolated head injury. A review of the patient's history reveals atrial fibrillation, and he is currently on anticoagulation with apixaban. A rapidly obtained CT scan of the head shows a subdural hematoma. As you resuscitate the patient, you wonder how best to assess his anticoagulation status and how best to address reversal.

Later in the shift, a 50-year-old woman is brought in by EMS for intentional overdose of medications, in a suicide attempt. Her list of home medications includes sedatives as well as dabigatran, prescribed for a recently diagnosed DVT. The patient is somnolent, so specific ingestants cannot be ascertained. You wonder if there are monitoring tests, beyond PT/PTT, that might determine whether a dabigatran overdose is present, and if so, how should it be managed to prevent further injury?

As your shift is coming to a close, a 45-year-old man presents with leg swelling and erythema after a recent airplane trip. Your bedside ultrasound is consistent with DVT. The patient hates the thought of frequent blood tests, and he asks whether there are any options for treatment besides warfarin. You know that DOACs may be an option for him, but you wonder what the best way is to engage in shared decision-making with him.

Introduction

Since the approval by the United States Food and Drug Administration (FDA) of dabigatran in 2010, the prescription market for this new class of medications with direct anticoagulation effect has increased markedly. In the United States, DOACs now account for a similar proportion of office visits for anticoagulant use as warfarin. This trend has also been seen in other countries, as DOAC use has grown rapidly.[1-3] Assuming that this trend continues, emergency clinicians will continue to see more patients taking DOACs, as these drugs replace alternative anticoagulant therapies.

Compared with warfarin and other oral anticoagulants, DOACs offer potential benefits, including reduced need for monitoring and a potential for reduced bleeding complications. However, the advisability of using the DOACs was initially challenged, due to the lack of an effective reversal agent to use in the event of an emergency and for the risk of unintentional overdose in patients with altered drug metabolism. As with traditional anticoagulants, patients using DOACs are often medically complex, and they may frequently present for emergency department (ED) care.

This issue of *Emergency Medicine Practice* focuses on updates to the body of literature on DOACs since the last review in 2013. Since that time, many studies, including longer-term follow-up from large trials and registry data for patients taking DOACs, have become available. Given the likelihood that these medications will continue to increase in popularity, emergency clinicians need to have expertise in dosing, monitoring, reversal, and risks in clinical practice. This review will focus on use of DOACs for the indications of stroke prevention in atrial fibrillation and treatment and prevention of recurrence in venous thromboembolism (VTE).

Critical Appraisal of the Literature

Terminology for this class of anticoagulants has included, most commonly, *DOAC* (for direct oral anticoagulant) or *NOAC* (for "novel" oral anticoagulant or "non–vitamin K" oral anticoagulant).[4] Given their direct mechanism of action, and the time since approval for these agents, *DOAC* may be the preferred term in the future.

A literature search was performed in PubMed using the following terms: *DOAC, NOAC, dabigatran, apixaban, edoxaban, rivaroxaban, betrixaban, pulmonary embolism, deep venous thrombosis,* and *prothrombin complex concentrate.* Over 200 articles from 2000 to the present were reviewed. The Cochrane Database of Systematic Reviews was searched for systematic reviews using the key term *DOAC*, which identified 5 reviews. Guideline statements specifically regarding DOAC treatment and reversal were released by the American Heart Association (AHA) in 2017, the European Society of Cardiology in 2015, and the American College of Cardiology in 2017. These guidelines include data based on large randomized controlled trials for multiple conditions.

An appraisal of literature was performed, which favored large randomized trials over smaller cohort studies and case reports. Good-quality evidence regarding safety and efficacy of these medications in comparison to warfarin and heparin-based anticoagulants has been published based on long-term cohort studies. Unfortunately, direct comparisons between DOACs are limited to small numbers of studies with predominantly poor-quality evidence. Differences in inclusion and exclusion criteria, primary endpoints, and assessment of safety outcomes between studies also limits comparability between trials. When available, recommendations in this article are evidence-based. Recommendations based on accepted practice or expert consensus are explicitly noted as such.

Pathophysiology

Control of coagulation in the human body is a delicate balance between hemorrhage and thrombosis that is mediated by an extensive number of procoagulant and anticoagulant proteins. A pathological imbalance between these conditions can arise through any of the constituents of the Virchow triad of thrombosis. These include a hypercoagulable state (such as factor V

Leiden thrombophilia), a mechanical stimulus (such as vessel injury), or a condition of stasis with interrupted blood flow (as in atrial fibrillation).

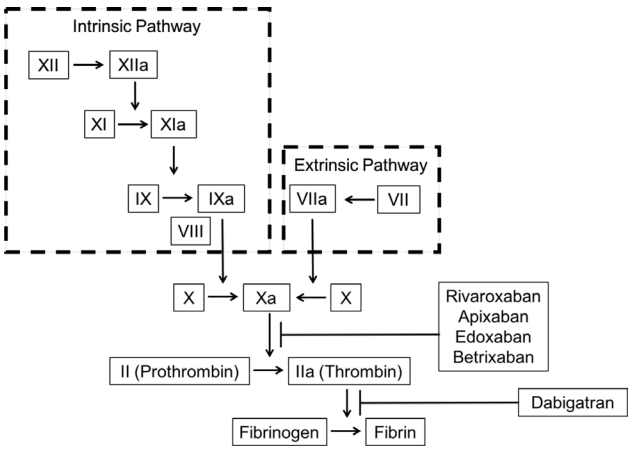
Traditionally, the prothrombotic risk from these states was mediated through vitamin K antagonists (VKAs), warfarin in particular, which inhibits the action of vitamin K in the liver.[5] This inhibition leads to reduced production of clotting factors II, VII, IX, and X, as well as the anticoagulant proteins C and S. Since any clotting factors already present in the circulation remain active, reversal of VKAs may be performed directly through factor repletion. Because VKAs have narrow therapeutic windows and common drug interactions, they require frequent monitoring. Despite this disadvantage, after approval in 1954, warfarin has remained the first choice for oral anticoagulation in the United States for over 60 years. The pharmacology, risks, and reversal strategies of warfarin have been studied extensively over that period.

Before the 2010 FDA approval of the first DOAC, dabigatran, alternate agents for anticoagulation, including direct thrombin inhibitors and factor Xa (FXa) inhibitors, had existed for many years as intravenous (IV) agents, with mostly limited application in the ED setting. The relatively recent availability of oral direct anticoagulants has become a milestone in anticoagulation treatments. In comparison to warfarin, the DOACs exert a more targeted effect on the clotting cascade. Sites of action for DOACs are shown in **Figure 1**.

Mechanisms and Comparison of Direct Oral Anticoagulants

The DOACs currently FDA-approved for use fall into 2 categories: (1) direct thrombin inhibitors (DTIs) and (2) factor Xa (FXa) inhibitors. **Table 1 (page 4)** summarizes the pharmacokinetics, pharmacodynamics, and

Figure 1. Clotting Factor Cascade and Site of Action of Oral Anticoagulant Agents



FDA-approved indications for DOACs, which include stroke prevention in patients with nonvalvular atrial fibrillation, treatment of VTE, prophylaxis against VTE in certain populations, and reduction of major cardiovascular events in stable cardiovascular disease.

Although the list of FDA-approved indications for the DOACs remains short, off-label investigations or case reports have described the efficacy of DOACs in many settings, including both arterial and venous thromboembolism,[6] prevention of embolic stroke in atrial fibrillation, acute coronary syndromes, cancer-associated thrombosis,[7] upper extremity deep venous thrombosis (DVT),[8] and mesenteric thrombosis.[9] Some of these trials, such as a randomized controlled trial of dabigatran use for anticoagulation in patients with a left ventricular assist device, have failed to demonstrate the utility of the DOACs.[10]

Direct Thrombin Inhibitor

Dabigatran, the first DOAC introduced to the market in 2010, works via direct inhibition of thrombin. Thrombin (factor IIa) is a serine protease, which has a primary role in the coagulation cascade, converting soluble fibrinogen into fibrin for clot formation. Dabigatran is available in both 75 mg and 150 mg tablets, and it is dosed at either 75 mg by mouth twice a day or 150 mg by mouth twice a day, depending on renal function. The half-life for dabigatran is approximately 12 to 15 hours, and maximal effect occurs within 2 to 3 hours after each dose. The RE-LY trial for atrial fibrillation found that, at a dose of 150 mg twice daily, dabigatran had a lower rate of stroke and systemic embolism compared to warfarin, and a similar rate of major hemorrhage.[11] A smaller dose, 110 mg/day, resulted in lower rates of hemorrhage in that trial as well as in a 2.3-year follow-up study, but this dose was not approved by the FDA.[12] The rates of fatal and traumatic intracerebral hemorrhage were lower for patients taking dabigatran compared to warfarin.[13] A randomized controlled trial using dabigatran in the treatment of VTE at a strength of 150 mg, following 5 to 10 days of parenteral anticoagulation, also found similar efficacy in treating acute episodes of VTE and preventing recurrence, compared with warfarin, with reduced rates of hemorrhage.[14-16] Among patients with atrial fibrillation, temporary interruption of dabigatran was associated with similar rates of stroke compared to warfarin interruption.[17]

Factor Xa Inhibitors

Rivaroxaban, apixaban, edoxaban, and betrixaban are different from the DTIs in that they work through the inhibition of clotting factor Xa. FXa acts in the clotting cascade by converting prothrombin to thrombin, acting to amplify clotting activity in both the intrinsic and extrinsic pathways.

Rivaroxaban

Rivaroxaban, the second DOAC to be approved by the FDA, in July 2011, is used for stroke prevention in patients with nonvalvular atrial fibrillation, as well as in VTE treatment, at an oral dose of 20 mg daily (or 15 mg daily for patients with CrCl < 50 mL/min). The ROCKET AF trial, published in 2011, evaluated patients with atrial fibrillation randomized to either rivaroxaban or warfarin.[18] It found that rivaroxaban is noninferior to warfarin for stroke and systemic embolism prevention, with no significant between-group difference in the risk of major bleeding overall. As a subset, the rate of gastrointestinal (GI) bleeding may be higher in patients on rivaroxaban compared to warfarin, but overall GI bleeding rates and mortality outcomes were low in both groups in this trial, around 0.4% of patients per year.[19] The rates of major GI bleeding were similar among the 3 largest trials for FXa agents in nonvalvular atrial fibrillation, which led to their FDA approval, but they cannot be compared directly since inclusion/exclusion criteria were different.

The EINSTEIN trial randomized patients with VTE to rivaroxaban or standard therapy, and reported similar rates of recurrence and bleeding outcomes for acute treatment.[20] There was a dose reduction for VTE treatment from 15 mg by mouth twice daily for 3 weeks down to 20 mg by mouth once daily. Continuing therapy with rivaroxaban beyond the acute treatment period resulted in rates of VTE recurrence and bleeding episodes similar to aspirin therapy. [21,22] Compared to placebo, there were fewer VTE recurrences and higher rates of bleeding.[21,22] Trials evaluating the effectiveness of rivaroxaban in comparison to dalteparin for cancer-related VTE found lower rates of recurrence but higher rates of clinically relevant nonmajor bleeding over 6 months.[23]

Apixaban

Apixaban was approved by the FDA in December 2012 for prevention of stroke in patients with nonvalvular atrial fibrillation as well as for VTE treatment. The ARISTOTLE trial, published in 2011, found that, for patients with atrial fibrillation, in addition to superiority in preventing stroke and systemic embolism, apixaban caused less bleeding and resulted in lower mortality than warfarin.[24] Dosing for atrial fibrillation is 5 mg by mouth twice daily. The dose should be reduced to 2.5 mg twice daily if a patient has any 2 of the following conditions: Age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL. The rate of major and minor hemorrhage was significantly lower in patients taking apixaban, with rates of major hemorrhage-related mortality halved at 30 days.[25,26]

When used for treatment of VTE, apixaban has similar efficacy to warfarin in preventing recurrence, but it is associated with less bleeding than warfarin.[27] Similar to rivaroxaban, a dose reduction occurs after initiation, from 10 mg by mouth twice daily down to 5 mg by mouth twice daily after the first 7 days of therapy. The association of polypharmacy with increased thromboembolic and hemorrhagic risks appears similar between warfarin and apixaban.[28] A randomized controlled trial of apixaban therapy after antiplatelet therapy in acute coronary syndromes (ACS) was stopped early (after 7392 patients were recruited) after increased rates of bleeding and no decrease in ischemic events were seen with apixaban.[29] Apixaban, compared to low-molecular-weight heparin (LMWH), resulted in higher bleeding rates without reducing VTE events when used for thromboprophylaxis in medically ill patients.[30]

Table 1. Comparison of Pharmacokinetics/Pharmacodynamics of Direct Oral Anticoagulant Agents

Agent	Trade Name	Mechanism	Dosing for NVAF[a]	Dosing for VTE[a]	Half-Life (hours)	Protein Binding (%)	Renal Excretion (%)
Dabigatran	Pradaxa®	Direct thrombin inhibitor	150 mg BID	150 mg BID after 5-10 days of parenteral anticoagulation	12-15	35	80
Rivaroxaban	Xarelto®	FXa inhibitor	25 mg once daily	15 mg BID for first 21 days, followed by 20 mg BID	6-9	94	66
Apixaban	Eliquis®	FXa inhibitor	5 mg BID[b]	10 mg BID for 7 days, followed by 5 mg BID	9-14	87	24-30
Edoxaban	Savaysa®	FXa inhibitor	60 mg once daily	60 mg once daily	10-14	55	50
Betrixaban	Bevyxxa®	FXa inhibitor	N/A	N/A	19-27	60	11

[a]Oral dosing noted is for patients with normal renal function. See the "Renal Impairment" section, page 11, for dosing adjustments for other groups.
[b]Reduce dose to 2.5 mg BID if any of the following: Age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL.

Abbreviations: BID, 2 times per day; FXa, factor Xa; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.

Edoxaban

Edoxaban received FDA approval in January 2015.[31,32] Approved indications for edoxaban are the same as the other FXa inhibitor agents, although 5 to 10 days of parenteral therapy is recommended prior to starting edoxaban for VTE treatment, similar to dabigatran. For VTE, edoxaban had similar levels of VTE recurrence, with fewer episodes of major bleeding, compared to warfarin at both a higher dose of 60 mg and a lower dose of 30 mg, which was used in patients with a estimated glomerular filtration rate (eGFR) < 50 mL/min or < 60 kg body weight.[32] Similar effects were also seen for stroke prevention with atrial fibrillation, also with lower risks of major bleeding at both the high and low doses.[31] Dosing for atrial fibrillation is 60 mg by mouth daily or 30 mg by mouth daily for patients with eGFR < 30 mL /min. Both of the major trials evaluating edoxaban therapy excluded patients with creatinine clearance (CrCl) < 30 mL/min. Edoxaban has also been studied for cancer-related DVT in comparison to LMWH, and a randomized controlled trial using a dose of 60 mg by mouth daily showed lower rates of VTE recurrence but higher rates of major bleeding compared to dalteparin.[33]

Betrixaban

Betrixaban is the latest of the FXa inhibitors to receive FDA approval, in June 2017. Data regarding management of betrixaban is more limited in comparison to the other agents in this class. Approved indications for betrixaban are limited to VTE prophylaxis in medically ill patients, based on a large randomized controlled trial comparing it to enoxaparin.[34] In this trial, with betrixaban, there was a reduced rate of VTE in the overall population but an equivalent rate of bleeding events. In a follow-up trial, continued dosing of betrixaban for 35 to 42 days reduced the risk of stroke in medically ill patients, compared to enoxaparin for 10 days (+/- 4 days), 0.54% versus 0.97%, but with an increase in the rate of major bleeding and clinically relevant nonmajor bleeding from 1.6% to 3.1%.[35] Given its more restricted indications (primarily for inpatients), betrixaban is less likely to be encountered by most emergency clinicians in usual practice, since long-term rehabilitation and skilled nursing facility patients are not considered to be at high risk for DVT/pulmonary embolism (PE) (compared to hospital inpatients), despite reduced physical activity, and they are not typically given prophylaxis for DVT/PE.

Prehospital Care

Limited prehospital studies have been performed relating specifically to DOACs. Given the increased risk for complications and the potential need for advanced surgical or hematological consultation, general principles of hemorrhage control and triage to an appropriate receiving facility are warranted. Emergency medical services (EMS) recognition of the patient's use of DOACs, including the name of the medication and the timing of the last dose taken, is a critical prerequisite for appropriate triage of these patients. A retrospective study found limited agreement between EMS reports with actual hospital records on current DOAC use in older patients with blunt head trauma.[36] EMS medical directors should incorporate education on DOACs into their curricula.

Emergency Department Evaluation

The initial evaluation of an anticoagulated patient begins with a directed history and physical examination. **(See Table 2.)** Emergency clinicians should make a particular effort to determine the name of the drug, the dosage taken, the time of administration of the last dose, and the indication for the anticoagulant. A patient's past medical history, including whether the patient has chronic kidney disease or end-stage renal disease, and other medications taken by the patient are also important. Hemorrhagic losses and volume status should be assessed, since this will determine the role of fluid and blood product administration.

The site of any bleeding guides the ED therapy. The location of a patient's pain, appearance of bruising on the skin, and the mechanism of any trauma should be elicited. A new headache, abnormal neurologic findings, or other signs or history of head trauma should prompt a workup for intracranial hemorrhage. A rectal examination should be per-

Table 2. Key Elements From the History and Physical Examination of Patients on Direct Oral Anticoagulant Agents

History

- Time and dose of last DOAC
- History of VTE, malignancy, hypercoagulable state
- Use of additional anticoagulants or antiplatelet agents
- Use of any nephrotoxins, particularly NSAIDs
- History of renal insufficiency
- Mechanism of trauma/estimated blood loss (if applicable)
- Time last seen well (if neurologic symptoms are present)

Physical Examination

- Vital signs
- Volume status (tachycardia, jugular venous pressure, mucous membranes)
- Site of bleeding and presence of active hemorrhage
- Presence of bruising or epistaxis
- Rectal examination
- Neurologic examination

Abbreviations: DOAC, direct oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs; VTE, venous thromboembolism.

www.ebmedicine.net

formed if GI bleeding is a possibility, since higher risks of GI bleeding can be seen with anticoagulated patients, including those on DOACs.[37] In at least one ED-based prospective observational study, 80% of patients presenting with major bleeding episodes while on dabigatran had a GI source of their hemorrhage.[37] Fecal occult blood testing may be used as an adjunct in this evaluation.

Diagnostic Studies

Imaging Studies

Computed Tomography

Guidelines and high-quality data for imaging workup of patients taking DOACs are lacking, and most studies are observational reports. Older recommendations for patients taking antiplatelet agents or warfarin have also been used to estimate risks of hemorrhage in this population. Imaging guidelines for low-risk trauma, such as the Canadian Computed Tomography (CT) Head Rule or the NEXUS criteria, are less accurate for anticoagulated patients.[38]

A low threshold for head imaging has been recommended in previous studies, even with minor head trauma, but follow-up imaging or admission of patients with negative CT scans of the head may present significant healthcare costs with limited yield of clinically important findings.[39-42] A single-center prospective observational cohort study of 1180 patients on either antiplatelet or anticoagulant medications, including 3% on rivaroxaban therapy, with an initial negative head CT found that only 7 patients (0.51%), of which 1 was on rivaroxaban, had a positive head CT 12 hours later, and 0 patients required surgical intervention.[43] A retrospective observational report of 156 patients suggested reduced mortality (4.9% vs 20.8%) in patients on a DOAC with traumatic intracranial hemorrhage compared to those taking warfarin, although this study did not assess medication adherence or control for the size of hemorrhage.[44] Given the difference in drug effects of DOACs in comparison to warfarin, more studies are needed to clarify outcomes after head trauma, including risks of delayed intracranial hemorrhage.

Until additional studies are performed, we believe that a low threshold for neuroimaging is appropriate in patients anticoagulated with DOACs following even minor head injury, as has been the approach for therapeutically anticoagulated patients in the past.[45] With positive radiologic findings or very high suspicion, we obtain repeat head imaging within 4 to 6 hours, in consultation with neurosurgical services, or earlier in cases of unexpected clinical decline.

Ultrasound

Trauma guidelines continue to recommend focused assessment with sonography for trauma (FAST) examination in the setting of blunt abdominal trauma where injury is suspected.[46] For anticoagulated patients following blunt abdominal trauma, guidelines for diagnostic testing should be followed as usual, but with an increased index of suspicion for bleeding complications and an awareness of the limitations of FAST for hemorrhage in certain sites (eg, retroperitoneal).[47] Once again, although high-quality evidence is lacking, observational data suggest reduced mortality (8.3% vs 29.5%) in abdominal trauma patients on DOACs compared to patients on warfarin.[48]

Laboratory Studies

General Testing

Results of hemoglobin and creatinine testing provide important data regarding hemorrhage rate and metabolism of anticoagulants in the system. Assessment of renal function is particularly important for agents reliant on renal excretion (primarily dabigatran, edoxaban, and rivaroxaban).[49] None of the DOACs inhibit platelet function, but testing of platelet quantity on complete blood cell (CBC) count remains an important part of all trauma evaluations, particularly if other antiplatelet agents may be in the system. Although studies have shown reduced qualitative platelet function after trauma, no consensus exists on the current clinical utility of platelet function testing in this setting.[50] Platelet function testing, if possible prior to platelet transfusion, has been recommended in patients who have aspirin-associated or ADP-inhibitor-associated intracranial hemorrhage who are undergoing a neurosurgical procedure.[51]

All of the tests of hemostasis described here are performed by most laboratories using blue-top (sodium citrate) tubes, the same as those used for prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) testing. Actual plasma concentration of DOACs may be measured by chromatography, but these levels do not necessarily correspond to bleeding outcomes, giving these tests limited utility outside research settings.[52]

Since one of the benefits of DOAC therapy is the lack of monitoring requirements, the indications for evaluating DOAC effect are limited, compared to warfarin, and include situations in which knowledge of the DOAC concentration or effect will guide clinical decision-making. Potential indications for quantitative assessment of DOAC level include treatment of life-threatening bleeding, development of VTE despite compliance with DOAC therapy, and treatment of patients at risk for bleeding because of overdose. In patients with a need for urgent or emergent surgical therapy, if the procedure cannot be delayed, assays in order to guide reversal may also be of benefit, or empiric reversal may be performed, depending on the clinical context. Given the short half-life of these agents, if invasive procedures can be delayed long enough for metabolism, anticoagulant assays could be deferred. For nonurgent

surgical procedures and non–life-threatening hemorrhage, waiting additional half-lives for metabolism to occur can also obviate the need for reversal of DOAC effect.

Prothrombin Time/ International Normalized Ratio and Partial Thromboplastin Time

Laboratory studies that are commonly used as proxies for efficacy of anticoagulation with warfarin and heparin are less useful for DOACs. Dabigatran may cause prolongation of either test, but overall correlation is poor between DOAC plasma concentration and PT, PTT, and INR levels.[53-55] In the absence of more specific tests (eg, thrombin time [TT] or ecarin clotting time [ECT]), PTT may be used to provide some estimate of the anticoagulant effect of dabigatran.[55] Similarly, the FXa inhibitors elevate PT in a weakly concentration-dependent manner, and this test may be helpful if anti-FXa level testing is unavailable.[54,55]

Nonetheless, the limitations of these conventional clotting tests for DOACs must be emphasized. Since the affinity of these agents for reagents in PT/INR testing varies, and since the anticoagulant effect of DOACs does not correlate linearly with INR values in the same way as VKAs, this test should not be used to quantify the anticoagulant effect of DOACs.[56] Given that the anticoagulant effect of DOACs at trough levels may be clinically significant, but that both PT/INR and PTT tests may be normal at these concentrations, neither test can be recommended to determine normal coagulation status.[57] Abnormalities on either test can suggest the presence of a DOAC, but values should not be interpreted as reliable measures of either therapeutic or supratherapeutic clinical anticoagulant effect.

Anti-Factor Xa Activity Levels

Chromogenic anti-FXa assays have been available for measurement of the effect of LMWHs for years, and they have proven useful for oral FXa inhibitors as well.[58,59] Direct measurement of the anti-FXa effect demonstrates a strong linear correlation with plasma concentrations of these agents, but the anticoagulant effect does not follow the same linear pattern.[31,60,61] Anti-FXa effect measurements that are calibrated specifically to oral FXa inhibitors (rather than heparin-based agents) may not be available at all treatment sites.

In trials, drug concentrations and anti-FXa levels have correlated with hemorrhagic and thrombotic outcomes, but monitoring is typically not recommended in patients on DOACs who do not have bleeding complications.[62] Long testing times and limited availability may also reduce the value of this test in an emergent setting. Normal anti-FXa levels have been interpreted as excluding significant anticoagulant effect of DOACs, except dabigatran.

Thrombin Time

Although TT is insensitive for FXa inhibitors, it shows good correlation with dabigatran concentration across normal ranges.[55] Even at therapeutic levels, however, TT may be elevated above the upper limit of this assay's detection, making it a poor predictor of overdose.[56,63] The dilute thrombin time (dTT) is more reliable for this purpose, since it correlates across a wider range of therapeutic concentrations. Availability of these tests may be limited outside tertiary referral centers, or results may not be available in timely fashion in community hospitals. A normal TT measurement can reliably exclude dabigatran presence.

Ecarin Clotting Time

Ecarin, an enzyme that cleaves prothrombin to an active intermediate that can be inhibited by dabigatran in the same way as thrombin, can be used to assess anticoagulant presence. The ECT demonstrates high accuracy for dabigatran concentration.[55,63] Currently, no therapeutic range based on ECT for anticoagulant effect exists, but a normal value could be used to exclude the presence of dabigatran.[56,64] ECT is not useful for testing presence of FXa inhibitors.

Treatment

General Principles

Resuscitation of a patient on a DOAC with potential bleeding complications proceeds regardless of the specific agent, with the exception of consideration of specific reversal agents. **(See the Clinical Pathway, page 10.)** Any patient on a DOAC should be assessed first for severity of their bleeding.[65] In patients with bleeding at a critical site (central nervous system, pericardium, airway, and other areas if it results in a critical illness), patients with hemodynamic instability, or in patients with clinically overt bleeding and either a hemoglobin decrease ≥ 2 g/dL or administration of ≥ 2 units packed red blood cells, bleeding should be considered major.[65] For those patients in whom bleeding is at critical sites or in whom continued bleeding may be life-threatening, then reversal agents should be administered in addition to standard care.

For all patients on DOACs with bleeding, standard practices for hemorrhage management, including site-specific bleeding control strategies and cessation of further anticoagulant administration, should be initiated as applicable. These practices include tourniquet application or direct pressure for bleeding at compressible sites, as well as intravenous proton-pump inhibitors for suspected upper GI bleeding. The effect on bleeding time of either kaolin-based products (which activate factor XII) or chitosan products (which act as a platelet scaffold) with DOACs remains unknown.[66,67] Further studies may clarify their role,

and they may prove useful in some settings.

A type and screen should be obtained if bleeding is a possibility, with cross-matched blood used, when available, in preference to type-specific or universal donor blood. Guidelines for transfusion of stable critically ill patents recommend red blood cell transfusion at restrictive hemoglobin levels of 7 g/dL unless patients are at increased risk for complications at this level.[68-71] Use of restrictive transfusion thresholds may avoid the risks of unnecessary transfusion, including infection, fluid overload, and adverse transfusion reactions. However, since unstable patients and those with active bleeding have hemoglobin levels that may not reflect their ongoing losses, these guidelines have more limited application for emergent resuscitation, and further studies are needed in this area. Desmopressin, although not evaluated in patients on DOACs, may be administered if qualitative platelet dysfunction is suspected.[72] No platelet transfusion triggers specifically for use in patients on DOACs have been evaluated, but guidelines generally recommend levels of 50×10^9 cells/L for surgery or trauma, and up to 100×10^9 cells/L for patients with intracerebral hemorrhage or those undergoing neuraxial surgery.[73]

With regard to overdose on DOACs, although dabigatran, rivaroxaban, and apixaban overdoses have all been reported, bleeding episodes in overdose appear to be rare, at 5% or less, based on case series.[74,75] Treatment decisions in overdose vary widely, but they include all options for reversal of specific agents, as well as conservative management in nonbleeding patients, with good outcomes reported despite laboratory abnormalities.[74,75]

Specific Reversal Agents

Idarucizumab

A specific reversal agent, idarucizumab (Praxbind®), received conditional approval by the FDA in October 2015 (with full approval April 2018) for reversal of dabigatran.[76,77] Idarucizumab is a humanized murine monoclonal antibody directed to dabigatran, delivered as two 2.5-g IV boluses, given 15 minutes apart, totaling 5 g. It reverses dabigatran up to the 99th percentile of levels measured in the RE-LY trial.[11,77] A study of this agent used emergently for GI bleeding and urgent procedures showed rapid and essentially complete reversal of dabigatran's effect, but more clinical outcome studies are needed. Guidelines for reversal of DOACs now recommend idarucizumab in major life-threatening bleeding events for patients on dabigatran.[78-80] Idarucizumab does not possess prothrombotic side effects, but any underlying clotting abnormality will be revealed by its use. Timeliness of DOAC reversal has not yet been shown to improve clinical outcomes, but the rapid reversal of DOACs in major hemorrhage is likely to be beneficial.

Coagulation Factor Xa (Recombinant), Inactivated-zhzo (Andexanet Alfa)

In May 2018, the FDA approved the first reversal agent for FXa inhibitors, called coagulation factor Xa (recombinant), inactivated-zhzo (brand name, Andexxa®; previously known as andexanet alfa or r-Antidote). Coagulation factor Xa is a recombinant FXa derivative that acts as a decoy receptor for the FXa agents, eliminating their anticoagulant effect.[81-83]

Coagulation factor Xa is administered as a "high-dose" infusion to reverse rivaroxaban doses > 10 mg or apixaban doses > 5 mg taken within the previous 8 hours, and also for unknown doses or unknown last time of administration of these agents. A "low-dose" infusion is used for known doses smaller than these amounts taken within the previous 8 hours, or for all known doses if last taken ≥ 8 hours before infusion. In a trial of 352 patients treated for major bleeding occurring within 18 hours of taking anti-FXa agents, treatment with coagulation factor Xa using a combination of IV bolus and 2-hour infusion was highly effective in normalizing anti-FXa levels.[81] Hemostasis was achieved in 82% of patients assessed at 12 hours, but thrombotic events were noted in 10% of patients at 30-day follow-up.

The effect of coagulation factor Xa may be limited outside of the time of continuous infusion, and there is a possibility for rebound of the measured anti-FXa level and anticoagulant effect. Change in anti-FXa level was not predictive of hemostatic efficacy in the overall population in this study.[81] No direct comparison of coagulation factor Xa to the nonspecific reversal agents has been conducted, and the cost per dose of this new reversal agent is substantial. Further studies with coagulation factor Xa to assess cost-effectiveness and mortality benefit are forthcoming, including a comparison of coagulation factor Xa with usual care to assess efficacy in acute intracranial hemorrhages (Clinical Trial NCT03661528).

Nonspecific Reversal Agents

Prothrombin Complex Concentrate

Prothrombin complex concentrate (PCC) has been recognized for decades as an FDA-approved rapid reversal agent for VKA-related hemorrhagic events, but data regarding its use off-label in DOACs are still emerging.[84,85] Both 3-factor and 4-factor PCC (3F-PCC and 4F-PCC) have been made available in the United States for anticoagulant reversal. 3F-PCC is marketed in the United States as Profilnine® SD and contains factors II, IX, and X as well as trace amounts of factor VII. 4F-PCC, marketed as Kcentra® (Octaplex®/Beriplex® outside of the United States), contains purified factor VII in addition to II, IX, and X, as well as the anticoagulant proteins C and S. Most PCC products contain some heparin and so cannot be used in patients with a history of

heparin-induced thrombocytopenia.

For FXa inhibitors, administration of 4F-PCC has been shown to be effective at normalizing PT abnormalities and bleeding times in healthy volunteers, as well as achieving effective bleeding control in patients on rivaroxaban, apixaban, and edoxaban who have active major bleeding events.[53,86,87] The proposed mechanism for reversal of anticoagulant effect of the FXa inhibitors using PCC is overwhelming of the inhibitor agent by increased concentration of upstream clotting factors.[53]

A cohort study of 64 patients on anticoagulants (including 3 using rivaroxaban) demonstrated superiority of 4F-PCC to 3F-PCC for normalization of INR.[86,88] In a comparison of 4F-PCC and 3F-PCC for healthy volunteers, a single dose of 50 factor IX units/kg of 4F-PCC was more effective than 3F-PCC at reversing PT prolongation caused by rivaroxaban.[89] Fixed-dose PCC has become a topic of increasing interest, since studies of this strategy suggest that it may decrease time to medication administration, as well as costs of reversal.[90] Since this strategy has not been evaluated for DOACs specifically, protocols should be developed locally, in conjunction with pharmacy and hematology guidance.

In guidelines for management of FXa-inhibitor-induced bleeding, 4F-PCC is recommended over 3F-PCC, if available.[70,80] Two cohort studies, with 84 and 66 patients, of 4F-PCC for treatment of FXa-inhibitor-associated hemorrhage have estimated the effectiveness of 4F-PCC at 69% and 65%, respectively.[86,88] A randomized controlled trial evaluating the effect of 4F-PCC on dabigatran, conversely, showed no improvement in the PTT, ECT, or TT in healthy volunteers.[53] Given this evidence, 4F-PCC has become an agent of choice in the rapid reversal of anticoagulation in patients on FXa inhibitors with major bleeding.

Activated PCC (Factor VIII Inhibitor Bypassing Activity)

Activated PCC (aPCC), also known as FEIBA® (anti-inhibitor coagulant complex), is a 4F-PCC with the modification of activated factor VII. It is named for its role in reversing bleeding in hemophiliac patients with factor VIII inhibitors. Studies supporting the use of aPCC in DOAC-induced bleeding are poor in quality, with 1 case series of 6 patients with intracerebral hemorrhage using aPCC reversal having no cases of hematoma expansion, and 1 study in 10 healthy volunteers, showing reversal of coagulopathy as seen in laboratory assessment of dabigatran and rivaroxaban.[91,92] For dabigatran, aPCC may be more effective than typical 4F-PCC, as suggested by in vitro studies.[93] Given its limited evidence base, aPCC is not considered to be first-line over 4F-PCC in the reversal of any DOAC, but it may be used if other PCCs are not available. Dosing is the same as for 4F-PCC.

Recombinant Factor VIIa (rFVIIa)

Recombinant factor VIIa (rFVIIa, marketed in the United States as NovoSeven®) activates factors IX and X, resulting in a rapid increase in thrombin.[94,95] Although limited data suggest that rFVIIa may reverse the effect of dabigatran by causing overwhelming thrombin generation, it has also been associated with a higher risk of thrombosis development in comparison to PCC, since it lacks any balancing anticoagulant factors (eg, protein C or S).[91] rFVIIa should not be considered first-line for reversal if any of the other agents is available.

Fresh-Frozen Plasma

Generally speaking, fresh-frozen plasma (FFP) is not recommended for reversal of either class of DOAC. A murine model suggested inconsistent improvement on dabigatran effect after FFP transfusion, and a single case report on dabigatran-related bleeding also did not find benefit from FFP.[96,97] Likewise, the volume of FFP required to reverse the effect of the FXa inhibitors is likely to be prohibitive, although studies on this point are lacking.[78] Nonetheless, plasma resuscitation should always be considered as part of balanced resuscitation with increased platelet and plasma ratios in the setting of a massive transfusion, as supported by recent randomized controlled trials.[98]

Adjunct Therapies

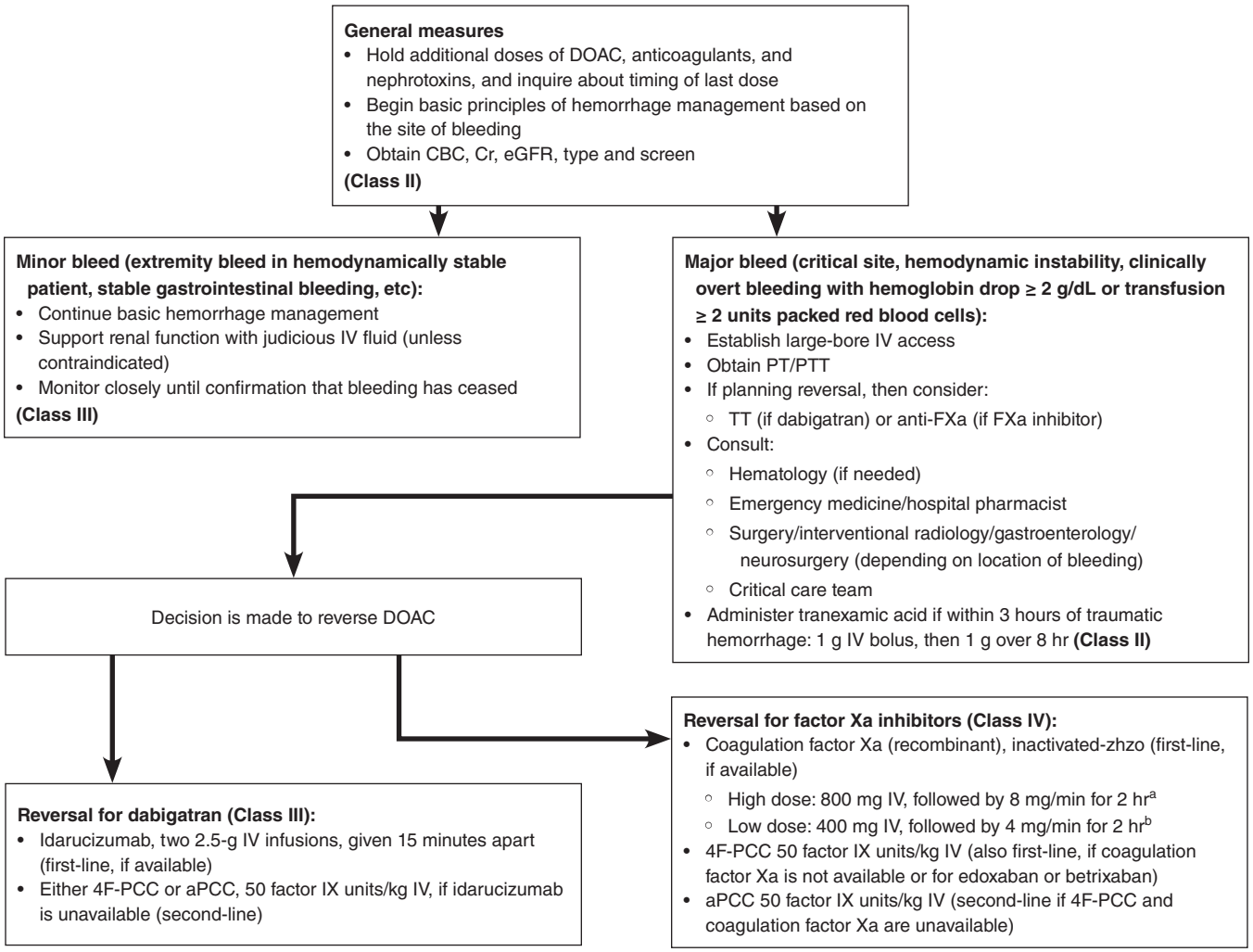
Activated Charcoal for Oral Agents

Limited weak data exist suggesting a beneficial effect of activated charcoal in the removal of recently ingested doses of dabigatran and apixaban, with similar theoretical benefits, but there are no published data for other FXa inhibitors.[99,100] Recommendations from the Thrombosis and Hemostasis Summit of North America published in 2012 advocated for the use of activated charcoal for recent (< 2 hour) ingestions of DOACs, but the 2016 update of these recommendations does not address charcoal use.[49,101]

Tranexamic Acid

Tranexamic acid (TXA) is a synthetic lysine analogue that has antifibrinolytic activity through reversible binding of plasmin. A randomized controlled trial of more than 20,000 patients (CRASH-2) suggested reduced mortality with administration following trauma, if given within 3 hours.[102,103] No studies have evaluated the benefit of TXA after trauma or major hemorrhage specifically in the setting of DOAC effect, but a case-control study and a randomized controlled trial in the perioperative setting showed reduced transfusion requirements when TXA was given following orthopedic surgery in patients on rivaroxaban for VTE prophylaxis.[104,105] We do not recommend modification of standard trauma guidelines regarding TXA usage in patients who are on DOACs.

Clinical Pathway for Management of Hemorrhage in Patients Taking Direct Oral Anticoagulant Agents



[a]Dose for rivaroxaban doses > 10 mg or apixaban doses > 5 mg taken within previous 8 hr, and also for unknown doses or unknown last time of administration of these agents.

[b]Dose for rivaroxaban doses ≤ 10 mg or apixaban doses ≤ 5 mg taken within the previous 8 hr, or for all known doses if last taken > 8 hr before infusion.

Note: Fresh-frozen plasma is unlikely to be effective for either DOAC class.

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; CBC, complete blood cell (count); Cr, creatinine; eGFR, estimated glomerular filtration rate; IV, intravenous; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time.

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Vitamin K

There are no data to support the routine use of vitamin K with DOACs, due to differences in the mechanism of action as well as the long time to effect of vitamin K when compared to the short half-life of the DOACs.

Hematology Consultation/Transfer

Given the time-sensitive nature of bleeding, the decision to reverse a DOAC with specific agents should be considered to be within the scope of practice for emergency physicians. While consultant support structures provide valuable recommendations for complex cases, reliance on emergent hematology consultation can delay treatment in life-threatening situations. We recommend that hematology experts be involved in the development of institutional reversal policies for implementation in the ED setting. In the setting where a facility lacks access to appropriate specific reversal agents or subspecialty teams capable of treating a major hemorrhage, consideration should be given to patient transfer after initial efforts at stabilization.

Special Circumstances/Populations

Patients With Valvular Disease

Patients with mechanical heart valves were excluded from the major DOAC trials, and a trial of dabigatran in mechanical heart valves was stopped early due to unacceptable bleeding and thromboembolic complications in the dabigatran group.[78,106] The American College of Cardiology guidelines state that DOAC use is reasonable in patients with atrial fibrillation and native valve disease.[107,108]

Pregnant, Breastfeeding, and Pediatric Patients

Package inserts for all the DOACs urge caution with use among pregnant patients, breastfeeding patients, and children.[78] A case series of 233 pregnancies that occurred among patients taking a DOAC reported high rates of miscarriage and elective termination, but low rates of embyropathy.[109]

Patients With Renal Impairment

All of the DOACs require some degree of renal elimination, and therefore their use in patients with low GFR must be cautioned. Current guidelines from the Anticoagulation Forum recommend avoiding use of dabigatran and rivaroxaban for patients with CrCl < 30 mL/min, and avoiding the use of edoxaban and betrixaban with CrCl < 15 mL/min.[78] Although patients with reduced renal function in the ROCKET-AF trial did not have worse outcomes with rivaroxaban compared to warfarin, a dose adjustment from 20 mg/day to 15 mg/day was used for patients with CrCl of 30 to 49 mL/min.[18,110] Patients with renal failure in all groups of ROCKET-AF had higher rates of both bleeding and stroke that did not differ between treatment group.[111] RE-LY excluded patients with CrCl < 30 mL/min from evaluation of dabigatran's effect.[11] Edoxaban dosing in patients with renal dysfunction is halved.[31,78] Apixaban, with relatively lower renal clearance, has been used more often in patients with end-stage renal disease, and a retrospective cohort did not suggest worsened bleeding rates compared to warfarin.[24,112] Apixaban dosing adjustments are noted in the "Apixaban"section on page 4.

A 2017 Cochrane review found similar efficacy, without increased risk of major bleeding, using DOACs in patients with eGFR > 30 mL/min (chronic kidney disease stages 3b or better) compared to patients with normal renal function. They found limited evidence for safety below this eGFR level.[113] Decisions to reverse the anticoagulant effect of DOACs in the setting of major bleeding should not be different in patients with low eGFR or end-stage renal disease.

Controversies and Cutting Edge

Treatment of Ischemic Stroke in Patients Taking Direct Oral Anticoagulants

In cases of acute ischemic stroke in patients on DOACs, the safety and efficacy of IV thrombolysis with recombinant tissue plasminogen activator (rt-PA) or endovascular therapy continues to be debated. Although DOACs reduce the risk of stroke in patients with atrial fibrillation, the rate of stroke with DOACs in large trials is approximately 1.2% per year.[11,24]

Current guidelines do not recommend administration of rt-PA if it is < 48 hours since last DOAC use, unless laboratory testing specific to these agents shows normal results.[114] The AHA suggests that INR and aPTT be normal in all cases, and that ECT and TT be tested for dabigatran, with calibrated anti-FXa level testing for the FXa inhibitors. AHA registry data including 251 patients who received rt-PA while taking DOACs, as well as cohort analysis of 26 ROCKET-AF trial patients, suggest that the risk of intracranial hemorrhage is similar both to patients on warfarin with INR < 1.7 and to patients not on any anticoagulation who are given rt-PA.[115,116] For the 3 groups in the trial (taking DOACs, on warfarin with low INR, and not taking an anticoagulant), rates of symptomatic intracranial hemorrhage after rt-PA in the AHA Stroke Registry were 4.8%, 4.9%, and 3.9%, respectively, for these 3 groups.[116] Given the retrospective nature of this data, we cannot exclude the possibility of increased risk of adverse events with rt-PA administration in patients on DOACs.

Likewise, although endovascular thrombectomy has become a cornerstone of stroke therapy, the major trials of this technology did not include large numbers of patients on DOACs.[117] An observational study of 28 patients on DOACs who received endovascular therapy found intracranial hemorrhage in 13 patients (46%), although only 1 (4%) was symptomatic, with the study concluding that this therapy is safe but requires further study.[117]

These results indicate that, in consultation with the stroke team, IV thrombolysis or endovascular thrombectomy may still be considered in select patients on DOACs, although shared decision-making must be undertaken to ensure that the patient and family understand the risks.

Scoring Systems for Bleeding Risk

The HAS-BLED score has been used since 2010 to determine bleeding risk in patients with atrial fibrillation, but it is designed for patients taking warfarin and includes assessment of INR lability and time in therapeutic range for VKAs.[118,119] The ORBIT score was validated in a cohort that included patients on DOACs and is similarly easy to use, but it does not include reference to INR values.[120] Although another score, the ABC score, has demonstrated slightly better prediction characteristics for bleeding risk, its requirement for biomarker measurements, including high-sensitivity troponin and GDF-15, significantly limits its practical value.[121] To assess bleeding risks quantitatively, we recommend either the ORBIT or HAS-BLED score, in conjunction with clinical history, be used in patients with atrial fibrillation or VTE who are starting DOACs in the ED **(See Table 3.)**

Using the ORBIT score, totals of 0 to 2 are considered low bleeding risk, with an estimated 2.4 bleeds per 100 patient-years. A score of 3 on ORBIT is medium risk, with 4.7 bleeds per 100 patient-years, and alternatives may be considered at this level or above.

For the HAS-BLED score, a score of 0 or 1 is low risk, with rates < 1.13 bleeds per 100 patient-years. A score of 2 reflects moderate bleeding risk (1.88 bleeds per 100 patient-years), and anticoagulation alternatives should be considered with scores > 2.

Hemodialysis for Dabigatran Removal

Multiple small case series have described successful removal of dabigatran from circulation using hemodialysis.[122] Extracorporeal removal of dabigatran is effective, given its small size and low protein binding; however, for FXa inhibitors, the higher protein binding would not be amenable to removal via the same method, and no studies have been published using dialysis for removal of FXa inhibitors. Intermittent hemodialysis may reduce the half-life of dabigatran to < 4 hours, and intermittent hemodialysis is more efficient than continuous renal replacement therapy for this purpose. Dialysis catheters should be placed in compressible locations in case bleeding occurs during the procedure. Now that a specific reversal agent has been approved for

Online tools for assessing bleeding risk are available at www.MDCalc.com:

- ORBIT: www.mdcalc.com/orbit-bleeding-risk-score-atrial-fibrillation
- HAS-BLED: www.mdcalc.com/has-bled-score-major-bleeding-risk

Table 3. Scoring Systems for Bleeding Risk

ORBIT[120]		**HAS-BLED[119]**	
Variable	**Points**	**Variable**	**Points**
Older age (> 74 years)	1	Elderly (age > 65 years)	1
Reduced hemoglobin (< 13 mg/dL for men, < 12 mg/dL for women)	2	Labile INR (or time in therapeutic range < 60%)	1
Bleeding history	2	Bleeding (history or predisposition)	1
Insufficient kidney function (GFR < 60 mL/min/1.73m^2)	1	Renal disease (dialysis, transplant, Cr > 2.26 mg/dL)	1
Treatment with antiplatelet therapy	1	Antiplatelet or NSAID therapy	1
		Stroke history	1
		Hypertension (uncontrolled, > 160 mm Hg SBP)	1
		Liver disease (cirrhosis or bilirubin > 2x normal with AST/ALT/ALP > 3x normal)	1
		Drug use or alcohol use ≥ 8 drinks/week	1

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; Cr, creatinine; GFR, glomerular filtration rate; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INR, elderly, drug/alcohol usage; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; ORBIT, older, reduced hemoglobin, bleeding history, insufficient kidney function, treatment with antiplatelets; SBP, systolic blood pressure.

dabigatran, the role of hemodialysis for overdose may be limited.

Viscoelastic Testing

Some of the more specific tests for anticoagulant activity of the DOACs may provide delayed results that limit their utility in the ED. Viscoelastic testing, including thromboelastography (TEG) and rotational thromboelastometry (ROTEM) tests, has been used as a point-of-care assay to evaluate for coagulopathy in trauma patients and to guide resuscitation.[123,124] Several studies have examined the utility of viscoelastic testing to detect presence of DOACs, with varying results.[55,125-128] Overall, prolongation of clotting time on ROTEM and R time on TEG appear to correlate with concentration, but these tests have not emerged as a gold standard to determine anticoagulant effect of DOACs. In some cases, normal, or even paradoxically hypercoagulable patterns, may emerge on viscoelastic testing.[127]

Ciraparantag

A new type of "universal" anticoagulant reversal agent, ciraparantag (PER977, aripazine) remains under investigation but has a potential role in the reversal of all DOACs (DTI and FXa inhibitors) as well as LMWH and unfractionated heparin.[129] This agent binds and inactivates all of these agents and does not appear to have a procoagulant effect. Clinical trials have shown rapid and durable reversal of edoxaban effect, but further trials as well as FDA approval are needed for this agent.[130,131]

Disposition

Patients Currently Taking Direct Oral Anticoagulants

There remains no high-quality evidence to guide disposition decisions regarding patients on DOACs after evaluation for trauma or a potential bleeding episode in the ED. A checklist has been proposed for inpatients starting these medications to enhance safety.[78] Patients considered for discharge should be reliable for follow-up or have caretakers to monitor them, have no worsening of renal or hepatic function from baseline, and be without major short-term risk of hemorrhagic event. We recommend that all patients who receive pharmacological reversal of coagulopathy for major bleeding be admitted to the hospital, with strong consideration of intensive care unit placement if bleeding and coagulopathy are not definitively controlled.

Emergency Department Initiation of Direct Oral Anticoagulants

For patients with newly diagnosed VTE or atrial fibrillation who require anticoagulation, consideration should be given to DOAC initiation in the ED. Patients with an elevated CHA_2DS_2-VASc score ≥ 1 in a man or ≥ 2 in a woman can start maintenance therapy, without bridging, using a DOAC that is the preferred therapy for nonvalvular atrial fibrillation in eligible patients.[118] In new cases of atrial fibrillation, initiation of anticoagulation in the ED was evaluated in a prospective cohort of 1162 patients, and it demonstrated reduced mortality and no increased risk of bleeding, although only 7.8% of patients received DOACs in that study.[132]

For patients with VTE, both dabigatran and edoxaban can be started following 5 days of anticoagulation with heparin or LMWH, but apixaban or rivaroxaban may be started without bridging therapy.[14,20,27,31,32] Case control and prospective cohort studies of this practice, comparing rivaroxaban to LMWH-warfarin for treatment of VTE have suggested the potential for cost savings with low risk of hemorrhagic complications.[133,134]

The American College of Emergency Physicians (ACEP) Clinical Policy on acute VTE, published in May 2017, endorses the option of initiating treatment in the ED for VTE, with discharge the same day for low-risk patients, with a Level C recommendation.[135] Both the American Thoracic Society (ATS) and British Thoracic Society (BTS) also suggest consideration of home treatment of PE and DVT in select patients (ATS, Grade 2B; BTS, Grade B).[49,136] The ACEP policy and ATS/BTS guidelines recommend either the PESI (pulmonary embolism severity index), simplified PESI, or Hestia criteria be used to risk stratify patients with PE to a low-risk group that is appropriate for discharge.[137-139] Although the degree of clot burden, presence of right ventricular dysfunction on imaging, and troponin and brain natriuretic peptide measurements have been discussed as possible additions, none of these are currently included in these risk stratification tools.

The trials evaluating outpatient treatment of PE have significant heterogeneity regarding recruitment practices, exclusion criteria, and anticoagulation regimens, and most older trials used LMWH/VKA regimens for their outpatient therapy. An open-label trial randomized 114 low-risk patients (by the Hestia criteria) to treatment with rivaroxaban with early discharge or to standard of care, finding reduction of hospital days and costs with discharge, but otherwise similar outcomes.[140] When considering discharge of patients with newly diagnosed PE/DVT in addition to the use of a scoring system to assess risk, we suggest performing shared decision-making with the patient regarding risks of this therapy. Development of institutional policies that ensure rapid outpatient follow-up and availability of support should also contribute to the safety of an outpatient disposition.

Since no high-quality comparison studies have been undertaken between DOAC agents, no strong recommendation for choosing a particular

medication can be given at this time. Patient insurance, drug costs, dosing schedule (either once daily or twice daily), hospital formulary options, and primary caregiver preferences should all factor into prescription choice. VKAs can also be discussed as an option for patients and clinicians who feel more comfortable using warfarin, since they have the longest record of clinical use and the most data regarding safety outcomes and monitoring. Warfarin may also be less expensive than DOACs in some cases, although quality of life considerations and costs of monitoring should be considered when discussing options with patients. Pharmacy, case management, and social work consultants may help with options for patients who would be suited for DOACs but find the cost prohibitive.

Based on very low-quality evidence, consideration may be given to starting either apixaban or edoxaban for patients with higher risks for bleeding.[118] In a large Danish observational cohort following patients with atrial fibrillation up to 4 years, apixaban had lower adjusted rates of 30-day and total major bleeding, defined by hospitalization, compared to rivaroxaban or dabigatran.[141] In a retrospective cohort study of patients with atrial fibrillation in a United States insurance database, both apixaban and dabigatran had lower risks of major bleeding, with apixaban also having lower risk of stroke.[142] Neither study included edoxaban, which had low rates of bleeding in comparison to warfarin in clinical trials, and further studies are needed to determine risks for edoxaban during expanded clinical use. Both of these studies used statistical adjustment to match patients on different agents, and caution should be applied in interpreting these findings causally.

Risk Management Pitfalls for Patients Taking Direct Oral Anticoagulant Agents

1. **"The patient denied taking warfarin or enoxaparin for his DVT, but we didn't ask about other anticoagulants."**
   DOACs are now being prescribed frequently, and patients should be questioned specifically about these medications if they have a condition that indicates they might be using them.

2. **"The patient had a totally normal neurological exam after her head trauma, so I didn't order any imaging."**
   Patients on anticoagulants have increased risk of intracranial and intracerebral hemorrhage, and they can rapidly worsen without treatment.

3. **"We gave FFP for reversal of the dabigatran, but it didn't seem to help."**
   FFP is ineffective for reversal of a DTI such as dabigatran, but a specific antidote, idarucizumab, does exist.

4. **"Getting the reversal agent took hours for the consultants to approve, and the patient deteriorated in that time."**
   Having prewritten protocols can help to speed and clarify reversal procedures for DOACs.

5. **"The INR was below 2.0, so I didn't think the anticoagulation effect was present."**
   Standard coagulation testing is insensitive for evaluating DOAC anticoagulant effect, and even normal results can be present, despite therapeutic levels of medication.

6. **"The patient kept taking his regular dose of dabigatran, even after he started missing dialysis sessions – why did he bleed?"**
   All of the DOACs are renally cleared, and with a low GFR, anticoagulation effects may be unpredictable.

7. **"The patient described being lightheaded, but she never mentioned her melena."**
   Patients on anticoagulants are at higher risk of GI bleeding.

8. **"I called nephrology to ask about dialysis for the rivaroxaban overdose, but they were very unhelpful."**
   FXa inhibitors are not removed by hemodialysis, although dabigatran can be, since it has lower protein binding.

9. **"I didn't think the patient would be at risk of clotting after DOAC reversal."**
   Reversing DOACs can put patients at higher risk of new thrombosis, and discussion of the risks and benefits of reversal should be documented, if possible.

10. **"He denied taking warfarin before he got stroke thrombolysis, but we only found out about the DOAC after his subsequent intracranial hemorrhage."**
    Safety of thrombolysis while taking DOACs remains in question, and rt-PA use in this setting remains controversial. Neurology consultants may be beneficial in these cases to direct therapy.

Summary

Frequency of DOAC use in the population is increasing, and knowledge of the risks and reversal strategies for these agents has now become essential for emergency clinicians. These medications have distinct advantages for both patients and providers in the management of anticoagulation, since they do not require monitoring as frequently and have relatively short half-lives, but evaluating their anticoagulant effect in the ED remains complex. Since the last review on this topic, additional information regarding the longer-term outcomes with DOACs has emerged, and specific reversal strategies are now available. However, the treatment of bleeding episodes on DOACs continues to evolve, based on the costs and benefits of these agents. Familiarity with the newer reversal agents should accompany their increased availability within the community.

For now, hospital guidelines for anticoagulant reversal should follow traditional strategies for general hemorrhage management and prevention of ongoing bleeding, while specifying instances where specific reversal agents, such as PCC and possibly coagulation factor Xa (recombinant) for FXa inhibitors, plus idarucizumab for dabigatran, should be included. A collaborative and multidisciplinary approach to managing DOAC complications should also be the goal.

Time- And Cost-Effective Strategies

- Establishing protocols for rapid PCC administration, including consideration of fixed-dose PCC in conjunction with hematology consultants, can expedite administration of reversal agents.
- Choosing a DOAC over VKA for newly diagnosed VTE may allow for safe discharge with a reduced risk for bleeding complications.
- Using specific and effective reversal agents (eg, idarucizumab) may improve outcomes over nonspecific agents, such as PCC or factor VII.
- Limiting DOAC-specific testing to situations with major bleeding risk or possible indications for reversal agents can save laboratory resources.

Case Conclusions

Your first patient on apixaban with traumatic subdural hematoma received initial resuscitation focusing on maintenance of the airway, breathing, and circulation, as appropriate for head trauma. After reviewing your hospital's policy on DOAC reversal and local availability of specific reversal agents for this DOAC, you administered a dose of 4-factor PCC at 50 units/kg in the ED. He was admitted to the neurosurgical ICU for continued care, and a repeat CT of the head showed no interval expansion of the hemorrhage.

The patient with the intentional overdose of multiple medications underwent similar stabilization, and labs were sent, including thrombin time, to evaluate for the effect of dabigatran. The results were elevated, and a toxicology consult was called. Use of idarucizumab as a specific antidote was considered, but because there was no active bleeding, the patient was observed in the ICU with frequent neurological checks. The patient recovered and went on to receive further psychiatric care.

Your last patient with the DVT underwent a full lab evaluation to determine the best treatment for his thrombus. His renal and hepatic function were both normal, so you prescribed rivaroxaban 15 mg twice daily for treatment of the clot, with the first dose starting today. The patient was at low risk for adverse events, so after engaging in shared decision-making with the patient and discussion with his PCP, you discharged him from the ED for follow-up with his PCP in the next 2 days.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

1. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. *Am J Health Syst Pharm.* 2017;74(16):1237-1244. **(Cross-sectional longitudinal analysis)**
2. Barnes GD, Lucas E, Alexander GC, et al. National trends in ambulatory oral anticoagulant use. *Am J Med.* 2015;128(12):1300-1305. **(Review of national outpatient database)**
3. van den Heuvel JM, Hovels AM, Buller HR, et al. NOACs replace VKA as preferred oral anticoagulant among new patients: a drug utilization study in 560 pharmacies in the Netherlands. *Thromb J.* 2018;16:7. **(Prescription review of 247,927 patients)**
4. Barnes GD, Ageno W, Ansell J, et al. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. *J Thromb Haemost.* 2015;13(6):1154-1156. **(Recommendation statements)**
5. Hirsh J, Fuster V, Ansell J, et al. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation.* 2003;107(12):1692-1711. **(Guidelines)**
6. Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis: role of the direct oral anticoagulants. *Circ Res.* 2016;118(9):1409-1424. **(Review)**
7. Li A, Garcia DA, Lyman GH, et al. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. *Thromb Res.* 2019;173:158-163. **(Meta-analysis; 15 articles, 2 randomized controlled trials)**
8. Montiel FS, Ghazvinian R, Gottsäter A, et al. Treatment with direct oral anticoagulants in patients with upper extremity deep vein thrombosis. *Thromb J.* 2017;15:26. **(Registry analysis; 83 patients)**
9. Nery F, Valadares D, Morais S, et al. Efficacy and safety of direct-acting oral anticoagulants use in acute portal vein thrombosis unrelated to cirrhosis. *Gastroenterol Res.* 2017;10(2):141-143. **(Case report; 1 patient)**
10. Andreas M, Moayedifar R, Wieselthaler G, et al. Increased thromboembolic events with dabigatran compared with vitamin K antagonism in left ventricular assist device patients: a randomized controlled pilot trial. *Circ Heart Fail.* 2017;10(5). **(Randomized controlled trial; 30 patients)**
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. **(Randomized controlled trial; 18,113 patients)**
12. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation*. 2013;128(3):237-243. **(Randomized controlled trial; 5851 patients)**
13. Hart RG, Diener H-C, Yang S, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. *Stroke.* 2012;43(6):1511-1517. **(Randomized controlled trial; 18,113 patients)**
14.* Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352. **(Randomized controlled trial; 2539 patients)**
15. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772. **(Randomized controlled trial; 2589 patients)**
16. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med.* 2013;368(8):709-718. **(Randomized controlled trial; 2856 patients)**
17. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation.* 2014;129(18):1850-1859. **(Randomized controlled trial; 14,286 patients)**
18.* Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891. **(Randomized controlled trial; 14,264 patients)**
19. Sherwood MW, Nessel CC, Hellkamp AS, et al. Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF trial. *J Am Coll Cardiol.* 2015;66(21):2271-2281. **(Randomized controlled trial; 14,286 patients)**
20. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510. **(Randomized controlled trial; 3449 patients)**
21. EINSTEIN-PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297. **(Randomized controlled trial; 4832 patients)**
22. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med.* 2017;376(13):1211-1222. **(Randomized controlled trial; 3396 patients)**
23. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol.* 2018;36(20):2017-2023. **(Randomized controlled trial; 203 patients)**
24.* Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. **(Randomized controlled trial; 18,201 patients)**
25. Hylek EM, Held C, Alexander JH, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE trial (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation): predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol.* 2014;63(20):2141-2147. **(Randomized controlled trial; 18,140 patients)**
26. Bahit MC, Lopes RD, Wojdyla DM, et al. Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. *Heart.* 2017;103(8):623-628. **(Randomized controlled trial; 18,140 patients)**
27. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.*

2013;369(9):799-808. **(Randomized controlled trial; 5395 patients)**
28. Jaspers Focks J, Brouwer MA, Wojdyla DM, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ.* 2016;353:i2868. **(Randomized controlled trial; 18,140 patients)**
29. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med.* 2011;365(8):699-708. **(Randomized controlled trial; 7392 patients)**
30. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med.* 2011;365(23):2167-2177. **(Randomized controlled trial; 6528 patients)**
31.* Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104. **(Randomized controlled trial; 21,105 patients)**
32. Hokusai VTEI, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415. **(Randomized controlled trial; 4921 patients)**
33. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378(7):615-624. **(Open-label randomized controlled trial; 1050 patients)**
34.* Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med.* 2016;375(6):534-544. **(Randomized controlled trial; 7513 patients)**
35. Gibson CM, Chi G, Halaby R, et al. Extended-duration betrixaban reduces the risk of stroke versus standard-dose enoxaparin among hospitalized medically ill patients: an APEX trial substudy (Acute medically ill venous thromboembolism Prevention with Extended duration betrixaban). *Circulation.* 2017;135(7):648-655. **(Randomized controlled trial; 7513 patients)**
36. Nishijima DK, Gaona S, Waechter T, et al. Do EMS providers accurately ascertain anticoagulant and antiplatelet use in older adults with head trauma? *Prehosp Emerg Care.* 2017;21(2):209-215. **(Retrospective cohort; 2110 patients)**
37. Berger R, Salhanick SD, Chase M, et al. Hemorrhagic complications in emergency department patients who are receiving dabigatran compared with warfarin. *Ann Emerg Med.* 2013;61(4):475-479. **(Prospective observational study; 138 patients)**
38. Nishijima DK, Offerman SR, Ballard DW, et al. Risk of traumatic intracranial hemorrhage in patients with head injury and preinjury warfarin or clopidogrel use. *Acad Emerg Med.* 2013;20(2):140-145. **(Prospective cohort; 982 patients)**
39. Shah KH, Newman DH, Raja AS. Repeated CTs-let's use our heads. *Ann Emerg Med.* 2012;60(4):537-538; author reply 538. **(Letter)**
40. Menditto VG, Lucci M, Polonara S, et al. Management of minor head injury in patients receiving oral anticoagulant therapy: a prospective study of a 24-hour observation protocol. *Ann Emerg Med.* 2012;59(6):451-455. **(Prospective case series; 97 patients)**
41. Li J. Admit all anticoagulated head-injured patients? A million dollars versus your dime. You make the call. *Ann Emerg Med.* 2012;59(6):457-459. **(Editorial)**
42. Nishijima DK, Offerman SR, Ballard DW, et al. Immediate and delayed traumatic intracranial hemorrhage in patients with head trauma and preinjury warfarin or clopidogrel use. *Ann Emerg Med.* 2012;59(6):460-468. **(Prospective cohort; 1064 patients)**
43. Bauman ZM, Ruggero JM, Squindo S, et al. Repeat head CT? Not necessary for patients with a negative initial head CT on anticoagulation or antiplatelet therapy suffering low-altitude falls. *Am Surg.* 2017;83(5):429-435. **(Prospective observational analysis; 1180 patients)**
44. Feeney JM, Santone E, DiFiori M, et al. Compared to warfarin, direct oral anticoagulants are associated with lower mortality in patients with blunt traumatic intracranial hemorrhage: a TQIP study. *J Trauma Acute Care Surg.* 2016;81(5):843-848. **(Registry retrospective analysis)**
45. Jagoda AS, Bazarian JJ, Bruns JJ, et al. Clinical policy: neuroimaging and decisionmaking in adult mild traumatic brain injury in the acute setting. *Ann Emerg Med.* 2008;52(6):714-748. **(Clinical policy)**
46. Hoff WS, Holevar M, Nagy KK, et al. Practice management guidelines for the evaluation of blunt abdominal trauma: the East Practice Management Guidelines Work Group. *J Trauma.* 2002;53(3):602-615. **(Guidelines statement)**
47. Sunga KL, Bellolio MF, Gilmore RM, et al. Spontaneous retroperitoneal hematoma: etiology, characteristics, management, and outcome. *J Emerg Med.* 2012;43(2):e157-e161. **(Prospective cohort; 346 patients)**
48. Feeney JM, Neulander M, DiFiori M, et al. Direct oral anticoagulants compared with warfarin in patients with severe blunt trauma. *Injury.* 2017;48(1):47-50. **(Retrospective trauma registry analysis)**
49.* Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest.* 2016;149(2):315-352. **(Guidelines statement)**
50. Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. *J Trauma Acute Care Surg.* 2012;73(1):13-19. **(Prospective study; 101 patients)**
51. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: executive summary. A statement for healthcare professionals from the Neurocritical Care Society and the Society of Critical Care Medicine. *Crit Care Med.* 2016;44(12):2251-2257. **(Guideline)**
52. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol.* 2014;63(4):321-328. **(Retrospective analysis; 9183 patients)**
53. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation.* 2011;124(14):1573-1579. **(Randomized controlled trial; 12 volunteers)**
54. Testa S, Legnani C, Tripodi A, et al. Poor comparability of coagulation screening test with specific measurement in patients receiving direct oral anticoagulants: results from a multicenter/multiplatform study. *J Thromb Haemost.* 2016;14(11):2194-2201. **(In vitro study)**
55. Samuelson BT, Cuker A, Siegal DM, et al. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. *Chest.* 2017;151(1):127-138. **(Review)**
56. Steiner T, Böhm M, Dichgans M, et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. *Clin Res Cardiol.* 2013;102(6):399-412. **(Review)**
57. Cuker A, Siegal DM, Crowther MA, et al. Laboratory measurement of the anticoagulant activity of the non–vitamin K oral anticoagulants. *J Am Coll Cardiol.* 2014;64(11):1128-1139. **(Review)**
58. 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):183-187. **(In vitro study)**
59. Stengel D, Ottersbach C, Matthes G, et al. Accuracy of single-pass whole-body computed tomography for detec-

tion of injuries in patients with major blunt trauma. *CMAJ.* 2012;184(8):869-876. **(Retrospective cohort; 1756 patients)**
60. Samama MM, Contant G, Spiro TE, et al. Evaluation of the anti-factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. *Thromb Haemost.* 2012;107(2):379-387. **(In vitro study)**
61. Samama MM, Martinoli J-L, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban--an oral, direct factor Xa inhibitor. *Thromb Haemost.* 2010;103(4):815-825. **(In vitro study)**
62. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet.* 2015;385(9984):2288-2295. **(Randomized controlled trial; 21,105 patients)**
63. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost.* 2009;15 Suppl 1:9S-16S. **(In vitro study; healthy volunteers)**
64. Nowak G. The ecarin clotting time, a universal method to quantify direct thrombin inhibitors. *Pathophysiol Haemost Thromb.* 2003;33(4):173-183. **(Review)**
65.* Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College Of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol.* 2017;70(24):3042-3067. **(Guidelines statement)**
66. Brown MA, Daya MR, Worley JA. Experience with chitosan dressings in a civilian EMS system. *J Emerg Med.* 2009;37(1):1-7. **(Case series; 34 patients)**
67. QuikClot® - FAQs–learn more about our hemostatic devices. http://quikclot.com/FAQ. **(Website)**
68. Carson JL, Hill S, Carless P, et al. Transfusion triggers: a systematic review of the literature. *Transfus Med Rev.* 2002;16(3):187-199. **(Review)**
69. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA.* 2016;316(19):2025-2035. **(Guidelines statement)**
70. Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. *N Engl J Med.* 2017;377(13):1261-1272. **(Review)**
71. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med.* 2017;377(22):2133-2144. **(Randomized controlled trial; 5243 patients)**
72. Kim JH, Baek CH, Min JY, et al. Desmopressin improves platelet function in uremic patients taking antiplatelet agents who require emergent invasive procedures. *Ann Hematol.* 2015;94(9):1457-1461. **(Prospective study; 23 patients)**
73. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med.* 2015;162(3):205-213. **(Guidelines statement)**
74. Spiller HA, Mowry JB, Aleguas A, et al. An observational study of the factor Xa inhibitors rivaroxaban and apixaban as reported to eight poison centers. *Ann Emerg Med.* 2016;67(2):189-195. **(Prospective cohort; 138 patients)**
75. Conway SE, Schaeffer SE, Harrison DL. Evaluation of dabigatran exposures reported to Poison Control centers. *Ann Pharmacother.* 2014;48(3):354-360. **(Retrospective review; 806 cases)**
76.* Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015;373(6):511-520. **(Prospective cohort; 90 patients)**
77. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med.* 2017;377(5):431-441. **(Prospective cohort; 503 patients)**
78.* Burnett AE, Mahan CE, Vazquez SR, et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis.* 2016;41:206-232. **(Guidelines statement)**
79. Alikhan R, Rayment R, Keeling D, et al. The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. *Emerg Med J.* 2014;31(2):163-168. **(Review)**
80.* Raval AN, Cigarroa JE, Chung MK, et al. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: a scientific statement from the American Heart Association. *Circulation.* 2017;135(10):e604-e633. **(Guidelines statement)**
81. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med.* 2019;380(14):1326-1335. **(Prospective cohort; 352 patients)**
82. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med.* 2016;375(12):1131-1141. **(Prospective cohort; 47 patients)**
83. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med.* 2015;373(25):2413-2424. **(Randomized controlled trial; 24 patients)**
84. Fredriksson K, Norrving B, Strömblad LG. Emergency reversal of anticoagulation after intracerebral hemorrhage. *Stroke.* 1992;23(7):972-977. **(Retrospective case series; 17 patients)**
85. Cartmill M, Dolan G, Byrne JL, et al. Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. *Br J Neurosurg.* 2000;14(5):458-461. **(Retrospective)**
86. Majeed A, Ågren A, Holmström M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130(15):1706-1712. **(Prospective cohort; 84 patients)**
87. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation.* 2015;131(1):82-90. **(Randomized controlled trial; 110 patients)**
88. Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost.* 2018;118(5):842-851. **(Prospective cohort; 66 patients)**
89. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost.* 2014;12(9):1428-1436. **(Case control; 35 volunteers)**
90. Hall ST, Molina KC. Fixed-dose 4-factor prothrombin complex concentrate: we don't know where we're going if we don't know how to get there. *J Thromb Thrombolysis.* 2018;46(1):50-57. **(Review)**
91. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. *Thromb Haemost.* 2012;108(08):217-224. **(Case series; 10 patients)**
92. Dibu JR, Weimer JM, Ahrens C, et al. The role of FEIBA in reversing novel oral anticoagulants in intracerebral hemorrhage. *Neurocrit Care.* 2016;24(3):413-419. **(Prospective cohort; 127 patients)**
93. Lindahl TL, Wallstedt M, Gustafsson KM, et al. More efficient reversal of dabigatran inhibition of coagulation by activated prothrombin complex concentrate or recombinant factor VIIa than by four-factor prothrombin complex concentrate. *Thromb Res.* 2015;135(3):544-547. **(In vitro study)**
94. Levi M, Levy JH, Andersen HF, et al. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med.* 2010;363(19):1791-1800. **(Meta-analysis; 4468 subjects)**

95. Dentali F, Marchesi C, Giorgi Pierfranceschi M, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost.* 2011;106(3):429-438. **(Meta-analysis; 27 studies, 1032 patients)**
96. Harinstein LM, Morgan JW, Russo N. Treatment of dabigatran-associated bleeding: case report and review of the literature. *J Pharm Pract.* 2013;26(3):264-269. **(Case report; 1 patient)**
97. Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke.* 2011;42(12):3594-3599. **(Animal study)**
98. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA.* 2015;313(5):471-482. **(Randomized controlled trial; 680 patients)**
99. van Ryn J, Sieger P, Kink-Eiband M, et al. Adsorption of dabigatran etexilate in water or dabigatran in pooled human plasma by activated charcoal in vitro. *Blood.* 2009;114:1065. **(In vitro studies)**
100. Wang X, Mondal S, Wang J, et al. Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. *Am J Cardiovasc Drugs.* 2014;14(2):147-154. **(Case control; 18 subjects)**
101. 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-e88S. **(Guidelines statement)**
102. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet Infect Dis.* 2010;376(9734):23-32. **(Randomized controlled trial; 20,211 patients)**
103. CRASH-2 collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet Infect Dis.* 2011;377(9771):1096-1101. **(Randomized controlled trial; 20,211 patients)**
104. Clavé A, Fazilleau F, Dumser D, et al. Efficacy of tranexamic acid on blood loss after primary cementless total hip replacement with rivaroxaban thromboprophylaxis: a case-control study in 70 patients. *Orthop Traumatol Surg Res.* 2012;98(5):484-490. **(Case-control study; 70 patients)**
105. Wang J-W, Chen B, Lin P-C, et al. The efficacy of combined use of rivaroxaban and tranexamic acid on blood conservation in minimally invasive total knee arthroplasty a double-blind randomized, controlled trial. *J Arthroplasty.* 2017;32(3):801-806. **(Prospective case control; 70 patients)**
106. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369(13):1206-1214. **(Randomized controlled trial; 252 patients)**
107. Di Biase L. Use of direct oral anticoagulants in patients with atrial fibrillation and valvular heart lesions. *J Am Heart Assoc.* 2016;5(2). **(Review)**
108. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 135(25):e1159-e1195. **(Guideline)**
109. Beyer-Westendorf J, Michalski F, Tittl L, et al. Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting. *Thromb Haemost.* 2016;116(4):651-658. **(Review)**
110. Fordyce CB, Hellkamp AS, Lokhnygina Y, et al. On-treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin: insights from ROCKET AF. *Circulation.* 2016;134(1):37-47. **(Randomized controlled trial re-analysis; 12,612 patients)**
111. Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J.* 2011;32(19):2387-2394. **(Randomized controlled trial; 14,264 patients)**
112. Sarratt SC, Nesbit R, Moye R. Safety outcomes of apixaban compared with warfarin in patients with end-stage renal disease. *Ann Pharmacother.* 2017;51(6):445-450. **(Retrospective cohort; 160 patients)**
113. Kimachi M, Furukawa TA, Kimachi K, et al. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev.* 2017;11:CD011373. **(Cochrane review)**
114. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2016;47(2):581-641. **(Scientific advisory statement)**
115. Chen ST, Hellkamp AS, Becker RC, et al. Outcome of patients receiving thrombolytic therapy while on rivaroxaban for nonvalvular atrial fibrillation (from rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *Am J Cardiol.* 2017;120(10):1837-1840. **(Case series; 28 patients)**
116. Xian Y, Federspiel JJ, Hernandez AF, et al. Use of intravenous recombinant tissue plasminogen activator in patients with acute ischemic stroke who take non-vitamin K antagonist oral anticoagulants before stroke. *Circulation.* 2017;135(11):1024-1035. **(Case series; 251 patients)**
117. Purrucker JC, Wolf M, Haas K, et al. Safety of endovascular thrombectomy in patients receiving non-vitamin K antagonist oral anticoagulants. *Stroke.* 2016;47(4):1127-1130. **(Prospective multicenter observational study; 28 patients)**
118. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest.* 2018;154(5):1121-1201. **(Guidelines)**
119. Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol.* 2011;57(2):173-180. **(Observational cohort; 7329 patients)**
120. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J.* 2015;36(46):3258-3264. **(Observational cohort; 7411 patients)**
121. Hijazi Z, Oldgren J, Lindbäck J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet Infect Dis.* 2016;387(10035):2302-2311. **(Randomized controlled trial re-analysis; 14,537 patients)**
122. Chai-Adisaksopha C, Hillis C, Lim W, et al. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost.* 2015;13(10):1790-1798. **(Review)**
123. Sakamoto Y, Koami H, Miike T. Monitoring the coagulation status of trauma patients with viscoelastic devices. *J Intensive Care.* 2017;5:7. **(Review)**
124. Cotton BA, Faz G, Hatch QM, et al. Rapid thrombelastography delivers real-time results that predict transfusion within 1 hour of admission. *J Trauma.* 2011;71(2):407-414. **(Prospective study; 272 patients)**

125. Solbeck S, Ostrowski SR, Stensballe J, et al. Thrombelastography detects dabigatran at therapeutic concentrations in vitro to the same extent as gold-standard tests. *Int J Cardiol.* 2016;208:14-18. **(In vitro study; 8 subjects)**
126. Seyve L, Richarme C, Polack B, et al. Impact of four direct oral anticoagulants on rotational thromboelastometry (ROTEM). *Int J Lab Hematol.* 2018;40(1):84-93. **(In vitro study)**
127. Xu Y, Wu W, Wang L, et al. Differential profiles of thrombin inhibitors (heparin, hirudin, bivalirudin, and dabigatran) in the thrombin generation assay and thromboelastography in vitro. *Blood Coagul Fibrinolysis.* 2013;24(3):332-338. **(In vitro study)**
128. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med.* 2011;365(21):2039-2040. **(Letter)**
129. Milling TJ, Kaatz S. Preclinical and clinical data for factor Xa and "universal" reversal agents. *Am J Med.* 2016;129(11 Suppl):S80-S88. **(Review)**
130. Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost.* 2017;117(2):238-245. **(Randomized controlled trial; 80 patients)**
131. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med.* 2014;371(22):2141-2142. **(Letter)**
132. Coll-Vinent B, Martín A, Sánchez J, et al. Benefits of emergency departments' contribution to stroke prophylaxis in atrial fibrillation: the EMERG-AF Study (emergency department stroke prophylaxis and guidelines implementation in atrial fibrillation). *Stroke.* 2017;48(5):1344-1352. **(Prospective cohort; 1162 patients)**
133. Kahler ZP, Beam DM, Kline JA. Cost of treating venous thromboembolism with heparin and warfarin versus home treatment with rivaroxaban. *Acad Emerg Med.* 2015;22(7):796-802. **(Case control; 97 patients)**
134. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two U.S. emergency departments: a one-year preplanned analysis. *Acad Emerg Med.* 2015;22(7):788-795. **(Prospective cohort; 106 patients)**
135. Wolf SJ, Hahn SA, Nentwich LM, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected acute venous thromboembolic disease. *Ann Emerg Med.* 2018;71(5):e59-e109. **(Clinical policy)**
136. Howard L, Barden S, Condliffe R, et al. British Thoracic Society guideline for the initial outpatient management of pulmonary embolism (PE). *Thorax.* 2018;73(Suppl 2):ii1-ii29. **(Guideline)**
137. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med.* 2005;172(8):1041-1046. **(Retrospective cohort; 221 patients)**
138. Zondag W, Mos ICM, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. *J Thromb Haemost.* 2011;9(8):1500-1507. **(Prospective cohort; 297 patients)**
139. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med.* 2010;170(15):1383-1389. **(Retrospective cohort; 995 patients)**
140. Frank Peacock W, Coleman CI, Diercks DB, et al. Emergency department discharge of pulmonary embolus patients. *Acad Emerg Med.* 2018;25(9):995-1003. **(Randomized controlled trial; 114 patients)**
141. Lamberts M, Staerk L, Olesen JB, et al. Major bleeding complications and persistence with oral anticoagulation in non-valvular atrial fibrillation: contemporary findings in real-life Danish patients. *J Am Heart Assoc.* 2017;6(2). **(Cohort study; 54,321 patients)**
142. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc.* 2016;5(6). **(Cohort study; 125,243 patients)**

CME Questions

Current subscribers receive CME credit absolutely free by completing the following test. Each issue includes *4 AMA PRA Category 1 Credits™*, 4 ACEP Category I credits, 4 AAFP Prescribed credits, or 4 AOA Category 2-A or 2-B credits. Online testing is available for current and archived issues. To receive your free CME credits for this issue, scan the QR code below with your smartphone or visit www.ebmedicine.net/E0819.

1. **The mechanism of action of apixaban is:**
   a. To reduce the synthesis of factor X
   b. To directly inhibit the synthesis of thrombin
   c. To directly inhibit the action of thrombin
   d. The same as the mechanism of action of rivaroxaban

2. **The defining feature of the pharmacokinetics of DOACs as compared to warfarin is:**
   a. More cytochrome P450 interactions
   b. Reduced renal clearance
   c. Dramatically shorter half-life
   d. Slower time to maximum effect

3. **For a patient who wants to take a DOAC for atrial fibrillation, but would only be able to take once-daily dosing, what is the best option?**
   a. Rivaroxaban
   b. Dabigatran
   c. Apixaban
   d. Betrixaban

4. **Which of the following problems might limit your evaluation of patients on DOACs?**
   a. Unlike warfarin, DOACs are undetectable by laboratory tests available in the ED.
   b. Gastrointestinal bleeding on DOACs is more likely to be unnoticed by patients.
   c. Patients on DOACs may not be recognized as taking anticoagulants by prehospital providers.
   d. Patients on DOACs require different medications during intubation.

5. **The most sensitive test to determine the effect of dabigatran is:**
   a. Prothrombin time (PT)/international normalized ratio (INR)
   b. Thromboelastography
   c. Anti-Xa level
   d. Thrombin time

6. **The test of choice for monitoring rivaroxaban activity is:**
   a. PT
   b. Partial thromboplastin time
   c. Thrombin time
   d. Anti-factor Xa

7. **Based on the best available evidence, the best treatment for bleeding associated with factor Xa inhibitors is:**
   a. Tranexamic acid
   b. 4-factor prothrombin complex concentrate
   c. rFVIIa
   d. Fresh-frozen plasma

8. **Because of its protein-binding characteristics, dialysis would eliminate which DOAC best?**
   a. Edoxaban
   b. Dabigatran
   c. Apixaban
   d. Rivaroxaban

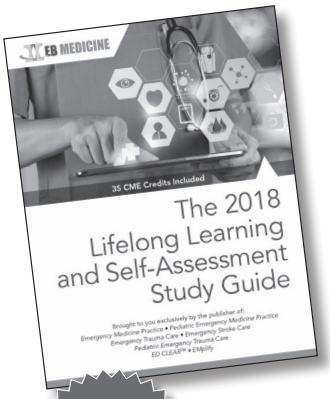
9. **What scoring system can assess bleeding risk in patients on DOACs with atrial fibrillation without requiring laboratory testing of troponin or INR?**
   a. PESI
   b. HAS-BLED
   c. ABC
   d. ORBIT

10. **For a patient with a newly found pulmonary embolism (PE) to be considered for discharge from the ED, which of the following scales can screen them as being at "low risk?"**
    a. Well's criteria for PE
    b. PERC (PE rule-out criteria) rule for PE
    c. PESI (PE severity index)
    d. SIRS (systemic inflammatory response system)

Meet all your LLSA needs now with The EB Medicine 2016-2019 LLSA Study Guides

Offer Expires Dec 15th

Receive FREE article reprints, CME, and more when you order yours today!*



Includes FULL Article Reprints*

**Due to copyright restrictions, 1 article from the 2018 LLSA and 2 articles and 1 table from the 2017 LLSA are not included in EB Medicine's LLSA Study Guides (or any others published by a third party).*

DESCRIPTION	AMOUNT
The 2019 Lifelong Learning And Self-Assessment Study Guide (now includes audio)	~~$219~~ $169 $50 Off
The 2018 Lifelong Learning And Self-Assessment Study Guide	~~$219~~ $169 $50 Off
The 2017 Lifelong Learning And Self-Assessment Study Guide	~~$219~~ $169 $50 Off
The 2016 Lifelong Learning and Self-Assessment Study Guide	~~$219~~ $169 $50 Off
• **Full reprints** of the original articles.*	FREE
• **35 *AMA PRA Category 1 Credits™*** or 35 ACEP Category I CME Credits.	FREE
• **A handy summary of key points** so you get the "must-know" information for each article.	INCLUDED
• **An in-depth discussion** of each article to clarify and elaborate on the key points.	INCLUDED
• **Sample questions** to help you quiz yourself on your knowledge of the material.	INCLUDED
• **Answers and explanations** to the sample questions that drive home the main points.	INCLUDED
• **A critical discussion and critique of the article** that answers the question "What does this article really tell us?"	INCLUDED
• **100% money-back guarantee:** If, for any reason, you are not completely satisfied simply call us to receive a full and immediate refund. No questions asked.	INCLUDED

New And Improved - 2019 LLSA With Audio

The 2019 Lifelong Learning and Self-Assessment Study Guide now includes quick high-impact summaries of each article.

Listen to renowned speaker Dr. Haney Mallemat as he summarizes the key points of the articles ABEM has chosen for the exam.

Order Your LLSA Study Guides Today

Published by EB Medicine
PO Box 1671/ Williamsport, PA 17703
Contact 678-366-7933 or ebm@ebmedicine.net
Order at www.ebmedicine.net/NMLJB

Name: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____

Email: _____

Hospital/Group (optional): _____

Email and phone are required for online delivery and to service your account.
We respect your privacy, and this information will not be shared with third parties.

EXCLUSIVE DISCOUNT OFFER

Yes! Please send me the LLSA Study Guide(s). Because I am a preferred customer, I am eligible for the exclusive discounted rate of $169 (a $50 savings). Promotion Code **NMLJB**

2019 LLSA Study Guide.....$169 each _____
2018 LLSA Study Guide.....$169 each _____
2017 LLSA Study Guide.....$169 each _____
2016 LLSA Study Guide.....$169 each _____

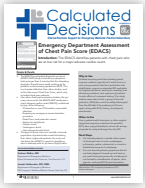
Delivery method: ☐ Online Download Only ☐ Mail & Online Download*
Check enclosed **or** Charge my Visa / MC / AmEx
Card # _____
Exp _____ Signature _____
Hospital/Group Name _____
Phone _____
Email _____

Your email address is required, and will only be used to service your account.

Have you heard about these FREE benefits of your subscription?

Your ***Emergency Medicine Practice*** and ***Pediatric EM Practice*** subscriptions now include all of this—at no extra charge!

Calculated Decisions – Clinical Decision Tools to Help in Clinical Care



NEW: *Calculated Decisions*—this must-read online supplement, published in collaboration with MDCalc, gives you how-to-use guidance and reviews of medical calculators. These formulas, algorithms, rules, and scores will help you make informed decisions when caring for your patients.

34+ Calculators

Get it now—absolutely free—at www.ebmedicine.net/topics by clicking Calculated Decisions next to the title of the issue.

EMplify – Evidence-Based Learning On-the-Go

8+ hours of content

Our exclusive podcast gives you access to *Emergency Medicine Practice* wherever you are - in the car, at the gym, or on break.

Get it now—absolutely free—at www.ebmedicine.net/topics by clicking PODCAST next to the title of the issue. Subscribe on iTunes or Google Play to avoid missing out!

EMplify podcast hosts: Nachi Gupta, MD, PhD and Jeff Nusbaum, MD

Points & Pearls – A Digest That Reinforces What You Learn

Points & Pearls—a two-page online digest of each monthly journal article. *Points & Pearls* features:

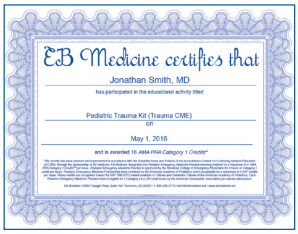
- Key points and clinical pearls from the full-length issue
- A key figure or table and relevant links
- A quick summary of the must-know recommendations from the full issue

230+ Points & Pearls

Get it now—absolutely free—at www.ebmedicine.net/topics by clicking DIGEST next to the title of the issue.

Points & Pearls contributors: Kathryn H. Pade, MD; Bryan Wilson, MD; Nachi Gupta, MD, PhD; and Jeff Nusbaum, MD

The CME You Need – At No Extra Charge



FREE CME: Each issue of ***Emergency Medicine Practice*** and ***Pediatric EM Practice*** **include 4 CME credits at no extra charge**. And did you know you can also receive 4 CME credits from any issue published within the last three years, all archived on our website for easy access to the journal content and CME tests? That's up to 144 additional CME credits—absolutely free! Credits include:

- ***Emergency Medicine Practice***: *AMA PRA Category 1 Credits™;* ACEP Category I Credits; AAFP Prescribed Credits; AOA Category 2-A or 2-B credits
- ***Pediatric EM Practice***: *AMA PRA Category 1 Credits™;* ACEP Category I Credits; AAP Prescribed Credits; AOA Category 2-A or 2-B credits

50+ credits available each year

Visit www.ebmedicine.net/CME to start earning credits today!

BIG DISCOUNTS: Did you know you can get a $75 coupon just for referring your colleagues to us? Simply visit www.ebmedicine.net/refer to take advantage of this offer.

If there are 5 or more clinicians at your hospital or group who are interested in subscribing, you can get even bigger discounts with a group subscription. Visit www.ebmedicine.net/groups to learn more.

EB MEDICINE

EB Medicine ● PO Box 1671 ● Williamsport, PA 17703-9800 ● Phone: 1-800-249-5770 or 678-366-7933 ● Fax: 770-500-1316 ● Email: ebm@ebmedicine.net ● Website: www.ebmedicine.net


EB MEDICINE
EMERGENCY MEDICINE PRACTICE
EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE
Influenza: Diagnosis and Management in the Emergency Department
December 2018
Volume 20, Number 12


EB MEDICINE
EMERGENCY MEDICINE PRACTICE
EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE
First Trimester Pregnancy Emergencies: Recognition and Management
January 2019
Volume 21, Number 1

In upcoming issues of *Emergency Medicine Practice....*

- Managing Air Travel Emergencies
- Dizziness
- Nonconvulsive Status Epilepticus
- NSTEMI

CME Information

Date of Original Release: August 1, 2019. Date of most recent review: July 10, 2019. Termination date: August 1, 2022.

Accreditation: EB Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This activity has been planned and implemented in accordance with the accreditation requirements and policies of the ACCME.

Credit Designation: EB Medicine designates this enduring material for a maximum of 4 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Specialty CME: Included as part of the 4 credits, this CME activity is eligible for 4 Pharmacology credits.

ACEP Accreditation: *Emergency Medicine Practice* is approved by the American College of Emergency Physicians for 48 hours of ACEP Category I credit per annual subscription.

AAFP Accreditation: This Enduring Material activity, *Emergency Medicine Practice,* has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 07/01/2019. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 4 AAFP Prescribed credits.

AOA Accreditation: *Emergency Medicine Practice* is eligible for 4 Category 2-A or 2-B credit hours per issue by the American Osteopathic Association.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Objectives: Upon completion of this article, you should be able to: (1) monitor and treat patients on direct oral anticoagulants (DOACs) in the emergency department (ED); (2) initiate specific reversal strategies for bleeding complications of DOACs; and (3) discuss potential applications and considerations for new DOAC prescriptions in the ED.

Discussion of Investigational Information: As part of the journal, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product.

Faculty Disclosure: It is the policy of EB Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. **The information received is as follows: Dr. Maher, Dr. Taub, Dr. Boatright, Dr. Tawil, Dr. Mishler, Dr. Toscano, Dr. Jagoda, and their related parties report no relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. Dr. Kreitzer reported receiving honoraria for Portola Pharmaceuticals speaker's bureau.**

Commercial Support: This issue of *Emergency Medicine Practice* did not receive any commercial support.

Earning Credit: Two Convenient Methods: (1) Go online to www.ebmedicine.net/CME and click on the title of the article. (2) Mail or fax the CME Answer And Evaluation Form (included with your June and December issues) to EB Medicine.

Hardware/Software Requirements: You will need a Macintosh or PC to access the online archived articles and CME testing.

Additional Policies: For additional policies, including our statement of conflict of interest, source of funding, statement of informed consent, and statement of human and animal rights, visit www.ebmedicine.net/policies.

Direct all inquiries to:
EB Medicine
Phone: 1-800-249-5770 or 1-678-366-7933
Fax: 1-770-500-1316
PO Box 1671
Williamsport, PA 17703
E-mail: **ebm@ebmedicine.net**
Website: **www.ebmedicine.net**
To write a letter to the editor, please email:
jagodamd@ebmedicine.net

Subscription Information

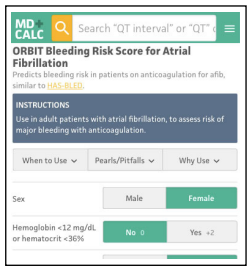
Full annual subscription: $449 (includes 12 monthly evidence-based print issues; 48 *AMA PRA Category 1 Credits™*, 48 ACEP Category I credits, 48 AAFP Prescribed credits, and 48 AOA Category 2A or 2B CME credits. Call 1-800-249-5770 or go to www.ebmedicine.net/subscribe to subscribe.

Individual issues: $49 (includes 4 CME credits). Call 1-800-249-5770 or go to www.ebmedicine.net/EMPissues to order.

Group subscriptions at discounted rates are also available.
Contact groups@ebmedicine.net for more information.

Emergency Medicine Practice (ISSN Print: 1524-1971, ISSN Online: 1559-3908, ACID-FREE) is published monthly (12 times per year) by EB Medicine (PO Box 1671, Williamsport, PA 17703). Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. This publication is intended as a general guide and is intended to supplement, rather than substitute, professional judgment. It covers a highly technical and complex subject and should not be used for making specific medical decisions. The materials contained herein are not intended to establish policy, procedure, or standard of care.

Calculated Decisions
POWERED BY MD+CALC
Clinical Decision Support for *Emergency Medicine Practice* Subscribers



Click the thumbnail above to access the calculator.

ORBIT Bleeding Risk Score for Atrial Fibrillation

The ORBIT score predicts bleeding risk in patients who are taking anticoagulants for atrial fibrillation.

Points & Pearls

- The derivation and validation studies for the ORBIT score (older, reduced hemoglobin, bleeding history, insufficient kidney function, treatment with antiplatelets) defined *major bleeding* as fatal bleeding, symptomatic bleeding in a critical organ, or bleeding with a hemoglobin drop requiring transfusion of ≥ 2 units of blood (O'Brien 2015).
- The ORBIT score does not consider the choice of anticoagulant.
- Unlike the HAS-BLED score (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile international normalized ratio, elderly, drug/alcohol usage), the ORBIT score was derived in a patient population that included patients who received vitamin K antagonists (eg, warfarin) as well as patients who received direct oral anticoagulants.
- Unlike the HAS-BLED score, the ORBIT score does not consider the time in therapeutic range, as there is no reliable or readily available objective measure for therapeutic range of the direct oral anticoagulants.

Critical Actions

Risk assessment is multifactorial for both stroke risk and bleeding risk.

CALCULATOR REVIEW AUTHORS

Hyunjoo Lee, MD
Department of Emergency Medicine, Stony Brook University Hospital, Stony Brook, NY

Jeffrey Marbach, MBBS, MS, FRCPC
Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Why to Use

The ORBIT score is not superior to the HAS-BLED score (see the "Evidence Appraisal" section), but it was derived more recently and has been validated in the era of direct oral anticoagulants, so it may be more useful. The ORBIT score can be used in conjunction with the CHA_2DS_2-VASc score to risk stratify patients for clinically significant bleeding and help guide decisions about anticoagulation for stroke prevention.

When to Use

The ORBIT score is used for patients with atrial fibrillation for whom treatment with oral anticoagulants is being considered.

Next Steps

The presence of risk factors that are not included in the ORBIT score may influence the clinician's decisions regarding anticoagulation in patients with atrial fibrillation. Patient preferences and values should also inform these decisions, in the context of the risks and benefits of taking oral anticoagulants for stroke prevention.

Evidence Appraisal

Stroke prevention is part of the management plan for patients with atrial fibrillation. The $CHADS_2$ or CHA_2DS_2-VASc scores are often used to calculate stroke risk in patients with atrial fibrillation. Drug therapies for stroke prevention can include antiplatelet therapy (eg, aspirin) or anticoagulation, depending on the risk for stroke; however, anticoagulation also creates bleeding risk. Other bleeding

risk scores include HAS-BLED, ATRIA, and others; among these scores, HAS-BLED is best validated and likely the most used.

O'Brien et al (2015) derived and validated the ORBIT score as a way to assess bleeding risk in patients with atrial fibrillation. Derivation was based on data from ORBIT-AF, a prospective registry of patients with atrial fibrillation from 176 sites in the United States. Of the 10,132 patients in the registry, 7411 were analyzed (2721 patients were excluded because they were not on oral anticoagulants or because there were no follow-up data available). *Major bleeding* was defined as fatal bleeding, symptomatic bleeding in a critical organ, or bleeding with a hemoglobin drop requiring transfusion of ≥ 2 units of blood. The simplified 5-item ORBIT score was based on the 5 predictors with the strongest association with major bleeding.

The authors also validated the ORBIT score with data from the ROCKET-AF trial, a cohort of patients receiving either once-daily rivaroxaban or a vitamin K antagonist. The validation study showed that the ORBIT score had better discrimination than ATRIA or HAS-BLED (C statistic = 0.67, 0.66, and 0.64, respectively).

Subsequent studies in different patient populations did not show the ORBIT score to be superior to the other scores. Senoo et al (2016) studied 2293 patients in the AMADEUS trial and found that the HAS-BLED score performed better than the ORBIT score for predicting major bleeding (C statistic = 0.65 and 0.61, respectively; $P = .001$). Esteve-Pastor et al (2016) found that the ORBIT score was not superior to the HAS-BLED score in predicting major bleeding in 406 patients who underwent electrocardioversion (C statistic = 0.82 and 0.77, respectively; $P = .08$), or in 1276 patients with persistent atrial fibrillation who were in the FANTASIIA registry (C statistic = 0.70 and 0.63, respectively; $P = .12$). Wang et al (2017) conducted a meta-analysis that showed the HAS-BLED score to be superior to the ORBIT score in predicting major bleeding in 8079 patients with anticoagulated, nonvalvular atrial fibrillation patients from the United States, Britain, Spain, and the Netherlands.

The same studies also showed that the ORBIT score places more patients in the low-risk category than the HAS-BLED score, potentially underpredicting the major bleeding risk for these patients (Senoo 2016, Esteve-Pastor 2016, Wang 2017). This raises the concern that some at-risk patients may not be identified by the ORBIT score. Lip et al (2018) suggest that the HAS-BLED score has higher sensitivity but lower specificity for major bleeding risk as compared to the ORBIT score. As a result, care must be taken when clinically applying the results of either score.

Use the Calculator Now

Click here to access the ORBIT score on MDCalc.

Calculator Creator

Emily C. O'Brien, PhD
Click here to read more about Dr. O'Brien.

References

Original/Primary Reference

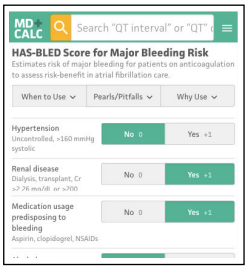
- O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J.* 2015;36(46):3258-3264. **DOI: https://doi.org/10.1093/eurheartj/ehv476**

Other References

- Senoo K, Proietti M, Lane DA, Lip GY. Evaluation of the HAS-BLED, ATRIA, and ORBIT bleeding risk scores in patients with atrial fibrillation taking warfarin. *Am J Med.* 2016;129(6):600-607. **DOI: https://doi.org/10.1016/j.amjmed.2015.10.001**
- Esteve-Pastor MA, Garcia-Fernandez A, Macias M, et al. Is the ORBIT risk score superior to the HAS-BLED score in anticoagulated atrial fibrillation patients? *Circ J.* 2016;80(10):2102-2108. **DOI: https://doi.org/10.1253/circj.CJ-16-0471**
- Wang C, Yu Y, Zhu W, et al. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. *Oncotarget.* 2017;8(65):109703- 109711. **DOI: https://doi.org/10.18632/oncotarget.19858**
- Lip GYH, Skjoth F, Nielsen PB, et al. The HAS-BLED, ATRIA, and ORBIT bleeding scores in atrial fibrillation patients using non-vitamin K antagonist oral anticoagulants. *Am J Med.* 2018;131(5):574.e13-574.e27. **DOI: https://doi.org/10.1016/j.amjmed.2017.11.046**

Related Calculators on MDCalc

- ATRIA Bleeding Risk Score
- $CHADS_2$ Score
- CHA_2DS_2-VASc Score



Click the thumbnail above to access the calculator.

HAS-BLED Score for Major Bleeding Risk

The HAS-BLED score estimates the risk of major bleeding for patients on anticoagulation, in order to assess risks and benefits in the care of patients with atrial fibrillation.

Points & Pearls

- For patients with atrial fibrillation, the clinical factors that contribute to stroke risk and support anticoagulation are frequently risk factors for bleeding as well. The HAS-BLED score (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile international normalized ratio [INR], elderly, drug/alcohol usage) was developed as a practical risk score to estimate the 1-year risk for major bleeding in patients with atrial fibrillation.
- The original HAS-BLED study provided risk percentages for given risk factors but did not stratify scores into low, medium, or high risk; subsequent studies have looked at risk stratification using the score (see the "Evidence Appraisal" section).
- The performance of the HAS-BLED score has been shown to be superior to the ATRIA and HEMORR$_2$HAGES scores, and similar to the ORBIT score.
- Clinicians should consider comparing the risk for major bleeding as calculated by the HAS-BLED score to the risk for thromboembolic events by CHADS$_2$ or CHA$_2$DS$_2$-VASc scores to determine whether the benefit of anticoagulation outweighs the risk.

Critical Actions

Risk assessment is multifactorial for both stroke risk and bleeding risk.

Evidence Appraisal

The HAS-BLED score was developed by Pisters et al (2010) as a practical risk score to estimate the 1-year risk for major bleeding in patients with atrial fibrillation. The study included 5333 ambulatory and hospitalized patients with atrial fibrillation from both academic and nonacademic hospitals in 35 member countries of the European Society for Cardiology. Patients were followed up at 1 year for survival and major adverse cardiovascular events, such as major bleeding. (*Major bleeding* was defined as any bleeding that required hospitalization, caused a decrease in hemoglobin level of > 2 g/dL, or required blood transfusion, excluding hemorrhagic stroke.)

Researchers performed a retrospective univariate analysis to find potential bleeding risk factors when comparing the groups with and without major bleeding at the 1-year follow-up, and developed the score based on the results of their analysis as well as known significant risk factors for major bleeding. Results showed that the annual bleeding rate increased with increasing risk factors, with an overall major bleeding rate of 1.5%.

These findings were validated in a study by Lip et al (2011), who studied the score in 7329 patients with atrial fibrillation who participated in the SPORTIF clinical trial. They found a stepwise increase in rates of major bleeding with an increasing HAS-BLED score (*P* for the trend < .0001, C statistic = 0.50-0.67).

Apostolakis et al (2012) compared the HAS-BLED score with 2 alternative bleeding risk scores, HEMORRH$_2$AGES and ATRIA, using data from the AMADEUS trial cohort. AMADEUS was a multicenter randomized open-label noninferiority study comparing fixed-dose idraparinux (a novel oral anticoagulant) with warfarin or acenocoumarol (vitamin K antagonists) in nonvalvular atrial fibrillation. They found that the HAS-BLED score performed best for the primary endpoint of any clinically relevant bleeding. Patients in the co-

Why to Use

The HAS-BLED score can be used to help guide the decision on whether to start anticoagulation in patients with atrial fibrillation.

Next Steps

The patient-specific risks and benefits of anticoagulation must be weighed carefully for all patients who are potential candidates for long-term anticoagulation therapy.

CALCULATOR REVIEW AUTHOR

Calvin Hwang, MD
Department of Orthopaedic Surgery, Stanford University, Palo Alto, CA

hort were already at low risk for stroke and major bleeding, which differs from many real-life scenarios.

Roldán et al (2013) conducted a study comparing the HAS-BLED score with the ATRIA score as both quantitative and dichotomized variables (ie, low-medium vs high risk) in 937 outpatients with atrial fibrillation on anticoagulation who had stable INR, and found that the HAS-BLED score more accurately predicted major bleeding. There were some criticisms of the study related to potential selection bias, as it excluded patients who were warfarin-naive and patients with unstable INR, and the study had limited applicability outside the clinic setting.

Use the Calculator Now

Click here to access the HAS-BLED score on MDCalc.

Calculator Creator

Ron Pisters, MD, PhD
Click here to read more about Dr. Pisters.

References

Original/Primary Reference

- Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.
  DOI: https://doi.org/10.1378/chest.10-0134

Validation References

- Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol.* 2011;57(2):173-180.
  DOI: https://doi.org/10.1016/j.jacc.2010.09.024
- Apostolakis S, Lane DA, Guo Y, et al. Performance of the HEMORR$_2$HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. *J Am Coll Cardiol.* 2012;60(9):861-867.
  DOI: https://doi.org/10.1016/j.jacc.2012.06.019
- Roldán V, Marín F, Fernández H, et al. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. *Chest.* 2013;143(1):179-184.
  DOI: https://doi.org/10.1378/chest.12-0608

Related Calculator on MDCalc

- HEMORR$_2$HAGES Score

This edition of *Calculated Decisions*, powered by MDCalc, is published as a supplement to *Emergency Medicine Practice* as an exclusive benefit to subscribers. *Calculated Decisions* is the result of a collaboration between EB Medicine, publisher of *Emergency Medicine Practice*, and MD Aware, developer of MDCalc. Both companies are dedicated to providing evidence-based clinical decision-making support for emergency medicine clinicians.

Contact EB Medicine:
Phone: 1-800-249-5770
or 678-366-7933
Fax: 770-500-1316
PO Box 1671
Williamsport, PA 17703

Contact MD Aware:
MDCalc
Phone: 646-543-8380
12 East 20th Street
5th Floor
New York, NY 10003

Emergency Medicine Practice (ISSN Print: 1524-1971, ISSN Online: 1559-3908, ACID-FREE) is published monthly (12 times per year) by EB Medicine (PO Box 1671, Williamsport, PA 17703-1671). Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. This publication is intended as a general guide and is intended to supplement, rather than substitute, professional judgment. It covers a highly technical and complex subject and should not be used for making specific medical decisions. The materials contained herein are not intended to establish policy, procedure, or standard of care.