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Idarucizumab (Praxbind®): A Novel Direct Thrombin Inhibitor Reversal Agent

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For more than half a century, warfarin has been the primary oral anticoagulant used for prevention of cardioembolic stroke and systemic embolism.[1] Despite popular use, warfarin has known drawbacks such as its narrow therapeutic index, food and drug interactions, need for regular monitoring, and frequent dose adjustments. These limitations have fueled the development of direct oral anticoagulants (DOACs) that are slowly changing the landscape of anticoagulation. The first FDA approved DOAC was a direct thrombin inhibitor, dabigatran etexilate (hereafter referred to as dabigatran).[2] As of now, dabigatran is indicated for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and treatment and prevention of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The RE-LY trial, a catalyst for dabigatran approval, demonstrated that compared to warfarin, dabigatran 150 mg twice daily reduces stroke risk without increasing the risk of major bleeding among patients with atrial fibrillation.[3] Furthermore, the RE-COVER and RE-COVER II trials demonstrated dabigatran's noninferiority to warfarin for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days.[4] However, dabigatran, as with all anticoagulation therapy, is associated with an increased risk of bleeding.[5] And unlike warfarin, which can be reversed with administration of vitamin K, dabigatran and other DOACs lack a reliable reversal agent.

In October 2015, the U.S. Food and Drug Administration granted accelerated approval to idarucizumab (Praxbind®) for use in patients who are taking dabigatran during emergency situations and when there is need to reverse anticoagulant effects of dabigatran.[6] Idarucizumab is specific to reversing dabigatran and is the only DOAC reversal agent currently approved. The purpose of this article is to describe idarucizumab pharmacology, review the efficacy and adverse events from clinical trials, and discuss its potential place in therapy.

IN THIS ISSUE

Pharmacology

Mechanism of Action

Idarucizumab is a humanized monoclonal antibody fragment (Fab) derived from a murine IgG1 isotype molecule, whose target is the direct thrombin inhibitor dabigatran.[7,10,12] In the coagulation pathway, thrombin acts to convert factors that ultimately catalyzes the formation of covalent bonds that increase the stability of the fibrin clot.[8] Thrombin also promotes platelet activation and aggregation via activation of protease-activated receptors on the cell membrane of platelets.[8] Dabigatran and its active metabolites are competitive, reversible, direct inhibitors of both free and clot-bound thrombin.[9,11] Dabigatran prevents thrombin-induced platelet aggregation and the development of a thrombus by preventing the thrombin-mediated conversion of fibrinogen into fibrin during the coagulation cascade (**Figure**).[9,11] Idarucizumab ultimately neutralizes the anticoagulant effect by binding to both free and thrombin-bound dabigatran with an affinity 350 times greater than that observed with thrombin (**Figure**).[10-12] This high affinity for dabigatran means any unbound dabigatran will preferentially bind to idarucizumab; in dynamic equilibrium, any thrombin-bound dabigatran will equilibrate with unbound dabigatran and rapidly thereafter be bound by any free idarucizumab. The idarucizumab-dabigatran complex showed a very rapid on-rate and slow-off rate of dabigatran to idarucizumab which results in a half-life of the idarucizumab-dabigatran complex of approximately 260 hours.[10-12]

Pharmacodynamics

In vitro, idarucizumab reverses dabigatran activity in a concentration-dependent manner, and complete neutralization occurs in equimolar concentrations of dabigatran and idarucizumab, defined as clotting time returning to baseline.[9,11] A single bolus injection of idarucizumab completely reverses the prolonged dabigatran anticoagulant activity within 1 minute of injection and maintains reversal until idarucizumab becomes saturated.[9,11-14] Idarucizumab saturation occurs once molar concentration of idarucizumab exceeds that of molar concentration of dabigatran. A dose of 2 gram idarucizumab was calculated to be approximately equimolar to median dabigatran body load from the RE-LY trial.[9,11-14] As long as idarucizumab is available and exceeds the molar concentration of total dabigatran, it will bind all dabigatran in plasma. Due to the long half-life of the dabigatran-idarucizumab complex (~260 hours), this binding is practically irreversible. Idarucizumab still binds at pH 6.7 and captures dabigatran even under acidotic conditions.[9,11] Idarucizumab mimics thrombin in its molecular recognition of dabigatran but lacks thrombin-like enzymatic activity and does not bind to thrombin substrates. In phase 1 studies, the primary pharmacodynamic biomarkers were diluted thrombin time (dTT) and ecarin clotting time (ECT) since these parameters had

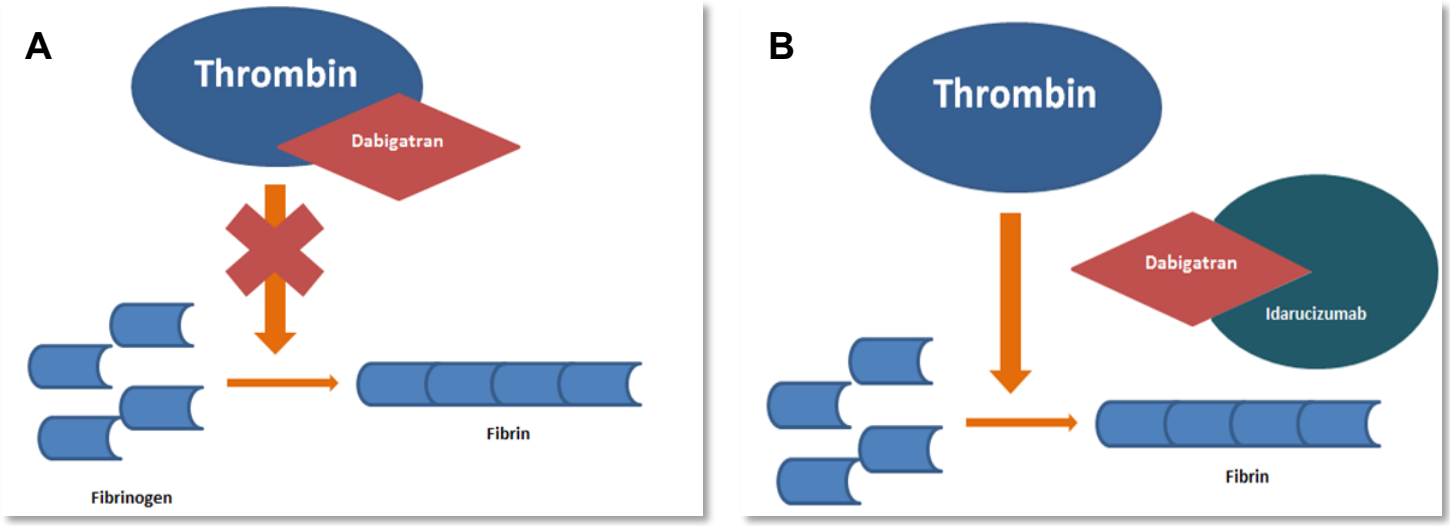

Figure | Mechanisms of action for dabigatran (panel A) and idarucizumab (panel B).

adequate sensitivity, were the least variable, and displayed linear relationship with dabigatran concentrations.[12-14] Simultaneously, activated partial thromboplastin time (aPTT), thrombin time (TT), and activated clotting time (ACT) were analyzed as supportive measures. Unfortunately, most hospitals lack tests for the rapid assessment of dabigatran levels apart from the aPTT.[9] The aPTT displays a curvilinear relationship with dabigatran concentrations.[15] Thus, at higher concentrations of dabigatran the aPTT assay levels off and a clear dose-response relationship is lost. Higher aPTT values only indicate significant anticoagulation, but a reversal of aPTT values to below the upper limit of normal does indicate reversal of significant anticoagulation.[15]

Pharmacokinetics

Idarucizumab is an active drug that is administered intravenously. It reaches C_{max} in less than 5 minutes and the plasma concentration time profile does not change significantly if administered alone or after dabigatran use.[9,11] Following administration, idarucizumab is mostly found intravascularly with a volume of distribution at steady state (V_{ss}) of 8.9 L.[12-14] This is relatively ideal since the drug is mainly confined in its site of action. Idarucizumab is rapidly eliminated with a total clearance of 47 mL/min. Elimination is mainly renal (33%) and the rest is eliminated via protein catabolism in the kidney or biodegradation to smaller molecules which are then imported in general protein synthesis. After treatment of idarucizumab, proteinuria has been observed and peaked 4 hours after administration and normalized within 24 hours. Studies of subjects with mild-to-moderate renal impairment showed an increase in area under the curve (AUC) by 43.5% -83.5%, suggesting that persons with renal impairment will have an increased idarucizumab exposure and decreased clearance.[13] A provider may consider the risk of a thromboembolic event in patients with renal impairment receiving 5 mg of idarucizumab. **Table 1** provides a summary of pharmacokinetic data for both dabigatran and idarucizumab.

Drug Interactions

No formal clinical drug-drug interactions between idarucizumab and other drugs have been reported. *In vitro* studies suggest that inhibition of dabigatran by idarucizumab is not affected by coagulation factor concentrates, including 3- or 4-factor prothrombin complex concentrates (PCC), activated PCC, or recombinant Factor VIIa.[10,11] Swine studies of the potential effect of the binding of idarucizumab to dabigatran in the presence of volume replacement agents (e.g., crystalloids, colloids, and retransfusion of washed red blood cells) suggest that the neutralization of dabigatran anticoagulant activity is not influenced by 50% hemodilution with routinely used volume replacement strategies.[16] Moreover, idarucizumab does not inhibit the anticoagulant activity of other anticoagulant drugs such as VKA, Factor Xa inhibitors (FXa), heparins or other direct thrombin inhibitors (DTI) of different structure than dabigatran (i.e., hirudin and argatroban). In an *in vivo* bleeding model where both dabigatran and platelet inhibitors were present in combination, idarucizumab only partially reversed bleeding time. This finding was likely due to the prolonged bleeding time being a consequence of both thrombin inhibition and platelet inhibition.

Clinical Studies

The safety and efficacy of idarucizumab have been investigated in pharmacokinetic/pharmacodynamic trials with healthy volunteers and in an ongoing single cohort case series trial (RE-

Table 1 | Pharmacokinetic Properties.[12-14]

Property	Dabigatran	Idarucizumab
Route	Oral	Intravenous
Bioavailability	3 to 7%	N/A
Time to C_{max}	1-hour	<5 minutes
V_d	50-70 L	8.9 L
Protein Binding	35%	N/A
Prodrug	Yes	No
Active Metabolite	Yes	No
Metabolism	Glucuronidation	None
$t_{1/2}$	Terminal: 13 hrs	Initial: 47 min Terminal: 10.3 hrs
Excretion	Mostly renal; P-gp	Protein catabolism; renal

C_{max}= maximum concentration; **P-gp** = P-glycoprotein; **$t_{1/2}$**= half-life; **V_d**= volume of distribution

VERSE AD) with dabigatran-treated patients who have life-threatening or uncontrolled bleeding, or who require emergency surgery or urgent procedure. The reversal of elevated anticoagulation tests in dabigatran-treated patients was considered a surrogate for clinical efficacy.

Phase I Trials

The analysis of three randomized, placebo-controlled trials in healthy volunteers demonstrated the utility of idarucizumab in dabigatran reversal (**Table 2**). Of these trials, trial 1321.2 observed coagulation parameters in order to assess dabigatran reversal. The other two trials, 1321.1 and 1321.5, assessed safety and adverse effects of idarucizumab and their results are discussed below in the adverse events section. Within each trial, the demographic characteristics were balanced across the subject groups. However, the inclusion criteria differed between the 3 trials regarding sex, age, and renal impairment. Of the pooled 283 patients from all three trials, approximately half (157 subjects) participated in trial 1321.1, about one sixth (46 subjects) participated in trial 1321.2, and about one third (80 subjects) were included in the 1321.5 trial.

Trial 1321.2 observed dTT and ECT times of dabigatran-pretreated subjects aged 45-64 years. These parameters had adequate sensitivity, were the least variable, and displayed linear relationship with dabigatran concentrations.[12-14] The plasma concentrations of unbound dabigatran were reduced to below the lower limit of quantification immediately after the administration of 5 g idarucizumab.[13] Subjects' dTT, ECT, aPTT, TT, and ACT parameters returned to baseline levels. Similar findings were also observed in elderly subjects (aged 65 to 80 years) as well as subjects with mild or moderate renal impairment.

Of the 283 subjects combined from all 3 trials, 224 received at least one dose of idarucizumab.[12-14] These pooled trials consists of mostly male subjects (only 19 women) and 30 subjects aged 65 years or older (median age 36 years). The median duration of complete reversal for doses >2.5 g was 72 hours (i.e., the length of the observation period). As a result of these three studies, in October 2015, the FDA granted accelerated approval of idarucizumab for the treatment of dabigatran-associated life-threatening or uncontrolled bleeding, or for urgent reversal of anticoagulation before an invasive procedure.

RE-VERSE AD Study

The RE-VERSal Effects of idarucizumab on Active Dabigatran (RE-VERSE AD) study is an ongoing multicenter, prospective cohort study evaluating the efficacy of idarucizumab in reversing the anticoagulant effects of dabigatran in patients with serious bleeding or in patients requiring an invasive procedure. An interim analysis of the first 123 patients (of 300 planned) in the study, who were recruited from June 2014 through February 2015 were recently published.[10] Of these, 123 subjects, only 90 subjects had central laboratory data. The study included patients aged ≥18 years who were taking dabigatran and judged to have overt, uncontrollable, or life-threatening bleeding needing treatment (Group A, n=51) or who required surgery or invasive procedures that could not be delayed for >8 hours (Group B, n=39). Patients in this study were predominantly elderly with a median age of 76 years, most were white (78%), and roughly 50% were men. The median creatinine clearance was 58 mL/min but renal function varied from 16-187 mL/min. Most of the subjects (96%) were receiving anticoagulation for atrial fibrillation, and median time since last dose of dabigatran was 15.4 hours.

Patients received a total dose of 5 g of IV idarucizumab as two 2.5-mg boluses, 15 minutes apart. Blood samples were obtained at baseline, after the first infusion, between 10 and 30 minutes, and at 1, 2, 4, 12, and 24 hours after the second bolus for pharmacological assessments. The primary endpoint was reversal of the anticoagulant effects of dabigatran based upon dTT or ECT at any time points from the first infusion to 4 hours after the second infusion. Secondary endpoints included clinical resolution of bleeding, normalization of dTT or ECT, and reduction in the concentration of unbound dabigatran. Clinical outcomes included the severity of bleeding, hemodynamic stability and modified Rankin Scale of all intracranial hemorrhage patients at 90 days in Group A and hemostasis (normal, mildly, moderately, or severely abnormal) in Group B. Patients received follow-up for at least one month after idarucizumab administration. In Group A, 20 (39%) patients met inclusion criteria because of GI bleeding, 18 (35%) because of intracranial hemorrhage, and 16 (31%) because of hemodynamic instability. A number of patients had normal dTT and/or ECT prior to idarucizumab administration and these patients were excluded from the efficacy analysis. Of these patients, 22 had normal dTT and 9 had normal ECT prior to idarucizumab administration. The maximum percentage reversal was 100% in both groups. Normalization of dTT was achieved in 98% of patients with acute bleeding and 93% of patients requiring an invasive procedure. ECT was normalized within minutes in 89% and 88% of patients in Groups A and B, respectively. The concentration of unbound dabigatran was <20 ng/mL in all but one patient. The median investigator-reported time to cessation of bleeding was 11.4 hours, excluding 13 patients for whom time to the cessation of bleeding could not be ascertained (i.e. 5 intracranial hemorrhage, 4 gastrointestinal bleeding, 2 intramuscular bleeding, 1 pericardial bleeding, 1 retroperitoneal bleeding). This finding is not dissimilar to the use of prothrombin-concentrate complexes for warfarin and Factor Xa inhibitors.[17-19] A normal intraoperative hemostasis was reported in 33 (92%) patients in Group B.[10] There were 18 deaths overall (9 in group A and 9 in Group B) that were thought to be related to the index event or co-existing conditions in this high-risk, older patient population. Thrombotic events occurred in 5 patients (i.e., DVT, PE, NSTEMI, ischemic stroke) who received idarucizumab, none of whom were receiving anticoagulation at the time their thrombosis was diagnosed; only one thrombotic event occurred within 72 hours after receiving idarucizumab.

Strengths of the study include the broad inclusion criteria that increases the generalizability of the study (i.e., any adults taking dabigatran), and the simple study design that may be easily replicated. A major limitation of the study is the lack of a comparator (placebo or otherwise), making it difficult to compare drug administration to lack-thereof. As for patients who continue to bleed, supportive care with any blood products are permitted. Out of the 90 subjects included in the analysis, 50 subjects received some form of blood product such as packed red cells (42.2%), fresh frozen plasma (25.6%), and activated prothrombin complex concentrate (4.4%). Nearly one-fourth of patients were enrolled despite what turned out to be normal initial coagulation profiles (inflating any measure of apparent reversal or bleeding time cessation). Lastly, these data represent preliminary results and only encompasses a small sample of the planned cohort, making it challenging to interpret these results.

Table 2 | Summary of idarucizumab studies.[9,12-14]

Trial Number	1321.1	1321.2	1321.5	1321.3 (RE-VERSE AD)
Completed	2013	2014	2014	Ongoing
Sample Size	N=157 • Part 1 (n=110) • Part 2 (n=35) • Part 3 (n=12)	N=46	N= 80 • Part 1 (n=32) • Part 2 (n=48)	N=90 of planned 300 • Grp A (major bleed; n=51) • Group B, urgent procedure (n=39)
Study Details	• Phase 1 RCT • Double blind • Single center	• Phase 1b RCT • Double blind • 2-way crossover • Single center	• Phase 1 RCT • Double blind • Sequential rising order • Single center	• Phase 3 trial, no control • Prospective cohort • Open-label • Multicenter
Patient Characteristics	• Male • 97.3% Caucasian • Age 18-45 • BMI 18.5-29.9	• Age 45 to 80 • BMI 18.5-32 • CrCl ≥30 mL/min	• Japanese males • Age 20 to 45 • BMI 18.5 to 24.9	• Age ≥18 • Currently taking dabigatran • 95% with atrial fibrillation • Mean CrCl 59-65
Dabigatran (oral) Regimen Before Idarucizumab	• Part 1: none • Part 2: 220 mg BID x 3 days, then 220 mg on day 4 • Part 3: 220 mg BID x 3 days, then 220 mg on day 4	• Healthy, age 45-65: 220 mg BID x 3 days, then 220 mg on day 4 • Healthy, age 65-80: 220 mg BID x 3 days, then 220 mg on day 4 • CrCl 30-90 mL/min: 150 mg BID x 3 days, then 150 mg on day 4	• 220 mg BID x 3 days, then 220 mg on day 4	Group A • 150 mg BID (27%) • 110 mg BID (67%) • 75 mg BID (2%) • Other (4%) Group B • 150 mg BID (38%) • 110 mg BID (62%)
Idarucizumab Regimen (intravenous)	Part 1: • Varying doses for 1-hour infusion (0.02 g -8 g) • 5-min infusion Part 2: • Varying doses as 5-min IV infusion (1 g, 2 g, 4 g) Part 3: • 5 g followed by 2.5 g (1-hour apart) as 5-min infusions	High dose: • 5 g single dose • Two 2.5 g doses. 5 -min infusions (1-hour apart) Medium dose: • 2.5 g single dose Low dose: • 1 g single dose	Part 1: • Varying doses for 5-min infusion (1 g, 2 g, 4 g) • 8 g single dose for 1-hour infusion Part 2 • Varying doses for 5-min infusion (1 g, 2 g, 4 g) • Two 2.5 g doses, 5-min infusions (15-min apart)	Two 2.5 g doses. 5-min infusions (15-min apart)
Primary Outcome	Drug-related adverse events observed	At least 1 coagulation parameter (dTT or ECT) was reversed to the upper limit of normal within 10 minutes after completion of idarucizumab infusion	Percentage of subjects with drug-related adverse events	Maximum reversal of dabigatran anticoagulant effect based on dTT or ECT, at any time between the end of the first infusion to 4 hours after the last infusion
Results	Headache, erythema, migraine, and epistaxis	All subjects (100%) showed reversal of dabigatran	No subject reported any adverse events due to idarucizumab	Group A: • dTT normalized in 98% • ECT normalized in 89% Group B: • dTT normalized in 93% • ECT normalized in 88%

BID= twice daily; **dTT**= diluted thrombin time; **ECT**= ecarin clotting time; **RCT**= randomized control trial

Table 3 | Idarucizumab pooled adverse events from phase 1 trials.[12-14]

Adverse Event	Idarucizumab Alone (n=107)	Dabigatran + Idarucizumab (n=117)
Any adverse event	29 (27.1)	26 (22.2)
Headache	9 (8.4)	3 (2.6)
Skin irritation	3 (2.8)	3 (2.6)
Dizziness	1 (0.9)	4 (3.4)
Back pain	4 (3.7)	0
Nasopharyngitis	2 (1.9)	1 (0.9)
Diarrhea	2 (1.9)	1 (0.9)
Constipation	1 (0.9)	1 (0.9)
Injection site hematoma	1 (0.9)	1 (0.9)
Migraine	2 (1.9)	0
Asthenia	0	2 (1.9)
Epistaxis	0	1 (0.9)
Fatigue	1 (0.9)	1 (0.9)
Nausea	1 (0.9)	0
Paraesthesia	0	1 (0.9)
Musculoskeletal stiffness	2 (1.9)	1 (0.9)
Abdominal pain	1 (0.9)	0
Myalgia	1 (0.9)	1 (0.9)
Pain in extremity	1 (0.9)	1 (0.9)

Data represent n (%).

Adverse Events

Adverse events of the pooled analysis of the three phase 1 trials are summarized in **Table 3**. The overall frequency of adverse events was similar between idarucizumab-treated subjects (n=55; 25%) and placebo-treated subjects (n=26; 25%). Among those subjects treated with idarucizumab, only headache was reported in ≥5% of subjects. In all phase 1 studies, antibody formation against idarucizumab following single administration was analyzed throughout the study, including 3-month follow-up. Overall, a low immunogenic potential was observed.

In a 120-day safety update report on idarucizumab, a total of 123 dabigatran-treated patients recruited to RE-VERSE AD were administered idarucizumab either because they required an emergency surgery or urgent procedure, or because they presented with life-threatening or uncontrolled bleeding. Adverse reactions reported in ≥5% of patients were hypokalemia (n=9; 7%), delirium (n=9; 7%), constipation (n=8; 7%), pyrexia (n=7; 6%), and pneumonia (n=7; 6%). Mild symptoms of potential hypersensitivity (i.e., pyrexia, bronchospasm, hyperventilation, rash, and pruritus) were reported following use of idarucizumab. **Table 4** summarizes adverse events from REVERSE-AD interim data.

As with all proteins, idarucizumab can potentiate immunogenicity. Pre-existing antibodies with cross-reactivity to idarucizumab were detected in approximately 13% (n=36) of the subjects. Treatment-emergent, and possibly persisting anti-idarucizumab antibodies with low titers were observed in 4% (n=9) of the subjects treated with idarucizumab. No impact on the pharmacokinetics or the reversal effect of idarucizumab or hypersensitivity reactions were observed in these subjects.

Indications and Usage

Place in Therapy

Idarucizumab is indicated in patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran are needed. Such instances include emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding. This indication received accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in studies of healthy volunteers. Continued approval for this indication may be contingent upon results of an ongoing cohort case series study.

Dosage and Administration

The recommended dose of idarucizumab is 5 g administered IV as two consecutive 2.5-g infusions or by consecutive bolus injections via syringe. A pre-existing intravenous line may be used for administration of idarucizumab and the line must be flushed with sterile 0.9% sodium chloride injection, USP solution prior to infusion. No other infusion should be administered in parallel via the same intravenous access. Idarucizumab needs to be administered within 1 hour once the solution has been removed from the vial. Idarucizumab can be used in conjunction with standard supportive measures (i.e., volume replacement agents or coagulation factor concentrates).

Limited data support administration of an additional 5-g dose of idarucizumab. If reappearance of clinically relevant bleeding together with elevated coagulation parameters is observed after administration of the initial 5-g dose of idarucizumab, administration of an additional 5-g dose may be considered. Similarly, patients who require second emergency surgery/urgent procedure and have elevated coagulation parameters may receive an additional 5-g dose.

Safety and effectiveness of idarucizumab during labor and delivery have not been studied in clinical trials. Whether idarucizumab causes fetal harm or affects reproduction capacity when administered to a pregnant woman is not known. Accordingly, idarucizumab should be given to a pregnant woman only if clearly needed. The effects of idarucizumab on the breastfed child or on milk production are unknown. Because many drugs are excreted in human milk, caution should be exercised when idarucizumab is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for idarucizumab and any potential adverse effects on the breastfed child from idarucizumab or from the underlying maternal condition.

A total of 111 (90%) patients treated with idarucizumab in the case series trial were 65 years of age or older, and 74 (60%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Safety and effectiveness have not been established in pediatric patients.

Table 4 | Idarucizumab adverse events from RE-VERSE-AD interim data.

Adverse Event	Group A (n=66)	Group B (n=57)
Any adverse events	59 (89.4)	44 (77.2)
Severe adverse events	23 (34.8)	16 (28.1)
Drug-related adverse event	4 (6.1)	1 (1.8)
Serious adverse events	31 (47.0)	22 (38.6)
Fatal	12 (18.2)	12 (21.1)
Immediately life threatening	1 (1.5)	1 (1.8)
Disability/incapacitation	1 (1.5)	1 (1.8)
Required hospitalization	11 (16.7)	9 (15.8)
Prolonged hospitalization	7 (10.6)	6 (10.5)
Congenital anomaly	0	0
Other	4 (6.1)	4 (7.0)

Data represent n (%).

Restarting Antithrombotic Therapy

Patients being treated with dabigatran therapy likely have underlying disease states or conditions that predispose them to thromboembolic events; reversing dabigatran therapy therefore exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate. In REVERSE-AD, only 72 out of 90 subjects reinitiated any antithrombotics (38 in group A and 34 in group B). Of the 72 subjects, 38 was restarted on dabigatran with or without a heparin bridge, while the rest was either put on low-molecular-weight heparin, unfractionated heparin, aspirin, apixaban, clopidogrel, warfarin, or rivaroxaban. The lag period of when to expect the anticoagulant effect of dabigatran to begin working again was not addressed in the trial. Pharmacologically, dabigatran should be effective if the body is free of unbound idarucizumab. If the molar concentration of idarucizumab exceeds that of dabigatran, then the unbound idarucizumab is theoretically available to bind dabigatran if reinitiated. Dabigatran can be reinitiated 24 hours after administration of idarucizumab but a lag may occur until all unbound idarucizumab is eliminated, which can take about 2 days.

Precautions and Contraindications

In clinical studies adverse events possibly indicative of hypersensitivity (e.g. anaphylactoid reaction) to idarucizumab or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment. Inactive ingredients include acetic acid (Glacial), polysorbate 20, sodium acetate trihydrate, and sorbitol. If an anaphylactic reaction or other serious allergic reaction occurs, idarucizumab should be immediately discontinued and proper treatment should be initiated.

In patients with the condition of hereditary fructose intolerance who have received parenteral administration of sorbitol, serious adverse reactions, including fatal reactions, have been reported. Reactions have included hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, and acute liver failure with breakdown of excretory and synthetic function. The recommended dose of idarucizumab contains 4 g sorbitol as an excipient and one should consider the combined daily metabolic load of sorbitol/fructose from all sources (i.e. idarucizumab and other drugs) especially in patients with hereditary fructose intolerance. The minimum amount of sorbitol at which serious adverse reactions may occur in these patients is not known.

Conclusion

Bleeding is the major adverse risk with all anticoagulants; however, unlike warfarin, dabigatran and other DOACs have until now lacked reliable reversal agents. Idarucizumab, which is specific for dabigatran reversal, is the first reversal agent with an FDA-approved indication for reversing anticoagulant effects of a direct thrombin inhibitor. Idarucizumab (Praxbind®) has been studied in three phase 1 randomized placebo-controlled trials and was recently granted accelerated approval by the FDA. Idarucizumab is used in patients who are taking dabigatran during emergency situations when there is need to reverse anticoagulant effects of dabigatran. The interim analysis of the ongoing REVERSE-AD trial showed normalization of dTT in majority of patients with acute bleeding or requiring an invasive procedure. Despite these promising results, the REVERSE-AD study outcomes are difficult to evaluate without a specific control or comparison group. Without a control population, no conclusive statement may be made. Overall, with the availability of a novel reversal agent for one of the DOACs as well as the possibility of others currently underway to approval (Table 5), the prospect of changing the landscape of long-term anticoagulation is promising. Reversal agents for DOACs can potentially be the catalyst in transitioning patients from VKAs to DOACs.

Table 5 | Anticoagulant reversal agents currently under clinical development.[20]

Agent	Description	Notes
Aripazine (PER977; Perosphere, Bedford, New York, USA)	Synthetic molecule that binds to DOACs via non-covalent bonding and charge-charge interactions	• Reduced bleeding in rivaroxaban-treated rabbit liver laceration model • Decreased whole-blood clotting times in edoxaban-treated healthy volunteers
Andexanet alfa (Portola Pharmaceuticals, San Francisco, USA)	A recombinant factor Xa derivative which lacks catalytic and membrane binding activity currently undergoing clinical development for specific reversal of factor Xa inhibitor anticoagulant effect	• Corrected abnormal anti-Xa activity due to rivaroxaban, apixaban, betrixaban, and edoxaban *in vitro* • Corrected coagulation assays and reduced blood loss following liver laceration of rivaroxaban-treated rabbits • Decreased anti-Xa activity and reduced plasma concentrations of free apixaban compared to placebo in healthy volunteers receiving apixaban

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Editor's Corner

Blood Pressure and Cholesterol Lowering for Primary Prevention in Patients with Intermediate Risk: HOPE-3 Trial

Three studies recently published in the *New England Journal of Medicine* investigated the efficacy and safety of lowering LDL cholesterol and/or blood pressure for prevention of major cardiovascular (CV) events in patients without CV disease.[1-3]

The study included men ≥55 years and women ≥65 years with ≥1 risk factor (or women ≥60 years with ≥2 risk factors) for CV disease. Patients with CV disease were excluded from the study. Through a 2x2 factorial design, a total of 12,705 patients were randomized into four groups: (1) candesartan/HCTZ and rosuvastatin, (2) candesartan/HCTZ and placebo, (3) rosuvastatin and placebo, or (4) dual placebo. Patients receiving candesartan/HCTZ and rosuvastatin were initiated at a dose of 16/12.5 mg and 10 mg, respectively. Follow-up visits occurred at 6 weeks after randomization, then every 6 months thereafter. The first coprimary outcome was the composite of death from CV causes, nonfatal MI, or nonfatal stroke. The second coprimary outcome was the composite of the first coprimary outcome plus resuscitated cardiac arrest, HF, or revascularization.

Over a median follow-up of 5.6 years, patients assigned to the combined-therapy group had significant reductions in both coprimary outcomes compared to dual-placebo (3.6% vs 5.0% for first coprimary outcome, p=0.005; 4.3% vs 5.9% for second coprimary outcome, p=0.003). In regards to cholesterol lowering alone, patients receiving rosuvastatin had the first coprimary outcome occur in 3.7% of patients compared to 4.8% of patients receiving placebo (p=0.002). A similar result was also observed with the occurrence of the second coprimary outcome (4.4% vs 5.7%, p<0.001). No significant differences were observed between candesartan/HCTZ and placebo in the occurrence of the first coprimary outcome (4.1% vs 4.4%, p=0.40) and the second coprimary outcome (4.9% vs 5.2%, p=0.51) in the overall population. Only patients in the highest baseline systolic BP tertile (>143.5 mm Hg) who received candesartan/HCTZ had lower rates in both coprimary outcomes compared to patients receiving placebo.

The results of the HOPE-3 trial support the use of statins to reduce CV events in patients who are deemed intermediate CV risk. However, BP lowering alone does not reduce CV events in patients with intermediate risk and appears to be only beneficial in patients with HTN. A caveat with the BP arm of the trial is the relatively low dose of candesartan and HCTZ used. Whether a more aggressive BP lowering approach would have provided better results remains to be seen. Nonetheless, this study reinforces the current guideline recommendations supporting a risk-based approach to statin use and adds additional evidence in the use of statins for primary prevention.

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Personalized Medicine Corner

Pharmacogenetics and SSRIs in the Treatment of Depression

Nearly 7% of U.S. adults have at least one major depressive episode annually.[1,2] SSRIs (e.g., sertraline, escitalopram) are first-line treatment options for major depressive disorder. Although SSRIs have been shown to be equally effective, approximately half of patients fail to respond well to their initial SSRI and require treatment modification.[3,4]

Optimizing therapy is further confounded by the slow onset of SSRI response, with the full therapeutic benefit often taking up to 8 weeks. This delay is important because of the potential for self-harm, suicidality, and other adverse events related to untreated depression. While data demonstrating a clear link between genetic factors and SSRI antidepressant effectiveness are lacking, recent studies show a genetic link with the risk for adverse effects.

Cytochrome P450 enzymes 2D6 (CYP2D6) and 2C19 (CYP2C19) are key metabolizers of several SSRIs. These genotypes confer the normal, intermediate, poor, rapid, and ultra-rapid metabolizer phenotypes. The Clinical Pharmacogenetics Implementation Consortium (CPIC; https://cpicpgx.org/) has released guidelines for incorporating CYP2D6 and CYP2C19 phenotype information into prescribing decisions for certain SSRIs - sertraline, escitalopram, citalopram, paroxetine, and fluvoxamine.[4] Guidelines do not address whether genotyping should be done, but rather provide guidance for use of genotype information when available. The recommendations from these guidelines are summarized as below.

Recommendations for Citalopram, Escitalopram, and Sertraline based on CYP2C19 Phenotype[4]

CYP2C19 Phenotype	Recommendation
Rapid or Ultrarapid Metabolizer	Consider alternative drug not predominantly metabolized by CYP2C19
Normal or Intermediate Metabolizer	Initiate therapy with recommended starting dose
Poor Metabolizer	Consider 50% reduction of starting dose or alternative drug not predominantly metabolized by CYP2C19

Recommendations for Fluvoxamine and Paroxetine based on CYP2D6 Phenotype[4]

CYP2D6 Phenotype	Recommendation
Rapid or Ultrarapid Metabolizer	Paroxetine: Consider alternative drug not predominantly metabolized by CYP2D6 Fluvoxamine: No recommendation due to lack of evidence
Normal or Intermediate Metabolizer	Initiate therapy with recommended starting dose
Poor Metabolizer	Consider 50% reduction of starting dose or alternative drug not predominantly metabolized by CYP2D6

Genotyping is likely to have the most clinical benefit in patients being newly initiated on an SSRI to help guide drug and dosage selection. Contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu) for more information about these findings or for assistance with interpreting *CYP2D6* or *CYP2C19* pharmacogenetic test results clinically.

Contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu) for more information about these findings or for assistance with interpreting CYP2C19 pharmacogenetic test results clinically.

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