Emerging Treatment Options for Direct Oral Anticoagulant-Related Bleeding

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The advent and brisk uptake of direct oral anticoagulants in the last decade has created a fresh dilemma for emergency physicians.[1-4] We have new tools to treat the dangerously anticoagulated patient, but when should they be used? These are substantial decisions: idarucizumab will cost a few thousand dollars per treatment in the United States, whereas andexanet can top $50,000. In this issue of *Annals*, Baugh et al[5] provide a detailed approach to the emergency department management of bleeding as a result of anticoagulation. This expert consensus article used a Delphi panel approach to define exactly when and how replacement, reversal, or both should be used for bleeding in the presence of direct oral anticoagulants, vitamin K antagonists (ie, warfarin), and heparin. It culminates in several clear pathways that clinicians will appreciate.

These pathways classify the drugs used to treat bleeding (or to allow an emergent surgery/urgent procedure) as either tier 1 or tier 2. Direct oral anticoagulant reversal agents idarucizumab and andexanet alfa[6,7] are classified as tier 1, whereas prothrombin complex concentrate is classified as tier 2.

The tier 1 recommendation for andexanet differs from that of several recently published guideline articles. The 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society Focused Update recommends (class of recommendation 1) idarucizumab for the reversal of dabigatran in the event of life-threatening bleeding or urgent procedure, based on a level of evidence B-NR (NR refers to data derived from one or more nonrandomized trials), whereas for andexanet alfa the guideline states that it "can be useful" for the reversal of rivaroxaban and apixaban, with a corresponding class of recommendation IIb (level of evidence B-NR).[8] The associated text notes that "[c]ontinued approval may be contingent on postmarketing studies to demonstrate an improvement in hemostasis in patients."

As did those of the American Heart Association, the 2018 Canadian Cardiovascular Society guidelines "recommend idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary (moderate-quality evidence)."[9] In accordance with the interim analysis of ANNEXA-4 (Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding), they conclude that "[a]lthough promising, there are insufficient data to recommend andexanet for reversal of life-threatening bleeding associated with factor Xa inhibitors at this time." The 2016 European Society of Cardiology guidelines do not make specific recommendations for either reversal agent;[10] a 2020 update is planned. Other guidelines are older and do not address these new therapeutic options.

How does one explain the variation in recommendations? One potential reason is the difference in approach. Guideline articles undertake a comprehensive review of the published evidence, using a standardized, rigorous process for grading evidence (eg, Grading of Recommendations Assessment, Development and Evaluation standards), and then separately make recommendations.[11] The strength of those recommendations is reflected with the use of the terms "strong" or "weak" recommendation, or alternatively "we recommend" versus "we suggest." Critically, this approach explicitly specifies that the level of evidence and the associated recommendation need not be congruent: the guideline committee members may vote to make a strong recommendation for a treatment for which the level of evidence is low. The presence of both level of evidence and recommendation provides the reader with a much fuller picture than either alone, and is a key advantage of guidelines articles over less structured approaches.

In contrast, less structured approaches, such as the Delphi panel used by Baugh et al, have the advantage of a

much shorter timeline for completion and publication, which allows them to provide expeditious guidance to clinicians who are already managing the patients in question. These consensus method approaches also allow experts to use their clinical judgment, particularly to answer questions not addressed adequately in the published literature.

Unfortunately, however, the less structured the approach, the more conflicts of interest can potentially cloud decisionmaking, particularly in situations in which the data are not clear and strong. Many readers will notice the long list of financial declarations associated with the article by Baugh et al. Financial ties to the companies that sell these drugs are, however, just one type of conflict of interest. Even those of us without such ties (myself included) may have intellectual conflicts of interest based on our experience, interests, career path, and need to maintain grant support. All of these conflicts of interest can lead to a difference in conclusions compared with guidelines that are based on the Grading of Recommendations Assessment, Development and Evaluation approach, as can the Delphi approach itself, because the reproducibility of the results can potentially be affected by the panel's membership.[12,13]

Of course, published guidelines are not immune to biases. Many guideline panels have long lists of financial disclosures, and although not necessarily exclusionary they raise questions about objectivity.[14] Some individuals believe that the fact that they have many financial conflicts of interest means they are no longer conflicted because they are funded by competing companies; although that is somewhat intuitive, some research institutes (including my own) explicitly reject this argument.[15] However, given their structured approach for grading evidence and the explicit acknowledgment of underlying values and preferences,[11] guidelines are currently our best available standard.

So by what measure is a conscientious, well-meaning clinician to gauge the value of this peer-reviewed contribution from a group of experts with the aforementioned potential conflicts of interest? Exactly how and to what degree should he or she translate the listed financial conflicts of interest into a recalibration of the article's output? As in many a conference presentation, in which a slide of sometimes dozens of disclosures is shown for a few seconds,[16] the audience is left uncertain about how to assemble the industry-funding revelation into a results filter.

If you are an expert in the area, you may fall back on your own knowledge of the methodology used in the trials on this topic (including the lack of a control group in the idarucizumab and andexanet trials[7,17]) to filter the outputs. Most of us, however, don't have the time to become an expert in the myriad of topic areas covered by emergency medicine.

Some readers may look to their national medical specialty society for assistance, noting that the American College of Emergency Physicians (ACEP) commissioned the work and funded the meetings. ACEP commissions consensus articles in areas for which clinicians need near-term direction, given the long timeline required to produce a guideline. Specifically, ACEP solicits topic areas of interest from its membership and then approaches authors who have published in that area to assemble a group to do the work. The article by Baugh et al is not an ACEP Clinical Policy article, which is developed in accordance with national guideline-development standards, nor is it a guideline, which would include an evaluation of the study quality. Therefore, the relationship of ACEP to this article has little bearing on its conclusions.

The article itself highlights the Food and Drug Administration (FDA) approval of andexanet alfa.[18] Approval may be interpreted as an endorsement of that medication over others; however, although much goes into an FDA approval (availability of therapeutic options, severity of the disease in question, etc), approval is not equivalent to a tier 1 drug recommendation. The FDA does not rely on comparative effectiveness data with other medication or treatments to garner approval, but rather maintains a bar above which a medication must rise. Regardless of the number or quality of therapeutic options on the market, any drug that performs "well enough" will be approved. Thereafter, the market is allowed to determine its utility. Many drugs have been approved by the FDA (many without reviewer disagreement[19]) that do not go on to be recommended as a first-line drug for their approved indication. Therefore, FDA approval is not itself justification for first-line recommendation of andexanet alfa. Of note, the 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society Focused Update was produced *after* FDA approval of andexanet alfa.[20]

The inconsistency will likely soon be addressed, after publication of an ongoing study of andexanet with a control group (ClinicalTrials.gov NCT03661528). In a perfect world, randomized controlled trials on both andexanet alfa and idarucizumab versus prothrombin complex concentrate will be performed, and these will be combined in a systematic review that includes any unpublished work on all of these agents.[21,22] In the meantime, readers should understand that in the early stages of clinical use of new agents, endorsements may

change as more data are published. It is only after a fairly lengthy process, during which time there is an expected element of uncertainty until a critical mass of data is accumulated, that knowledge reaches a state at which there is greater consensus.

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