Engineering Reversal — Finding an Antidote for Direct Oral Anticoagulants

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The need for oral anticoagulation is rising to combat an increasing prevalence of atrial fibrillation and venous thromboembolism in an aging global population. For more than 65 years, only one class of oral anticoagulants filled this role: vitamin K antagonists, which include warfarin and other coumarin derivatives. However, such drugs require monitoring of the international normalized ratio and subsequent dose adjustment owing to their slow onset and offset and unpredictable pharmacokinetics, along with dietary intake of vitamin K, coexisting illnesses, or other medications. These agents are highly effective in reducing thromboembolic complications (including stroke in patients with atrial fibrillation), but they increase the risk of hemorrhage, which is now the commonest cause of iatrogenic hospital admission. The incidence of the most dreaded complication of vitamin K antagonists, intracranial hemorrhage, is at least 0.2% per year.[1]

For all these reasons, the arrival of direct oral anticoagulants was a breath of fresh air, since the new agents had a predictable effect and thus no need for regular monitoring. Moreover, clinical trials showed an efficacy that was at least similar to that of vitamin K antagonists and a lower risk of intracranial bleeding. Globally, there has been an increasing move to use direct oral anticoagulants instead of coumarins, and large trials resulted in licensing of these agents for the prevention of thromboembolic complications in patients with atrial fibrillation, treatment and prevention of venous thromboembolism, and management of acute coronary syndromes.[2] Of note, direct oral anticoagulants are ineffective in patients with mechanical heart valves[3] and unsafe in those requiring renal-replacement therapy.

Despite evidence of the safety of direct oral anticoagulants, there has been concern that, unlike vitamin K antagonists, they arrived without an antidote. Many journals highlighted reports of patients taking these drugs who had major uncontrolled bleeding. In addition, when an immediate invasive procedure is required, most practitioners prefer the availability of a reversing agent to speed the return of clotting to normal and minimize the period during which the patient is at risk for thrombosis. Many patients were discouraged from taking direct oral anticoagulants (some by their own health professionals) until such antidotes were available.

Idarucizumab, a monoclonal antibody targeting the active site of the thrombin inhibitor, was developed as an antidote for dabigatran and was licensed in 2015 after it was shown to restore hemostasis in patients who had a serious hemorrhage or required an urgent invasive procedure.[4] However, all the other direct oral anticoagulants are in a different class in that they exhibit their anticoagulant effect by binding to active coagulation factor X. This class of drugs includes rivaroxaban, apixaban, edoxaban, and betrixaban. In a display of creative research, investigators developed andexanet alfa (andexanet), a recombinant modified human factor Xa decoy protein, as an antidote for these drugs.[5] Not only that, but andexanet is also an effective antidote for other anti–factor Xa inhibitors, including low-molecular-weight heparins (e.g., enoxaparin and dalteparin) and fondaparinux.

In a multicenter, open-label, single-group study reported in this issue of the *Journal*,[6] Connolly et al. describe the effective reversal of rivaroxaban, apixaban, and enoxaparin in patients with acute major bleeding. Within 12 hours after the administration of andexanet, more than 80% of the patients had effective hemostasis.

However, the administration of andexanet combined with the cessation of anticoagulants after the episode of bleeding was associated with a high thrombosis rate for 30 days after the reversal (in 12 of 67 patients [18%]). It is impossible to know whether andexanet had an intrinsic prothrombotic effect or whether the high rate of thrombosis was related to the absence of an antithrombotic agent in a high-risk situation, since the presence of major bleeding alone is associated with an increased subsequent rate of venous thromboembolism. Of side interest is the finding that a higher dose of andexanet was required to reverse rivaroxaban than to reverse apixaban. This result strongly suggests that the

currently licensed doses of rivaroxaban have a greater anti–factor Xa effect than the dose of apixaban, which may explain the slightly lower bleeding rates associated with apixaban.[7]

Despite the attitude-changing excitement this reversing agent brings, we suggest that the actual need for an antidote for direct oral anticoagulants is small in typical clinical practice. The rate of intracranial bleeding associated with direct oral anticoagulants is less than that associated with warfarin,[8] and the clinical severity of hemorrhage seems to be reduced.[9] Because the half-lives of direct oral anticoagulants are shorter than that of warfarin, the effects of the drugs wear off quickly, and unlike the case with warfarin, stopping the drug may be all that is required in most scenarios. In addition, even for patients who present with major hemorrhage while taking a vitamin K antagonist, the use of a reversing agent is infrequently required.[10] More critically, we do not yet have the data to show that fast reversal of a direct oral anticoagulant leads to a better clinical outcome.

The advent of andexanet completes the story of direct oral anticoagulants, since there are now effective and relatively safe antidotes. The availability of effective reversing agents will probably accelerate the widespread introduction of direct oral anticoagulants in clinical practice. However, what we have not yet learned is how long it is necessary to cease anticoagulation after reversal for a major bleeding episode, such as intracranial hemorrhage. This highly relevant practical question needs urgent attention from clinical researchers.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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1. Levi M. Epidemiology and management of bleeding in patients using vitamin K antagonists. J Thromb Haemost 2009;7: Suppl 1:103-6.
2. Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis: role of the direct oral anticoagulants. Circ Res 2016;118:1409-24.
3. Eikelboom JW, Brueckmann M, Van de Werf F. Dabigatran in patients with mechanical heart valves. N Engl J Med 2014;370: 383-4.
4. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20.
5. Lu G, DeGuzman FR, Hollenbach SJ, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med 2013;19:446-51.
6. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375:1131-41.
7. Lip GY, Pan X, Kamble S, et al. Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. Int J Clin Pract 2016 August 23 (Epub ahead of print).
8. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost 2012;108:476-84.
9. Eerenberg ES, Middeldorp S, Levi M, Lensing AW, Büller HR. Clinical impact and course of major bleeding with rivaroxaban and vitamin K antagonists. J Thromb Haemost 2015;13:1590-6.
10. Haverkamp D, Hutten BA, Büller HR, Gallus AS, Lensing AW, Prins MH. The use of specific antidotes as a response to bleeding complications during anticoagulant therapy for venous thromboembolism. J Thromb Haemost 2003;1:69-73.

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