JAMA Clinical Guidelines Synopsis

Management of Bleeding in Patients Taking Oral Anticoagulants

Irsk Anderson, MD; Adam S. Cifu, MD

GUIDELINE TITLE American College of Cardiology Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

DEVELOPER ACC Foundation

RELEASE DATE December 1, 2017

TARGET POPULATION Patients treated with direct oral anticoagulants (DOACs) or warfarin for any indication who have acute bleeding

MAJOR RECOMMENDATIONS

For patients treated with an oral anticoagulant (OAC) who experience either life-threatening bleeding or major bleeding at a critical site, management should include at least temporarily discontinuing the OAC, local therapy, supportive measures, and, when appropriate, administering a reversal agent.

- For warfarin, 5 to 10 mg of intravenous vitamin K and intravenous 4-factor prothrombin complex concentrate (4F-PCC)
- For dabigatran, intravenous idarucizumab or intravenous 4F-PCC/activated prothrombin complex concentrate (aPCC)
- For apixaban, edoxaban, and rivaroxaban, intravenous 4F-PCC or intravenous aPCC

Laboratory testing may be useful to determine reversal strategy for life-threatening bleeding or bleeding at a critical site or prior to urgent unplanned procedures.

For dabigatran

- Normal levels of any of the following probably indicate that drug levels are insignificant: dilute thrombin time (TT); ecarin clotting time (ECT); ecarin chromogenic assay (ECA).
- Normal activated partial thromboplastin time (aPTT) usually indicates that drug levels are insignificant. Prolonged aPTT suggests that a patient has a significant drug level (either therapeutic or supratherapeutic).

For apixaban, edoxaban, and rivaroxaban

- Negative anti–factor Xa assay activity usually indicates that drug levels are insignificant.
- Normal prothrombin time/aPTT does not exclude a significant drug level. Prolonged prothrombin time suggests that a patient has a clinically significant drug level (either therapeutic or supratherapeutic).

Summary of the Clinical Problem

More than 6 million people in the United States take OACs.[1] The most common indications for OACs are atrial fibrillation and treatment or prevention of venothromboembolism.[1] Hemorrhage and its related morbidity and mortality are the primary risks associated with these agents.[2] A meta-analysis of 13 randomized clinical trials involving 102 707 adults showed major bleeding case-fatality rates of 7.57% with DOACs and 11.05% with warfarin.[2] With the approval of 4 DOACs since 2010, management of OAC-associated bleeding has become more complex.

Characteristics of the Guideline Source

The ACC Expert Consensus Decision Pathways (ECDPs) focus on concise decision pathways, key points of care, or both. Unlike traditional guidelines, the pathways address clinical decisions for which there is insufficient high-quality evidence and that thus might be influenced by expert opinion. For this ECDP (**Table**),[3] the ACC supported the writing committee without outside or commercial support. All writing committee members and peer reviewers were required to disclose relationships with industry for the 12 months leading up to the writing of the pathway as well as during each conference call. Members were not asked to recuse themselves because of relationships with industry. The chair of the writing committee and the majority of its members had no relevant conflicts.

Evidence Base

This ECDP makes recommendations in the form of 6 algorithms offering guidance for all severities of OAC-related bleeding. For bleeding that occurs in an essential organ (eg, central nervous system, pericardium, airway) or that is life-threatening, the guideline recommends that the OAC be at least temporarily discontinued, that local therapy and supportive measures be provided, and, when indicated, that a reversal agent be administered. For patients taking DOACs, determining whether a patient has detectable drug levels,

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Fair
Establishing evidence foundations and rating strength for each of the guideline recommendations	Fair
Articulation of recommendations	Good
External review	Fair
Updating	Poor
Implementation issues	Good

and if so, knowing the drug concentration may be useful in certain situations (eg, need for an unplanned urgent procedure).[3] For dabigatran, normal levels of TT, ECT, or ECA probably exclude clinically meaningful drug levels. For apixaban, edoxaban, and rivaroxaban, negative anti–factor Xa assay activity probably excludes clinically significant drug levels.[3]

For warfarin reversal, the pathway recommends 4F-PCC as first-line therapy over plasma. This is based on a 2016 integrated analysis of 2 phase 3b randomized clinical trials (4F-PCC: n=191; plasma: n=197) that demonstrated similar rates of adverse events (60.2% for 4F-PCC; 62.9% for plasma) and serious adverse events (28.3% for 4F-PCC; 24.9% for plasma) in vitamin K antagonist–treated patients with major bleeding or need for urgent intervention.[4] Adverse events due to fluid overload, however, were more frequent in the plasma group (12.7%) than the 4F-PCC group (4.7%).[4]

Idarucizumab is a humanized monoclonal antibody fragment that reverses the anticoagulant effect of dabigatran. In an interim analysis of the REVERSE-AD trial, a prospective cohort study of 90 patients who presented with major bleeding or need for urgent intervention, 5 g of intravenous idarucizumab normalized dilute TT and ECT in 88% to 98% of patients with elevated dilute TT and ECT at baseline.[5] The REVERSE-AD study confirmed these results and demonstrated a median time to cessation of bleeding of 2.5 hours (n=203), and normal periprocedural hemostasis in 93% of patients (184/197).[6]

Four-factor PCC has been shown to reverse the anticoagulant effects of rivaroxaban (prothrombin time lowered by 2.5-3.5 seconds) and apixaban (peak thrombin generation 76% higher).[7,8] Intravenous administration of 4F-PCC, 50 IU/kg, has been shown to completely reverse the effects of edoxaban on bleeding duration and endogenous thrombin potential and partially reverse prothrombin time in patients undergoing a punch biopsy.[9] None of the DOAC in vitro studies have demonstrated a significant reduction of dilute TT, ECT/ECA, or anti–factor Xa levels after 4F-PCC administration.

Benefits and Harms

The benefit of this ECDP is that it provides concise algorithms for management of bleeding in patients taking OACs. Although the algorithms are not fully evidence based and knowledge gaps exist, they incorporate expert opinion and the best evidence currently available. Alternative strategies have not been studied in actual patients with comparisons of clinical end points. It is possible that if the algorithms suggested in the ECDP are compared with alternative algorithms, the ECDP could be found inferior.

Discussion

This ECDP provides guidance for physicians treating patients who develop acute bleeding while taking OACs. The pathway provides laboratory evaluation strategies for both specific and nonspecific assays to assess the presence of each OAC. Many of the specialized assays for DOAC quantification (dilute TT, ECT, ECA, and anti–factor Xa assays) are not readily available. It is currently unclear if knowing the exact drug level of a DOAC is useful in treatment of patients with bleeding. Idarucizumab is currently the only available DOAC reversal agent studied in emergency scenarios. In the meantime, 4F-PCC remains the first-line reversal agent for factor Xa inhibitors.

Areas in Need of Future Study or Ongoing Research

All US Food and Drug Administration–approved DOACs currently have laboratory tests that can detect clinically significant drug levels and quantify the amount of drug present. In patients with major bleeding and lack of measurable DOAC, the administration of reversal agents and the complication of thromboembolic events can be avoided. At present, no specific antidotes to the factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) exist. Four-factor PCC has been studied in humans taking rivaroxaban but not in patients with bleeding or those requiring urgent surgery. Andexanet alfa is a factor Xa reversal agent currently undergoing study in patients taking factor Xa inhibitors with major bleeding. Preliminary evidence shows significant reduction in factor Xa activity and successful hemostasis.[10]

Related guidelines and other resources

British Committee for Standards in Haematology Guideline on the Management of Bleeding in Patients on Antithrombotic Agents

International Society on Thrombosis and Hemostasis Scientific and Standardization Committee Subcommittee on Control of Anticoagulation

ARTICLE INFORMATION

Author Affiliations: University of Chicago, Chicago, Illinois.

Corresponding Author: Adam S. Cifu, MD, University of Chicago, 5841 S Maryland Ave, MC 3051, Chicago, IL 60637 (adamcifu@uchicago.edu).

Section Editor: Edward H. Livingston, MD, Deputy Editor, *JAMA*.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128(12):1300-5.e2.

2. Chai-Adisaksopha C, Hillis C, Isayama T, et al. Mortality outcomes in patients receiving direct oral anticoagulants. *J Thromb Haemost*. 2015;13(11):2012-2020.

3. 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.

4. Milling TJ Jr, Refaai MA, Sarode R, et al. Safety of a 4-factor prothrombin complex concentrate vs plasma for vitamin K antagonist reversal. *Acad Emerg Med*. 2016;23(4):466-475.

5. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511-520.

6. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.

7. Levi M, Moore KT, Castillejos CF, et al. Comparison of 3-factor and 4-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost*. 2014;12(9):1428-1436.

8. Nagalla S, Thomson L, Oppong Y, et al. Reversibility of apixaban anticoagulation with a 4-factor prothrombin complex concentrate in healthy volunteers. *Clin Transl Sci*. 2016;9(3):176-180.

9. 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.

10. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375(12):1131-1141.