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RECOMMENDATIONS AND GUIDELINES

When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

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Introduction

The direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, are licensed for stroke prevention in patients with atrial fibrillation and for prevention and treatment of venous thromboembolism [1]. As a class, the DOACs are at least as effective as vitamin K antagonists (VKAs) but are associated with less life-threatening bleeding, particularly intracranial hemorrhage [2]. Although all anticoagulants can produce bleeding, the outcomes of major bleeds with DOACs are no worse than those with VKAs even in the absence of clinically available antidotes [3]. Nonetheless, antidotes for the DOACs would be useful as one component of strategies for management of serious bleeding, or for rapid reversal of the DOACs before urgent interventions.

Three antidotes for the DOACs are under various stages of development. Idarucizumab (Praxbind®), the antidote for dabigatran, is now licensed in the United States and Europe. Andexanet alfa, the antidote for the oral factor Xa (FXa) inhibitors, is undergoing phase III investigation [4]. Ciraparantag (PER977), an agent reported to reverse the anticoagulant effects of all of the DOACs, is at an earlier stage of development. Although each of these agents reverses the anticoagulant effects of the DOACs through different mechanisms and some are more specific than others, for simplicity, we will refer to all of them as antidotes. This report (i) describes the mechanism of action of the antidotes, (ii) reviews the available clinical data, and (iii) provides guidance on potential indications for their use.

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Comparison of the mechanism of action of the antidotes

Each of the three antidotes is a distinct chemical entity with a unique mechanism of action. The properties of each are briefly reviewed.

Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with 350-fold higher affinity than that of dabigatran for thrombin. In addition to binding dabigatran, idarucizumab also binds the active glucuronide metabolites of dabigatran to form essentially irreversible 1:1 stoichiometric complexes [5]. Idarucizumab and idarucizumab-dabigatran complexes are cleared by the kidneys, as is dabigatran. After intravenous infusion, the half-life of idarucizumab is about 45 min in subjects with normal renal function [5]. Although the half-life of idarucizumab is prolonged in patients with renal impairment, the greater idaricuzimab exposure may be advantageous because these patients also have elevated plasma dabigatran levels.

In phase 2 studies in young or older volunteers with normal or moderately impaired renal function, idarucizumab rapidly reversed the anticoagulant effects of dabigatran in a concentration-dependent manner [5]. The efficacy and safety of idarucizumab are currently being evaluated in the phase 3 Study of the Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD; ClinicalTrials.gov number NCT02104947). This prospective study is enrolling two cohorts of dabigatran-treated patients: those with serious bleeding requiring reversal (group A) and those requiring urgent interventions that

cannot be delayed for at least 8 h (group B). All patients are given 5 g of idarucizumab as two intravenous boluses of 2.5 g, each administered over 5–10 min within 15 min of each other [6]. This dosage was chosen because it is sufficient to reverse the body loads of dabigatran measured in the majority of patients that were enrolled in the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial [7]. The planned sample size for RE-VERSE AD is 500, and the primary end point is maximum percentage reversal of the anticoagulant effects of dabigatran within 4 h of idarucizumab administration based on central laboratory measurements of the diluted thrombin time (dTT) and ecarin clotting time (ECT); tests that exhibit high correlation with dabigatran concentrations quantified using mass spectrometry.

Of the first 90 patients enrolled in RE-VERSE AD (51 in group A and 39 in group B), 81 had an elevated dTT or ECT at baseline, suggesting a significant dabigatran effect. At 4 h after idarucizumab administration, the median maximum reversal was 100%, and almost 90% of patients with an elevated dTT or ECT at baseline had normal test results 4 and 12 h after idarucizumab administration. In the 35 patients in group A where the time to cessation of bleeding could be assessed, hemostasis was restored at a mean of 11.4 h. In the 36 group B patients who underwent an intervention, intraoperative hemostasis was judged to be normal in 33, mildly abnormal in 1, and moderately abnormal in 2 patients [6]. One thrombotic event occurred within 72 h of idarucizumab administration and four occurred later; antithrombotic therapy had not been reinitiated in any of these patients.

Andexanet alfa

Andexanet alfa is a recombinant human FXa variant with the active-site serine residue replaced with alanine to eliminate catalytic activity and with the membrane-binding domain deleted to prevent incorporation into the prothrombinase complex [8]. Andexanet serves as a decoy for the oral FXa inhibitors because it binds them with affinities similar to those of native FXa. Because andexanet also binds tissue factor pathway inhibitor (TFPI) to form a non-productive andexanet–TFPI complex, it reduces TFPI activity and produces a transient increase in the levels of prothrombin fragment 1.2, thrombin–antithrombin complexes, and D-dimer. This phenomenon is attenuated in subjects receiving oral FXa inhibitors because these agents compete with TFPI for andexanet binding. The clinical significance of these changes is uncertain; to date, there have been no reported thrombotic complications with andexanet.

In phase 2 studies in healthy young volunteers, an intravenous bolus of andexanet transiently reversed the anti-FXa activity of apixaban, rivaroxaban, or edoxaban in a dose-dependent manner [4,9]. In volunteers 50–75 years of age, an intravenous andexanet bolus of 400 or 800 mg rapidly, but transiently, reversed > 90% of the anti-FXa activity of apixaban and rivaroxaban, respectively [4]. Lower doses of andexanet are needed to reverse apixaban than rivaroxaban because drug concentrations are lower with twice-daily dosing. More-sustained reversal was achieved when the bolus was followed by a 2-h intravenous infusion of andexanet at a dosage of 4 and 8 mg min^{-1}, respectively. When the infusion is stopped, FXa inhibition reappears to expected levels, but normalization of thrombin generation as measured by endogeneous thrombin potential is sustained. The clinical relevance of these observations is unclear. The Ability of Andexanet Alfa to Reverse the Anticoagulant Activity-4 (ANNEXA-4) study is evaluating the efficacy and safety of andexanet for management of serious bleeding in patients treated with rivaroxaban, apixaban, and, eventually, edoxaban. Its results will reveal whether a bolus of andexanet alfa followed by a 2-h infusion is sufficient to restore hemostasis in such patients. Additional studies will be needed to determine whether this andexanet alfa regimen is effective for reversal of the oral FXa inhibitors before urgent surgery.

Ciraparantag (PER977)

A synthetic, cationic small molecule, ciraparantag binds dabigatran, rivaroxaban, apixaban, and edoxaban via hydrogen bonds [10]. In a phase 1 study in healthy volunteers given a single 60-mg oral dose of edoxaban, an intravenous bolus of ciraparantag dose-dependently shortened the whole blood clotting time to within 10% of baseline and restored normal clot architecture based on scanning electron microscopic analysis [11]. Studies of ciraparantag in volunteers taking oral FXa inhibitors are under way, but the clinical development program is lagging behind that of andexanet alfa.

Potential indications for antidote administration

Potential indications for antidote administration, which are listed in Table 1, include life-threatening bleeding, bleeding into a critical organ or closed space, prolonged bleeding despite local hemostatic measures, high risk of recurrent bleeding because of overdose or delayed clearance of DOACs, and need for an urgent intervention associated with a high risk of bleeding. Reversal is unlikely to be necessary when bleeding can be managed with local hemostatic measures, bleeding has stopped, or when interventions can be delayed for at least 8 h to permit clearance of effects, especially in patients with normal renal function.

Laboratory testing

Delaying antidote administration until coagulation test results are available may be detrimental in DOAC-treated patients with life-threatening bleeding, such as intracra-

Table 1 Indications for use or non-use of the antidotes

Indications for use	• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage • Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome • Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose • Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance • Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery
Potential indication for use	• Need for urgent surgery or intervention in patients with acute renal failure
Antidotes should not be used	• Elective surgery • Gastrointestinal bleeds that respond to supportive measures • High drug levels or excessive anticoagulation without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance

nial bleeding, or in those requiring emergency surgery for life-threatening conditions such as a ruptured aortic aneurysm. With the exception of these patients, the decision as to whether an antidote is indicated can be guided by the time since the last intake of the DOAC, determination of the creatinine clearance, which influences the half-lives of the DOACs, and the results of laboratory tests, which measure the anticoagulant effects of the DOACs or the plasma drug concentrations. If an antidote is given, the latter tests are helpful to assess the extent of reversal.

All of the DOACs are cleared to some extent by the kidneys, and their half-lives are best estimated by measuring the serum creatinine and calculating the creatinine clearance. An antidote is unlikely to be necessary if the last dose of a DOAC was taken 24 h previously in patients with normal renal function because with a creatinine clearance > 60 mL min^{-1}, the half-lives of the DOACs will be no longer than 12 h. In contrast, the half-lives are prolonged when the creatinine clearance is < 30 mL min^{-1}, and delayed clearance may be an indication for reversal if the patient has ongoing bleeding.

Although the DOACs were developed to be given in fixed doses without routine coagulation monitoring, measuring their anticoagulant effects or plasma drug levels can help determine their contribution to bleeding or to determine when it is safe to perform an urgent or unplanned intervention. The DOACs have different effects on global tests of coagulation, such as the prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT), and the responsiveness of these tests to the DOACs is, to some extent, coagulometer and reagent dependent [12,13]. Dabigatran prolongs the APTT and TT more than the PT. A normal APTT with a sensitive reagent makes it unlikely that dabigatran is a major contributor to bleeding. The TT is the most sensitive test, and even low levels of dabigatran will prolong the TT. Consequently, a normal TT in dabigatran-treated patients who present with serious bleeding or require urgent surgery indicates the absence of dabigatran. Rivaroxaban and edoxaban prolong the PT more than the APTT and they have no effect on the TT. In contrast, apixaban has little effect on the PT or APTT; therefore, normal test results do not exclude a significant drug effect [14]. Because the responsiveness of the PT varies depending on the reagent and the drug, the PT cannot be used as a universal test to assess the anticoagulant effect of the oral FXa inhibitors.

Drug levels can be quantified using specific assays that are calibrated for each of the DOACs. These include the dTT, ECT, or ecarin chromogenic assay for dabigatran and chromogenic anti-FXa assays for rivaroxaban, apixaban, and edoxaban. Such assays are not available in many hospitals and, even when available, the turnaround time may be too long to render them of value. When interpreting drug concentrations, it is important to consider when the last dose of the DOAC was taken to determine whether the levels are likely to increase or fall over time. In patients with serious bleeding, a drug concentration > 50 ng mL^{-1} is likely sufficiently high to warrant antidote administration, whereas in those requiring an urgent intervention associated with a high risk of bleeding, antidote administration should be considered if the drug concentration exceeds 30 ng mL^{-1}.

Storage and administration of antidotes

Every hospital should develop a protocol for management of bleeding in patients taking anticoagulants, including the DOACs. These protocols should incorporate indications for antidote administration. The antidotes are likely to be expensive, so they should only be used when their benefits outweigh their disadvantages, which include cost, potential risks directly attributable to the antidote, and other adverse effects such as the risk of thrombosis once the patient is no longer anticoagulated.

The logistics of availability, storage, indications, and prescribers are important considerations for the timely administration of the antidotes. The need for refrigeration will impact where they are stored, whereas time-consuming

preparation may delay their administration. Andexanet and idarucizumab require refrigeration, whereas ciraparantag may not. Idarucizumab is supplied in two glass vials, each containing 2.5 g of drug; no mixing is required. In its current formulation, andexanet will require mixing. Antidotes are most frequently administered in the emergency department or the intensive care unit. They may occasionally be given in the operating room. Likely, these agents will be stored in the pharmacy or blood bank, although storage in a locked refrigerator in the emergency department may provide more-rapid access for management of patients with intracranial bleeding. Because of cost, the use of the antidotes will likely be restricted to certain prescribers, such as emergency medicine and critical care physicians, hematologists, pharmacists, and possibly others. In the United States, a 5-g dose of idarucizumab costs about $3500. Andexanet is likely to be considerably more expensive. Therefore, each hospital will need to develop pathways for approval and release of the antidotes.

Team approach to managing bleeding in anticoagulated patients

Although the antidotes will reverse the anticoagulant effects of the DOACs, they will not be panaceas. Patients may continue to bleed because of vascular injury, complex coagulopathies, or other issues associated with critical illness. Therefore, a team approach to patient management is important. Adjunctive treatment with antifibrinolytic agents may be useful, and there may be a role for prothrombin complex concentrate or recombinant FVIIa in patients with continued bleeding or in centers without access to antidotes.

Conclusion

Idarucizumab is already available in the United States and is likely to soon be licensed in other countries. Andexanet alfa will soon follow. Although the ongoing clinical studies with these agents will provide important safety information and evidence of their capacity to reverse the anticoagulant effects of the DOACs, in the absence of control groups, efficacy data will be limited. Postmarketing surveillance and registries will be needed to better determine their clinical utility, particularly in special circumstances such as reversal before thrombolytic therapy in patients with acute ischemic stroke or additional dosing if there is incomplete reversal or ongoing bleeding. It is important to point out that the antidotes are unlikely to improve clinical outcomes in patients with serious underlying disorders, such as those with ruptured aortic aneurysm, cardiac arrest, or septic shock. Nonetheless, with antidotes available, the safety profile of the DOACs will be enhanced.

Addendum

All of the authors developed the initial outline for the manuscript. J. H. Levy wrote the first draft. All of the authors contributed to critical review and revisions of the manuscript.

Disclosure of Conflict of Interests

M. Crowther has provided consultatory advice to Portola on the development of their antidote and has been paid by Boehringer Ingelheim for development and presentation of educational materials in relation to reversal agents. He also has financial and intellectual conflicts of interest with essentially all of the manufacturers of anticoagulants as well as the companies that make both specific and non-specific reversal agents. These relationships are indirectly relevant to the content of this manuscript. J. I. Weitz reports consultancy fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Portola, Daiichi-Sankyo, Pfizer, Janssen, and ISIS Pharmaceuticals, outside the submitted work. N. C. Chan reports grants from Sanofi and personal fees from Bayer, outside the submitted work. W. Ageno has participated in advisory boards for Boehringer Ingelheim. J. H. Levy has participated in steering committees for Boehringer-Ingelheim, CSL Behring, Grifols, Instrumentation Labs, Janssen, and Medicines Company, outside the submitted work. P. Verhamme reports grants and personal fees from Boehringer-Ingelheim, Bayer-Healthcare, Sanofi, and Leo-Pharma; personal fees from Pfizer, Bristol-Myers Squibb, and Daiichi-Sankyo; and honoraria from Portola, outside the submitted work. He was also an investigator in the REVERSE-AD and the ANNEXA-4 studies.

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