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Novel Reversal Agents for Non-Vitamin K Oral Anticoagulants

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Abstract

Background Non-vitamin K oral anticoagulants (NOACs) have become an appealing alternative treatment for the prevention of stroke in non-valvular atrial fibrillation and in treatment of venous thromboembolism. The major limitation to the use of these drugs is the lack of reversal agents. The purpose of this review is to investigate the development and efficacy of novel agents for reversal of NOACs. **Methods** Two separate literature searches were conducted in the PubMed database using the terms “prothrombin complex concentrate” and “idarucizumab”, respectively. Only in vivo clinical trials involving human subjects published within the last five years were included for possible analysis. Studies with disease-specific populations (i.e. non-valvular atrial fibrillation, etc.) were excluded. Three studies were chosen based on these inclusion and exclusion criteria. **Results** A phase I trial investigating Cofact, a non-activated, four factor prothrombin complex concentrate (PCC), demonstrated that Cofact normalized the prothrombin time (PT) and endogenous thrombin potential (ETP) in all participants anticoagulated with rivaroxaban but had no effect on the prolongation of the activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT) in participants anticoagulated with dabigatran etexilate. In another phase I trial clinical trial, idarucizumab, at doses of 4 and 5 + 2.5 g, effectively reversed anticoagulation with dabigatran etexilate immediately and at 24 hours, as assessed by the dilute thrombin time (dTT), ECT, thrombin time (TT), and aPTT. An ongoing phase III clinical trial with 5 g idarucizumab also demonstrated effective reversal of dabigatran etexilate in roughly 86 percent of patients at 24 hours. **Conclusion** Only idarucizumab has been approved by the FDA for clinical use. Therefore, dabigatran etexilate is preferable to the factor Xa inhibitors for oral anticoagulation in adult patients, based on the current availability of an approved, effective reversal agent.

Introduction

Until 2009, warfarin was the mainstay of treatment for patients with non-valvular atrial fibrillation (NAF), thrombophilia, or those at risk for venous thromboembolism (VTE). However,

due to warfarin's variable pharmacokinetic profile, researchers and clinicians were eager to find an effective alternative to the drug. Clinicians also recognized that patients would more readily comply with a treatment regimen that required fewer dietary restrictions and less frequent coagulation monitoring. Dabigatran etexilate (dabigatran), a direct thrombin inhibitor, was approved by the FDA in 2009 for treatment of NAF and in 2010 for treatment of VTE. The direct factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban) were subsequently approved by the FDA for treatment of NAF and VTE. These drugs collectively comprise the "NOAC" anticoagulants, that is, non-vitamin K oral anticoagulants. Since their approval, the NOACs have been an appealing alternative to treatment with warfarin, as these drugs do not require routine lab monitoring, dietary restrictions, and have a more reliable pharmacokinetic profile. However, the main clinical concern with the NOACs is that no reversal agents for these drugs exist.

In 2013, the FDA approved non-activated 4-factor prothrombin complex concentrate (PCC) for the rapid reversal of vitamin K antagonists (VKAs) such as warfarin. Recent studies have also examined the effectiveness of PCC in reversing direct factor Xa and direct thrombin inhibitors. PCC is a coagulation factor replacement product containing factors II, VII, IX and X, heparin, protein C and S, antithrombin III and human albumin. It is a blood product derived from human plasma and administered intravenously for emergent reversal of oral anticoagulants[1].

Recent studies have also investigated idarucizumab, a humanized mouse monoclonal antibody fragment, as a potential agent for dabigatran etexilate reversal. Idarucizumab is administered intravenously for patients requiring emergent reversal of anticoagulation therapy with dabigatran[2]. During in vitro and in vivo studies, idarucizumab binds dabigatran with an affinity that is 300 times greater than the affinity of dabigatran for thrombin, to such an extent that idarucizumab will bind dabigatran that is already in complex with thrombin. The dabigatran-idarucizumab complex is then excreted by the kidneys[2,3].

With the increasing clinical use of NOACs, there is a growing need for an effective antidote. As such, we conducted this review to examine ongoing research of reversal agents for NOACs, a riveting topic for both patients and clinicians.

Clinical Scenario

K.M. is a 57 year old black male who began taking dabigatran (Pradaxa) two years ago when he was diagnosed with non-valvular atrial fibrillation. The only other medication he takes is ibuprofen for chronic knee pain. Today, he presents to the emergency department with a two week history of epigastric abdominal pain, nausea, dizziness on standing, and dark stool. K.M. also has a history of gastroesophageal reflux disease and says he has been treated for a "stomach ulcer" in the past. Based on his history, physical examination, and chest X-ray showing free air under the right hemidiaphragm, the ER physician assistant determines that K.M. needs emergent surgery for a perforated gastric ulcer. Are there any existing agents clinically available for anticoagulation reversal?

Clinical Question

Among male and female patients taking NOACs as oral anticoagulant therapy, is reversal of direct factor Xa inhibitors with prothrombin complex concentrate (PCC) more effective than reversal of direct thrombin inhibitors with idarucizumab for cases of major bleeding or requiring emergent or invasive surgery ***(figure 1)***?

Population	Men and women taking oral anticoagulants
Intervention	prothrombin complex concentrate for reversal of direct factor Xa inhibitors (i.e. rivaroxaban)
Comparison	idarucizumab for reversal of direct thrombin inhibitors (i.e. dabigatran)
Outcome	effective reversal of major bleeding and for cases requiring emergent invasive surgery

Figure 1: Study PICO used to formulate the clinical question.

Methods

Two separate PubMed searches were conducted using the search terms “prothrombin complex concentrate” and “idarucizumab”, respectively. Inclusion criteria for both searches included publication within the last five years. The randomized control trial (RCT) filter was selected only during the PCC search because doing so in both searches would have excluded a pivotal prospective cohort study of idarucizumab that could not ethically be conducted as a RCT. Therefore, the “clinical trial” filter was selected during the idarucizumab search instead of “RCT”.

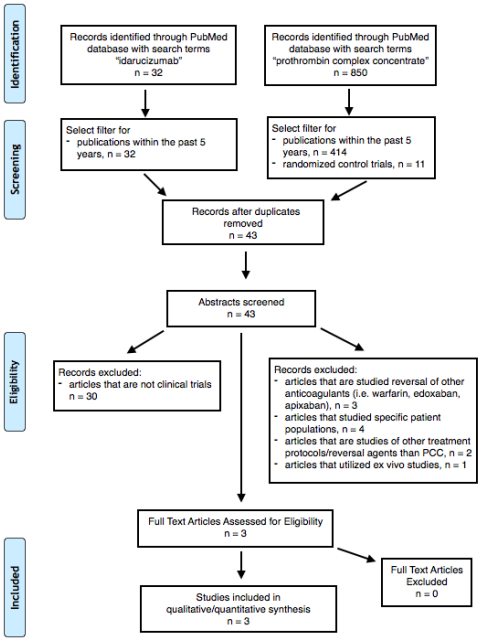

Figure 2: PRIMSA diagram.

Articles were excluded if the studies did not involve dabigatran or rivaroxaban, examined reversal agents other than PCC and idarucizumab, or included study populations that were too disease-specific (i.e. non-valvular atrial fibrillation, etc.). Further exclusion criteria included animal studies and ex vivo studies ***(figure 2)***.

Results - Idarucizumab Phase I Trial

Glund et al. examined a population of 47 white males deemed healthy based on their body mass index and normal creatinine clearance. The study design was a randomized, placebo-controlled phase I trial utilizing paid volunteers at a single study site in Belgium. Phase I trials are the first testing phase after animal testing in the FDA drug review process[4]. All participants were given at least one dose of 220 mg dabigatran etexilate prior to treatment with idarucizumab or placebo. One goal of the study was to determine a dose of idarucizumab to effectively reverse dabigatran, so participants were divided into four treatment

	Idarucizumab	Placebo	Total

groups, receiving 1, 2, 4, and 5 + 2.5 g of idarucizumab, respectively ***(table 1)***. Idarucizumab or placebo were given as a five minute infusion, except the 5 + 2.5 g dose, which was given as two separate infusions one hour apart. Blood samples were drawn from all participants at baseline, immediately following administration of idarucizumab or placebo, and at 2, 4, 6, 8, 10, 12, 14, 18, and 24 hours. Samples were assessed for reversal with the dilute thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), endogenous thrombin potential (ETP), and fibrinopeptide A concentrations in shed blood. The study authors created a study-specific upper limit of normal (ULN) for each of the coagulation assays, using data collected from the 47 study participants on two separate days before treatment with idarucizumab as well as data from 16 volunteers in a different arm of the study. Total and unbound dabigatran concentrations were assessed to correlate with coagulation assays. Participants were followed up at one and three months after idarucizumab administration to determine if any adverse events had occurred and to test for the formation of anti-drug antibodies to idarucizumab.

Dabigatran prolonged all coagulation assays in all participants, and the 2, 4, and 5 + 2.5 g infusions of idarucizumab completely and immediately reversed the prolongation of all assays. The 1 g dose completely and immediately reversed the effects of dabigatran, however at two hours after administration of idarucizumab, clotting times for all coagulation assays (dTT, ECT, aPTT, and TT) except the ACT had increased to greater than the ULN. Only the 4 and 5 + 2.5 g doses of idarucizumab were effective in sustaining reversal of coagulation assays at 72 hours,

1 g	9	3	12
2 g	9	3	12
4 g	8	3	11
5 + 2.5 g	9	3	12

Table 1: Number and distribution of patients randomized to the four dosing arms of the Glund et al. study examining the ability of idarucizumab to reverse anticoagulation with dabigatran etexilate.

indicating that the reversal of dabigatran's anticoagulant effects with idarucizumab is dose-dependent. No procoagulant effects or clinically relevant adverse events occurred among the participants at any time during the study or at follow-up. The main adverse events after idarucizumab administration included hot flashes, infusion site erythema, and hematoma. Because no significant adverse events occurred with idarucizumab administration, the drug was deemed an effective and well-tolerated reversal agent for dabigatran, and further study in the REVERSE-AD trial was able to proceed[2].

Results - Idarucizumab Phase III Cohort Study

Pollack et al. are conducting an ongoing phase III clinical trial, and the article in review is an interim analysis of 90 patients. Phase III clinical trials are the final testing phase in the FDA drug review process[4]. The study design is a prospective cohort study, as the study authors determined it would be unethical to withhold a potential treatment from patients presenting with major bleeding or in need of urgent surgery.

90 dabigatran-prescribed patients presented at 184 different international sites between June 2014 and February 2015 (see Table 2 for patient characteristics). Inclusion criteria were either (a) patients with overt, uncontrollable, or life-threatening bleeding or (b) patients requiring urgent surgery or other invasive procedure that could not be delayed for 8 hours. These patients

were divided into groups A (n = 51) or B (n = 39), respectively. Clinical characteristics of patients are presented in ***table 2***.

Table 2: Clinical characteristics of patients in the REVERSE-AD trial		
	Group A n = 51	**Group B n = 39**
Hemodynamically unstable with ongoing blood loss	16	
Intracranial hemorrhage	18	
GI bleeding	20	
Bleeding from trauma	9	
Other causes	11	
Patients taking 110 mg BID	34	24
Patients taking 150 mg BID	14	15
Elevated dTT at baseline	40	28
Elevated ECT at baseline	47	34
Median age (years)	77	76
Median weight (kg)	70.5	73
Median CrCl (mL/min)	54	60
Median time since last dose dabigatran (hours)	15.2	16.6
Bone fractures		8
Acute Cholecystitis		5
Acute renal insufficiency, catheter placement		4
Acute appendicitis		3
Joint wound infection		3
Abscess (suprapubic, scrotal)		2
Aortic dissection		1
Acute deterioration of aortic valve		1
Pericardial tamponade		1
Small bowel obstruction		1

Table 2: Clinical characteristics of patients in the REVERSE-AD trial		
	Group A n = 51	**Group B n = 39**
Pneumothorax		1
Perforation of viscera		1
Incarcerated umbilical hernia		1
Peritonitis		1
Lumbar puncture		1
Leg gangrene		1
Unstable angina		1
Hydronephrosis/ureteral obstruction		1

All patients were treated with 5 g of idarucizumab, which was administered as two 50 mL bolus IV infusions containing 2.5 g, separated by no more than 15 minutes. Blood samples were collected at baseline, after the first 2.5 g infusion of idarucizumab, between 10-30 minutes after the second 2.5 g infusion, and at 1, 2, 4, 12, and 24 hours. These blood samples were assessed by the dTT, ECT, and total and unbound plasma concentrations of dabigatran at a central laboratory to determine the maximum percentage reversal of dabigatran. The aPTT and TT were evaluated by local laboratories at 1, 2, 12, and 24 hours but also at a central laboratory. Any thrombotic events or deaths that occurred up to 90 days after idarucizumab was administered were evaluated by an adjudication committee. 88 patients were followed until death or for at least one month.

Only 68 of 90 patients were used to assess the maximum percentage reversal with idarucizumab by dTT, as 22 patients had a normal dTT at baseline. Only 81 of 90 patients were included in evaluation of maximum percentage reversal with ECT, as 9 patients had a normal ECT at baseline. These 9 patients also had a normal dTT. Patients with normal dTT and ECT

results at baseline had a greater creatinine clearance and longer time since the last ingested dose of dabigatran than those patients with elevated dTT and ECT results at baseline. Interestingly, within group A, intracranial hemorrhage occurred more frequently among patients with normal baseline coagulation assays than those with elevated baseline values. Other differences are described in ***table 3***.

After administration of idarucizumab, the dTT was normalized in 98% of patients in group A and 93% of patients in group B who could be evaluated after the first infusion. The ECT was normalized in 89% of patients in group A and 88% of group B who could be evaluated after the first infusion. At 24 hours, reversal based on dTT results was sustained below the study-specific ULN in 72% of group A patients and 54% of group B patients who could be evaluated.

	Patients with elevated coagulation assays at baseline	Patients with normal coagulation assays at baseline
Number of participants (dTT)	68	22
Number of participants (ECT)	81	9
Median creatinine clearance	67 mL/minute	48 mL/minute
Median time since last dose of dabigatran etexilate	12.8 hours	30.3 hours
Percentage with intracranial bleeding (group A)	28% (n=40)	64% (n=11)
Number of thrombotic events	3	2
Number of deaths	17	1

Table 3: Characteristics of patients with normal and elevated coagulation assay results at baseline in the phase III Pollack et al. study with idarucizumab. Patients with normal coagulation assay results at baseline were not included in the efficacy analysis with dTT and ECT but were still included in the study.

Concentrations of total and unbound dabigatran were assessed in all patients at baseline, after administration of the first vial of idarucizumab, after administration of the second vial of idarucizumab, and at 1, 2, 4, 12, and 24 hours. Before idarucizumab administration, median baseline plasma concentrations of unbound dabigatran were 84 ng/mL, and after the first 2.5 g were given, unbound dabigatran concentrations decreased to less than 20 ng/mL in 89 of 90 patients.

18 patients died during the clinical trial. The adjudication committee, independent from the Boehringer Ingelheim study group, determined that deaths occurring within 96 hours of receiving idarucizumab were attributable to the precipitating event, while deaths after 96 hours were due to existing comorbidities. Five patients experienced thrombotic events, including deep vein thrombosis, pulmonary embolism, myocardial infarction, and ischemic stroke, however none of these five patients had been restarted on anticoagulant therapy when the event occurred. Most patients were restarted on various anticoagulant therapies (n = 72). 21 patients experienced serious adverse events including death and thrombotic events, which are listed in ***table 4***[3].

Death	**18**
Thrombotic events	**5**
Gastrointestinal hemorrhage	**2**
Postoperative wound infection	**1**
Delirium	**1**
Right ventricular failure	**1**
Pulmonary edema	**1**

Table 4: Serious adverse events that occurred among study participants in the phase III trial with idarucizumab. Note: some patients experienced more than 1 adverse event.

Results - PCC Phase I Trial

Eerenberg et al. conducted the first randomized, double-blind, placebo-controlled phase I clinical trial to evaluate the efficacy and safety of Cofact, a prothrombin complex concentrate (PCC), in reversing the anticoagulant effects of rivaroxaban and dabigatran. This 2011 study included 12 healthy male participants, ages 20-28, with BMIs of 23 $\pm$ 3 kg/m^2 and normal liver and kidney function. Six of the participants received 20 mg rivaroxaban twice daily and six received 150 mg dabigatran twice daily, each for 2.5 days. Baseline coagulation assay values were determined prior to administration of PCC or placebo. Prothrombin time (PT) and endogenous thrombin potential (ETP) were the coagulation assays chosen to evaluate the Cofact's reversal of rivaroxaban. Ecarin clotting time (ECT), aPTT, thrombin time (TT), and ETP lag time were used to evaluate Cofact's reversal of dabigatran. 50 IU/kg of Cofact was chosen because this dose was seen to be the most effective in prior animal studies. Blood samples were collected at 15 minutes, 30 minutes, 1, 2, 3, 6, and 24 hours after PCC administration. After a "washout period" of 11 days, the same procedure was repeated, with each group of 6 participants receiving the other anticoagulant. All participants were observed at the clinical trial unit of the cardiac care unit at the Academic Medical Center in Amsterdam. An automated coagulation analyzer was used (Behring Coagulation System XP) for the PT, aPTT and TT. ETP was calculated by Thrombinoscope software.

Reversal of anticoagulation with rivaroxaban was demonstrated by normalization of the PT and ETP after administration of Cofact and shown to be statistically significant. Rivaroxaban prolonged the PT from a baseline of 12.3 $\pm$ 0.7 seconds to 15.8 $\pm$ 1.2 seconds ($P < 0.001$). PT normalized to 12.8 $\pm$ 1.0 seconds after the IV infusion of Cofact but remained at 16 seconds after IV infusion of the saline placebo ***(figure 3)***. The changes in PT were statistically significant ($P < 0.001$) and illustrated the effectiveness of Cofact on reversing rivaroxaban versus the placebo infusion of saline. ETP was 92 $\pm$ 22% at baseline and decreased after administration of

rivaroxaban to 51 ± 22% (P = 0.002). After administration of Cofact, the ETP normalized to 114 ± 26% (P < 0.001) but did not increase with placebo.

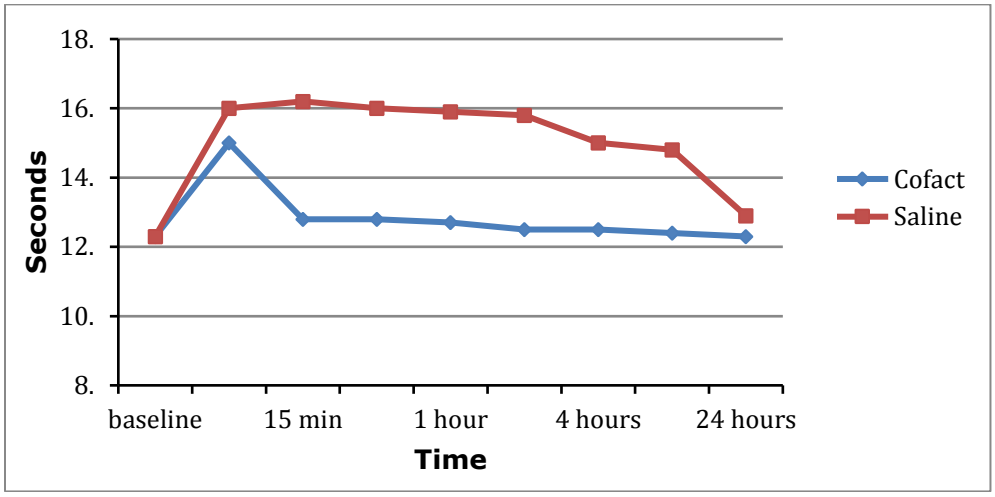

Figure 3: Changes in prothrombin time (PT) over time with Cofact versus saline administration.

Pre-treatment with dabigatran prolonged the ECT, TT and aPTT, and the administration of Cofact did not normalize these coagulation assays. Dabigatran prolonged the aPTT from a baseline of 33.6 ± 3.3 seconds to 59.4 ± 15.8 seconds, and Cofact did not normalize the aPTT (70.3 ± 15.1 seconds). TT was > 120 seconds after dabigatran pre-treatment and remained prolonged after both Cofact and saline infusion. At baseline, the ECT was 33 ± 1 seconds and significantly increased after dabigatran pre-treatment to 69 ± 26 seconds. Again, neither Cofact nor saline reversed ECT prolongation, which actually continued to increase to 86 ± 20 seconds. Cofact successfully reversed the anticoagulant effects of rivaroxaban but was not effective in neutralizing anticoagulation with dabigatran.

No major bleeding or adverse events occurred during the study. Two patients receiving rivaroxaban developed a minor hematoma at the infusion site. Among dabigatran-treated

patients, two developed a minor infusion-site hematoma, one experienced gingival bleeding, and one experienced a minute-long episode of epistaxis[1].

Discussion

The development of a reversal agent for NOACs is an exciting breakthrough for clinicians and patients, and it is important that research into the efficacy of these drugs be carried out meticulously and published in a manner that clearly and honestly explains the research findings. In reviewing the studies that have been previously discussed, there were several factors within each that threaten the accuracy, reliability, and validity of the studies, in spite of their favorable results.

Glund et al. demonstrated that idarucizumab doses greater than 2 g completely and sustainedly reverse of anticoagulation with dabigatran in healthy individuals and with minimal adverse events. These promising results allowed further study in a phase III clinical trial (REVERSE-AD) to proceed, yet there are key limitations to this phase I idarucizumab study. Most importantly, there is a major discrepancy and apparent deviation from study protocol concerning the amount of dabigatran each participant received prior to treatment with idarucizumab. The authors first state that all participants were given dabigatran for three days at a dosage of 220 mg twice daily. However, in the results section, the authors state that all study participants received at least one dose of dabigatran at 220 mg, which would produce very different levels of dabigatran in the body than a cumulative three days of twice daily dabigatran dosing. Dabigatran has a wide volume of distribution in the human body and equilibrates between the blood and tissues. As this study was performed on healthy volunteers who presumably had never taken dabigatran, they would not have stores of dabigatran in their tissues. However, after three days of twice daily dosing with 220 mg dabigatran, the volunteers could potentially accumulate dabigatran stores that would mimic that of patients who have been taking dabigatran long-term. All of the participants did not receive the same number of doses of

dabigatran, which could have contributed to the ease of reversal. With only one dose of dabigatran and reversal with idarucizumab as early as 2 hours later, dabigatran would not have built up a significant store in the tissues and would easily be neutralized by idarucizumab. The difference in the dabigatran tissue concentrations of healthy versus “unhealthy” study participants could also have contributed to the difference in the ability of idarucizumab to sustainedly reverse dabigatran-induced anticoagulation in the phase I and III idarucizumab trials.

There are several limitations in common among the studies. Statistical significance testing was not performed in either the phase I or phase III idarucizumab trials, however, it was performed in the PCC trial. In place of statistical significance testing, the phase III authors used descriptive statistics (quartiles, etc.), and the phase I authors used descriptive statistics with linear regression modeling. This lack of statistical significance testing introduces doubt concerning the validity of the results.

Reliability and validity can be further questioned based on the lack of statistical power calculations. Statistical power is limited among the three studies, as each had sample sizes of less than 100 participants. The PCC trial with 12 participants is especially limited in its statistical power, with a resultant increase in the probability of type I error.

Another limitation among the studies lies in the presentation of data. Unlike the PCC article, which has straightforward figures and graphs that include mean data points ± standard deviation values, the graphs in the phase I and III idarucizumab articles were difficult to interpret and did not clearly illustrate the results of the study. In figure 2 of the phase I article ***(figure 4)***, the size and range of the graphs’ y-axes resulted in overlap of data points and made the determination of precise data points difficult. In the phase III idarucizumab trial, the box and whisker plots would have been more effective if the scales of the y-axes had been increased and the range decreased. Tables with exact values were provided in the supplementary appendix, but the visual representation of the data in the primary published article were difficult

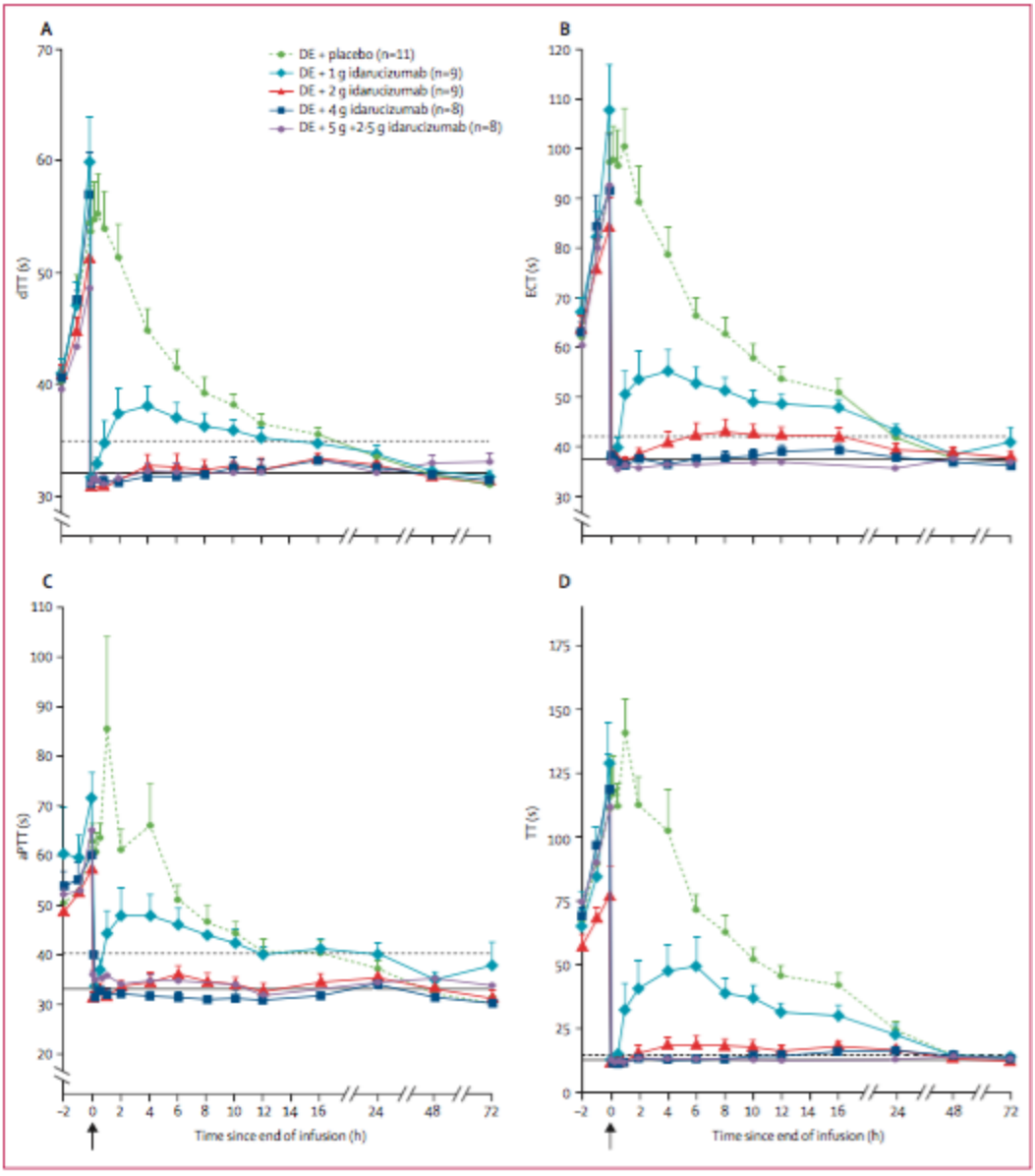

Figure 2: Effect of idarucizumab or placebo infusion on coagulation variables, by dose group
Effect of idarucizumab (1 g, 2 g, 4 g, or 5 g plus 2·5 g) and placebo on (A) diluted thrombin time (dTT), (B) ecarin clotting time (ECT), (C) activated partial thromboplastin time (aPTT), and (D) thrombin time (TT). Dotted horizontal lines show upper limit of normal. 0 h and the arrows on x-axes show when the idarucizumab or placebo infusion ended. Solid horizontal lines show the mean baseline measurement. Datapoints show mean; error bars show SE. DE=dabigatran etexilate.

Figure 4: Image of figure 2 from the phase I idarucizumab trial article "Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: A randomised, placebo-controlled, double-blind phase 1 trial".

to interpret independently. Another concern with the box and whisker plots is that many percent calculations were made throughout the article, presumably from data presented in these plots. This statistical approach may allow misrepresentation of the study results, as the box and whisker plots allow the authors to make statements about percent efficacy without revealing the

number of patients used to make these calculations. This statistical approach may allow for misrepresentation of the results of this study.

In addition to the unclear visual representation of data in the phase I and phase III idarucizumab trials, there are notable discrepancies in the textual presentation of data collection and results, specifically in the phase III idarucizumab study. The execution of this trial and the presentation of its results continually raises questions about the validity of the study findings and conclusion. The study authors make conflicting statements about the number of patients included in the efficacy analysis with the dilute thrombin time (dTT) and ecarin clotting time (ECT). At the beginning of their results, the authors state that 22 patients were excluded from efficacy analysis with dTT due to normal dTT results at baseline, and likewise that 9 patients were excluded from efficacy analysis with ECT due to normal baseline results. However, in a later figure caption, the authors state that all 90 patients were included in efficacy analyses using the dTT and ECT[3]. Blood samples were missing from four patients at four hours, seven patients at 12 hours, and 12 patients at 24 hours, with a total of 23 blood samples missing for the entire study population. 10 missing samples were due to the death of patients, which is understandable, however five samples were “not taken by mistake”, four were not taken because of “technical difficulties”, and one was not taken for an unknown reason[5]. These seem to be careless errors to make in a major phase III clinical trial, especially since the results and recommendations have the potential to effect profound change on clinical practice. Given the weight of this study, a more thorough explanation of the missing samples would have been appropriate.

Further discrepancies can be noted in the phase III idarucizumab trial. The median maximum percentage reversal for patients in both groups A and B was determined to be 100% based on dTT and ECT results, yet only 98% of group A and 93% of group B had normalized dTT results, and only 89% of group A and 88% of group B had normalized ECT results. The authors conclude that “idarucizumab rapidly and completely reversed the anticoagulant activity

of dabigatran in 88 to 98% of patients", but they do not say at what time interval or how many patients were able to be evaluated for inclusion in this calculation. They also gloss over the data showing that, at 12 and 24 hours, 10-46% of patients had dTT and ECT results greater than the ULN.

There is great potential for financial bias among these three studies. Boehringer Ingelheim Pharma funded both the phase I and phase III idarucizumab trials, provided financial compensation to the study participants and many of its authors, and produces both dabigatran (Pradaxa) and idarucizumab (Praxbind). Financial gain could provide an explanation for the discrepancies in the representation (or lack of) results. The same could be true for the PCC trial, as the study was funded by Sanquin, the producers of Cofact. However, the study's authors presented their data in a much more transparent and clear manner.

A final potential limitation is creation of a study-specific upper limit of normal (ULN) for the coagulation assays used in the phase I and phase III idarucizumab trials. It is unclear why the study authors did not use existing reference ranges for these assays. In phase I study with idarucizumab, coagulation assays of 16 participants from a different study arm were used to calculate the study-specific ULN, which could affect its validity. The phase III idarucizumab trial uses the same study-specific ULN as determined in the phase I trial, but the actual values of the ULN for dTT and ECT are not stated in the primary research article or the supplementary appendix, and again, the reasoning for not using an existing reference range is unclear. In contrast, the PCC trial used standard reference ranges for PT, aPTT, ETP, and ECT, removing any question of accuracy or applicability when examining the results of this trial.

Despite the limitations of these studies, each has noteworthy strengths. Although neither idarucizumab study discussed its limitations, the Cofact study highlighted its limitations and discussed areas in need of further research. For example, a single dose of 50 IU/kg was administered in attempting anticoagulant reversal, and it is not known whether repeated or higher doses could reverse anticoagulation with dabigatran. All three trials' simple design is a

strength in itself. Both the PCC and idarucizumab phase I trials were randomized, double-blind placebo-controlled trials, which are the gold standard for demonstrating efficacy. The phase III idarucizumab trial has a prospective cohort study design, an unavoidable weakness, as it would be unethical to without potential treatment from patients presenting with major bleeding. Yet although healthy participants are a criterion for phase I trials studying the efficacy of a new drug, a healthy study population does not generally represent the target patient population. In the phase III idarucizumab study, the lack of a control group is countered by the use of a clinically relevant study population.

Another strength of the phase I and phase III idarucizumab trials were their use of several coagulation assays to determine which was most reliable as a measure of outcome. The studies also used mass spectrometry to assess the plasma concentrations of total and unbound dabigatran, which were used to correlate with and assess the most reliable coagulation assay for observing dabigatran reversal by idarucizumab. Finally, adverse events were reported, and in the phase III idarucizumab study, a contracted company (SGS Life Sciences Clinical Research Services) was employed to adjudicate any adverse events and to decide on their relationship, if any, to treatment with idarucizumab.

While the results are favorable, the limitations of these studies are significant, and, as this clinical question is an important and relevant one, further studies should recognize these weaknesses to further address these limitations to improve the research.

Conclusion

Both Cofact and idarucizumab have demonstrated effective reversal of rivaroxaban and dabigatran, respectively. However, as of December 2015, Cofact has not been approved by the FDA for reversal of NOACs in the United States. Conversely, in October 2015, idarucizumab (Praxbind) was approved by the FDA for reversing anticoagulation with dabigatran. Current pricing of a single 5 g dose of idarucizumab is $3,500[6]. Because idarucizumab is currently

available for clinical use, dabigatran is a preferable alternative to rivaroxaban and the other factor Xa inhibitors for adults requiring oral anticoagulation, due to the existence of an effective reversal agent.. However, the decision about which oral anticoagulant to use remains at the discretion of the patient and clinician based on an assessment of patient-specific risks and benefits, and clinicians should continue to exercise caution in prescribing dabigatran etexilate, based on the limitations of the idarucizumab phase III trial. Idarucizumab did successfully reverse anticoagulation of dabigatran at up to 24 hours in most patients, but a subset of patients did not experience sustained or effective reversal with this drug. Clinical characteristics, particularly kidney function, comorbidities, and concurrent antithrombotic treatments such as Plavix or aspirin are not known for this subset of patients, which allow for ambiguous interpretation of the study data, as failure of reversal with idarucizumab could be due to patient characteristics or inefficacy of the drug. The authors and those conducting the phase III idarucizumab trial need to reevaluate their study protocols for blood sample collection and the presentation of relevant data. The distribution of patients, rather than quartiles, could be more useful in evaluating the clinical significance of the study results.

Additional study with idarucizumab is needed to determine if reversal outcomes could be improved by administering more than one dose of idarucizumab, as some patients had elevated dTT and ECT results one hour after receiving 5 g of idarucizumab. The reversal of rivaroxaban with Cofact is promising, however further, more current research must be conducted in a larger and different population, beyond phase I study.

A few weeks before submission of this review, an article was published in the *New England Journal of Medicine* detailing the results of an exciting clinical trial evaluating the efficacy of a new pharmaceutical, andexanet alfa, for the reversal of anticoagulation with factor Xa inhibitors. These studies, ANNEXA-A and ANNEXA-R, were randomized control trials examining reversal of anticoagulation with apixaban and rivaroxaban in 145 healthy volunteers ages 50 to 75 years. Both studies demonstrated safe, rapid, and effective reversal of apixaban

and rivaroxaban with andexanet alfa, and the authors proposed that andexanet alfa could be a potentially universal antidote for patients anticoagulated with direct and indirect factor Xa inhibitors. There are ongoing studies with andexanet alfa in patients with major bleeding as part of the ANNEXA-4 clinical trial (ClinicalTrials.gov Identifier: NCT02329327)[7]. This recent *NEJM* publication highlights again how important it is for clinicians who prescribe oral anticoagulants, particularly NOACs, to continually stay updated concerning new reversal agents for these drugs.

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