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Review

Evidence supporting idarucizumab for the reversal of dabigatran☆,☆☆,★

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ABSTRACT

Idarucizumab is a monoclonal antibody fragment specifically targeted to dabigatran. It has demonstrated prompt and durable reversal of the anticoagulant effects of dabigatran in animal studies and phase 1 studies of young, elderly, and renally impaired volunteers. Although elective invasive procedures and most bleeding complications in dabigatran-treated patients can be managed by temporarily stopping dabigatran therapy and using supportive measures, there are rare clinical situations that require urgent reversal of the anticoagulant effect of dabigatran. The effectiveness and safety of 5 g of intravenous idarucizumab is being investigated in a prospective, open-label, single-cohort study in patients with serious bleeding or in those requiring an urgent procedure. In an interim analysis of the first 90 participants, idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88%-98% of participants, and there were no safety concerns, with no deaths or serious adverse events being attributable to idarucizumab. Supported by these interim results, idarucizumab has been approved in the United States and the European Union for use when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or in patients with life-threatening or uncontrolled bleeding. Clinical use of idarucizumab should follow the same processes as patient enrollment in this study, which is projected to be completed in 2016. The outcomes achieved with this specific reversal agent are likely to be of continued interest to treating physicians.

Dabigatran is a direct oral anticoagulant (DOAC) that inhibits the function of thrombin without dependence on vitamin K antagonism [1]. In the penultimate step of the normal coagulation cascade, thrombin catalyzes the conversion of fibrinogen to fibrin, resulting in clot stabilization. Patients treated with dabigatran have normal synthesis and levels of thrombin, but competitive inhibition of thrombin activity by dabigatran effectively prevents completion of the coagulation process. This mechanism of action has been harnessed to provide effective anticoagulation in patients with nonvalvular atrial fibrillation (NVAF) to reduce the risk of ischemic stroke and systemic embolization, and in patients with or at risk of venous thromboembolic disease [1]. In clinical trials, dabigatran has been associated with similar or reduced rates of the key safety end points of major and intracranial bleeding, depending on the dose and the indication, as well as similar rates of fatal bleeding compared with vitamin K antagonists (VKAs), such as warfarin [2-4]. Nonetheless, some risk of bleeding unavoidably accompanies the decision to use an anticoagulant in a patient, especially older patients with the comorbidities that typically accompany NVAF. Most bleeding complications associated with the use of dabigatran are minor or at worst moderate in severity and can be managed by simply temporarily withholding the drug and supporting the patient with general physical or pharmacologic hemostatic measures, replacement of shed blood, and observation [5,6]. The short half-life of dabigatran relative to VKAs, which inhibit the synthesis of multiple coagulation factors over days, is an important consideration in these strategies [1,7]. Typically, the effect of dabigatran–in the absence of acute renal failure or acute overdose–dissipates within 12 hours of a 150-mg dose, with steady-state dabigatran plasma concentrations decreasing to <100 ng/mL and activated partial thromboplastin time to approximately 1.5 times baseline levels in that interval [8,9].

Similarly, the short half-life of dabigatran facilitates the timing of elective invasive procedures. Withholding the drug for 1-5 days, depending on renal status and the magnitude of the bleeding risk associated with the procedure, allows the intervention to be accomplished with restored hemostasis [1]. Because the onset of action of dabigatran is–like its offset–rapid [10], re-initiation of anticoagulation can generally be accomplished as soon as postprocedural hemostasis is restored.

In rare clinical situations, these general measures are insufficient to address bleeding complications or bleeding concerns in patients requiring emergent invasive procedures in the context of anticoagulation with dabigatran. In cases of uncontrolled or life-threatening hemorrhage or when an invasive procedure cannot be delayed long enough for natural decay of the anticoagulant effect of dabigatran, more definitive reversal of anticoagulation is desirable. If dabigatran was ingested within the preceding 2-3 hours, oral administration of activated charcoal may limit absorption of the most recent dose [8,11,12]. Elimination of dabigatran–which is 80% renal–can be maintained by vigorous fluid administration and resulting diuresis [1,5,8]. However, these approaches are of limited impact in most emergency situations. Unlike the other DOACs, dabigatran can be removed rather effectively from the circulation by hemodialysis, although data supporting this approach are limited [1,13,14]. Unfortunately, this is a cumbersome and logistically challenging approach in the emergency situation, in patients without established dialysis access.

Such patients, therefore, require urgent reversal of the anticoagulant effect of dabigatran (ie, normalization of thrombin activity in the presence of an effective antithrombin agent). It is not possible to administer pure thrombin to patients to overcome the competitive blockade of dabigatran. Exogenous thrombin can be given in combination with other coagulation factors using fresh frozen plasma or 3- or 4-factor prothrombin complex concentrates [12]. However, because levels of thrombin and other coagulation factors are presumably normal in dabigatrantreated patients, this approach introduces a concern for iatrogenic creation of a hypercoagulable or prothrombotic state, as has been demonstrated in an animal study [15], potentially trading one worrisome situation for another.

The preferred approach in such situations, therefore, would be to use a specific reversal agent to remove the anticoagulant effect of dabigatran, disinhibiting native thrombin and returning the patient to his or her baseline coagulation status. An ideal reversal agent would be specific to the administered anticoagulant, engage in no other drugdrug interactions, have no inherent pro- or anticoagulant effect, have rapid and predictable onset of action, be readily prepared and administered, and be dosed in a simple fashion. Additionally, it should have a sufficiently durable effect that in cases of bleeding, coagulation can be maintained while definitive source management is being accomplished, and in preprocedural patients, the procedure can be completed without the additional bleeding risk wrought by anticoagulation.

Idarucizumab meets these criteria for patients treated with dabigatran who require immediate anticoagulation reversal [16]. Idarucizumab is a humanized monoclonal antibody fragment specifically directed at dabigatran [17]. The active site of idarucizumab is structurally similar to the dabigatran binding site of thrombin, although the antibody lacks enzymatic activity. Idarucizumab binds dabigatran with approximately 350 times the avidity with which thrombin binds dabigatran. As such, in sufficient doses, idarucizumab readily displaces dabigatran from thrombin and tightly binds it, thereby allowing fibrin formation to ensue normally. The antibody can bind free and thrombinbound dabigatran, as well as extravascular dabigatran, as it enters the central compartment after changes in the concentration gradient [18], thus preventing the anticoagulant from the periphery from subsequent binding to thrombin.

The interaction between idarucizumab and dabigatran is characterized by an extraordinarily rapid on rate (measured in milliseconds) and a very slow off rate, consistent with the high-affinity binding typical of an antibodyeantigen bond [17]. Binding is effectively irreversible, with very little dissociation of the idarucizumabedabigatran complex before renal excretion, even in patients with renal compromise [16-18]. When infused intravenously, peak plasma concentrations of idarucizumab are achieved almost immediately, allowing prompt binding to dabigatran [19]. The key clinical findings from volunteer studies of idarucizumab are reviewed in detail in the review article by Reilly et al. within this special issue and are summarized in Table [20].

Table
Key Clinical Phase 1 Findings with Idarucizumab in Healthy Volunteers

Objective	No. of Subjects	Findings
Reversal of anticoagulant effect of dabigatran in healthy young (age 18-64 y) volunteers	59	Dose-dependent decrease in ECT, dTT, aPTT, TT, and ACT
Reversal of anticoagulant effect of dabigatran in elderly (age 65-80 y) volunteers	16	Dose-dependent decrease in ECT, dTT, aPTT, TT, and ACT
Reversal of anticoagulant effect of dabigatran in subjects with creatinine clearance 44–79 mL/min	18	Dose-dependent decrease in ECT, dTT, aPTT, TT, and ACT
Pharmacokinetics of idarucizumab alone in healthy volunteers	110	Initial $t_{1/2}$ ~45 minutes
Pharmacokinetics of dabigatran in volunteers given idarucizumab	93	Unbound dabigatran concentrations determined using HPLC/MS parallel results of clotting tests
Re-initiation of dabigatran 24 h after idarucizumab administration	12	Full anticoagulant effect of dabigatran 24 h after idarucizumab administration
Re-exposure to idarucizumab 2 mo after initial administration	6	No hypersensitivity, 1 subject developed new anti-drug antibodies
Evaluation of potential procoagulant activity of idarucizumab	104	No increase in thrombin generation compared with placebo
Safety of idarucizumab	203	No dose-related adverse events, no serious adverse events

See references [19,22].
ACT = activated clotting time; aPTT = activated partial thromboplastin time; dTT = dilute thrombin time; ECT = ecarin clotting time; HPLC/MS = high-performance liquid chromatography/tandem mass spectrometry.
Reproduced with permission from Pollack et al. [21]

Animal studies of idarucizumab likewise showed a prompt and durable reversal of the anticoagulant effects of dabigatran, without prothrombotic effect [17,23]. In addition, phase I studies showed only a low level of antibody formation after single or repeat exposure to idarucizumab [16,18,19]. No severe or serious drug-related adverse events were identified [16,18,19,22]. The only side effect was a transient, doserelated increase in urinary protein levels, which was to be expected from the excretion of the antigeneantibody complexes via a saturable renal protein transporter [19].

1. RE-VERSE AD, A Study in Patients

From all indications, then, idarucizumab seemed to be a promising specific reversal agent for dabigatran. A clinical study in patients to support registration was developed with input from various regulatory bodies, and ultimately the following key decisions were made concerning the design of this study of idarucizumab. An open-label, single-cohort design was selected. Although it was of course recognized, that a blinded, controlled study would represent better "science," this approach was not deemed feasible or appropriate for a study of idarucizumab. Blinded, placebocontrolled studies had already been conducted in healthy volunteers, demonstrating safety and efficacy according to reversal of clotting tests. The drug seemed to be so effective in these studies that it was not thought ethical to enroll a placebo-treated group. In addition, such a controlled study, with clinical outcomes as the primary end point, would require thousands of patients and could take 5-10 years to complete owing to the difficulties of finding, consenting, and treating eligible dabigatran-treated patients as soon as they appeared in emergency departments. Likewise, there seemed to be no rational comparator control, because there is no standard treatment for dabigatran-associated bleeding, and no studies have evaluated the effects of other reversal or repletion strategies for

dabigatran that could represent a "gold standard" alternative to idarucizumab [21].

Purely clinical inclusion criteria were selected because worldwide there are no readily available coagulation tests to evaluate the magnitude of dabigatran-associated anticoagulation. Meanwhile, the use of time-consuming, experimental tests or qualitative tests before enrollment was not deemed to be in the patient's best interest. The protocol was instead written to allow full discretion by the local investigator to make the clinical decision that immediate reversal of anticoagulation was warranted–whether in the management of hemorrhage or the prevention of procedural bleeding–and that open-label idarucizumab should be administered [21].

Two groups of dabigatran-treated patients were also selected because oral anticoagulation may occasionally result in 2 separate and distinct clinical challenges: management of hemorrhage abetted by the iatrogenic coagulopathy (enrolled as "group A") and management of anticoagulated patients who are not bleeding but who require urgent or emergent invasive procedures ("group B") that [1] cannot be safely postponed (for at least 8 hours) and [2] cannot be safely performed without baseline restoration of hemostasis. It was further decided not to impose clinical limits on the trial population so that it represented as best as possible the types of patients who would likely be given idarucizumab in "real-world" situations. The following patients were, therefore, eligible for inclusion in the trial: those with intracranial hemorrhages, with high expected mortality, those with other life-threatening conditions (eg, sepsis, multiple trauma with hemorrhagic shock), and those who had received other reversal/repletion therapies. In addition, measures to control bleeding in patients in group A were permitted during the trial. These could include mechanical and supportive measures, decontamination procedures (eg, activated charcoal or dialysis), factor repletion, or the administration of other hemostatic agents (eg, tranexamic acid) [21].

The primary efficacy end point for the study was based on laboratory assessments of coagulation, not clinical outcomes. The types of patients represented in the 2 study groups–bleeding and preprocedural–are quite heterogeneous in terms of presentation, source of bleeding or type of procedure needed, comorbidity burden, age, and indication for anticoagulation. Therefore, meaningful clinical end points could not be used to establish a sample size for the study. Additionally, idarucizumab is a specific reversal agent; that is, it is to be used when reversal of dabigatranassociated anticoagulation is deemed clinically necessary. However, successful reversal of anticoagulation in a hemorrhaging patient does not necessarily result in cessation of bleeding. Therefore, the best measure of reversal is the central laboratory assessment of coagulation parameters known to correlate with dabigatran concentrations. In fact, 2 coagulation assays–the dilute thrombin time (dTT) and the ecarin clotting time (ECT) can be used in this way [10,24]. Therefore, although numerous clinical outcomes were to be collected and reported in the study, the primary end point would be coagulation testing performed by a central laboratory that was geographically and temporally separated from patient care. These tests were supplemented by also directly measuring the amount of total and unbound dabigatran as a secondary end point, to confirm that the effects on clotting tests reflected the binding/elimination of dabigatran and were not artifacts of the patients' conditions.

The resulting "real-world" evaluation of idarucizumab was called the study of the REVERSal Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD) and is an ongoing, global, phase 3 prospective, single-cohort study aimed at investigating idarucizumab in dabigatran-treated patients who present with uncontrollable or life-threatening bleeding, and in those requiring urgent surgery or intervention [25]. The study is being pursued in more than 400 sites in nearly 40 countries and ultimately will enroll 500 patients. The originally planned sample size of 200-300 patients was increased to 500 as part of postapproval requirements by the U.S. Food and Drug Administration (FDA) [25,26].

The first patient was enrolled in June 2014, and interim results from the first 90 enrollees were presented at the *International Society of Thrombosis and Haemostasis congress* and published in the *New England Journal of Medicine* in June 2015 [25,27]. Idarucizumab was subsequently approved as Praxbind by the FDA in October 2015 and by the European Medicines Agency in November 2015 [28,29].

All patients in RE-VERSE AD receive 5 g idarucizumab administered as 2 successive intravenous infusions of 2.5-g vials, each given as a rapid infusion, no more than 15 minutes apart [25]. The only requirement for care between the 2 infusions is a blood draw for coagulation analysis; this would not be considered a necessary step in clinical practice. The primary end point is the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours of completion of idarucizumab dosing, as assessed by central laboratory measurement of the dTT or ECT. Key clinical end points include time to cessation of bleeding in group A patients and assessment of hemostasis during interventions in group B patients. An interim analysis of the first 90 patients enrolled (51 in group A, 39 in group B) revealed that most (>90%) were receiving dabigatran for stroke prevention in the setting of NVAF and, accordingly, were elderly (median age: 76.5 years) and had a typical ageappropriate comorbidity burden, including some degree of renal insufficiency.

In keeping with the "all-comers" approach to establishing eligibility for idarucizumab to reverse dabigatran-associated anticoagulation, 16 of the 51 group A patients were hemodynamically unstable at enrollment, and 18 had intracranial hemorrhage. In group B, the most common indications for emergency surgery were open bone fractures and acute abdomen. The median patient-reported time since the last dose of dabigatran was 15.2 and 16.6 hours in groups A and B, respectively, although this time included initial evaluation after arrival at the site of care [25].

Overall, 68 (76%) and 81 (90%) of the 90 patients had an elevated dTT or ECT at study entry as determined by central laboratory analysis. Normal dTTs were found in 11 of 51 patients in group A and in 11 of 39 patients in group B, and normal ECTs in 4 and 5 patients in the respective groups. It should be kept in mind that treating clinicians did not have access to these results in "real time" and that all enrollment criteria were clinical, based on a bedside evaluation that immediate reversal was warranted [25].

The efficacy analysis included only those patients with elevated clotting test results at baseline. After administration of 5-g idarucizumab, the median maximum percentage reversal in dTT or ECT within 4 hours in eligible patients was 100% (95% confidence interval, 100%-100%), and reversal was evident immediately after the first vial of idarucizumab was given. Idarucizumab normalized dTT in 98% (group A) and 93% (group B) and ECT in 89% (group A) and 88% (group B) of eligible patients (Fig. 1) [25].

Plasma concentrations of unbound dabigatran were reduced to at or near the lower limit of quantification in all but 1 patient immediately after idarucizumab administration. At 24 hours, 79% of patients had plasma concentrations of active (unbound) dabigatran that were <20 ng/mL, a level associated with little or no anticoagulant activity [9]. The subsequent increases in dabigatran concentrations observed in 6 and 16 patients, at 12 and 24 hours after idarucizumab administration, respectively, were accompanied by increases in clotting times. This response is most likely attributable to the redistribution of extravascular dabigatran into the intravascular compartment. If these elevations in clotting tests are associated with rebleeding, a second 5-g dose of idarucizumab may be considered in such patients, although the safety and effectiveness of a second dose has yet to be established [16].

In the 51 patients in group A, time to bleeding cessation could be determined in 38 patients (13 patients had bleeding at sites not readily accessible). The investigator-reported median time to cessation of bleeding was 11.4 hours, but this information is highly variable and was not guided by any specific evaluation schedule or definition. In group B, normal intraoperative hemostasis was reported in 92% of the 36 patients who underwent procedures after reversal [25]. The median
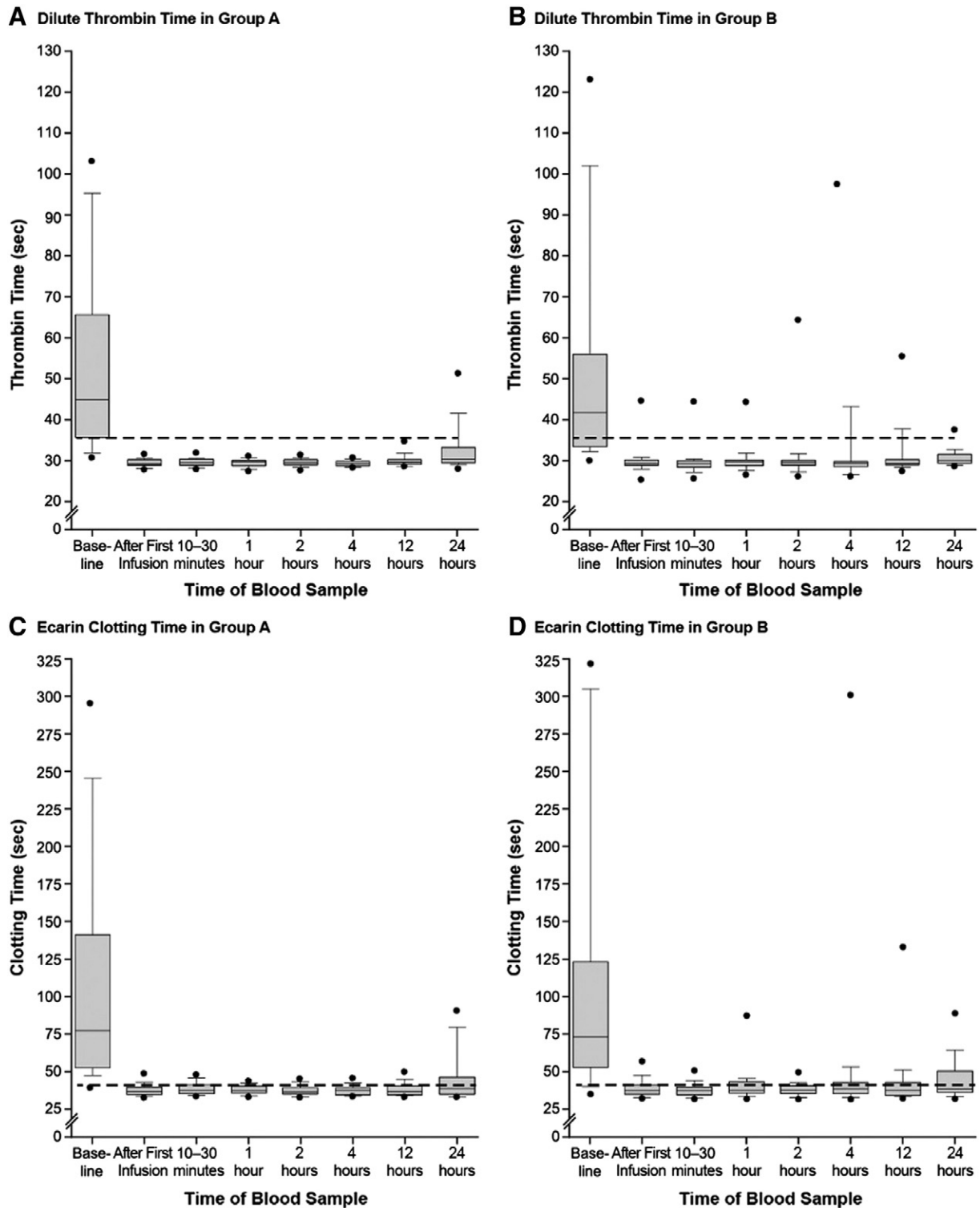
Fig. 1. Time course of the dilute thrombin time and ecarin clotting time before and after the administration of idarucizumab. Reprinted with permission of Massachusetts Medical Society from Pollack et al. [25] The analyses included 51 patients who had serious bleeding (group A; **A** and **C**) and 39 who required urgent surgery or intervention (group B; **B** and **D**). Idarucizumab was administered in 2 infusions. Blood samples were obtained at baseline, after the first infusion, at 10-30 minutes after the administration of the second infusion, and at 1, 2, 4, 12, and 24 hours. Data are presented as box-and-whisker plots, in which the top and bottom of the rectangles indicate the 75th and 25th percentiles, respectively; the horizontal lines within the rectangles indicate the 50th percentile; the lines above and below the rectangles indicate the 90th and 10th percentiles, respectively; and the dots above and below the lines indicate the 95th and 5th percentiles, respectively. The dashed lines indicate the upper limit of the normal range for the tests.

time between administration of idarucizumab and the start of the procedure was 1.7 hours, and no postsurgical bleeding complications were reported in the 24 hours after surgery for any of the 36 procedural patients [30].

Thromboembolic events (including deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke) occurred in 5 of the 90 patients in the interim analysis: 1 occurring within 48 hours of idarucizumab administration, and 4 more than 72 hours after

dosing. It is significant that at the time of the complication, none of these 5 patients had been re-initiated on any antithrombotic therapy after reversal of anticoagulation. Among these 90 patients, 18 (9 in each group) died during the 90-day follow-up period. The 9 deaths that occurred within 96 hours after reversal reflected the disease process or injury that prompted the need for reversal, whereas the 9 deaths that occurred later were related to pre-existing medical conditions. No deaths and no serious adverse events were attributable to idarucizumab [25].

Most patients had anticoagulation therapy re-initiated after reversal [25]. The time to restart varied, with a longer time for patients in group A who had experienced life-threatening bleeding events than for surgical patients in group B for whom hemostasis was more clearly established before re-initiation (median time: 4.1 vs 1.4 days, respectively) [31]. Approximately half of the patients who restarted on dabigatran were given an injectable anticoagulant first [31]. In patients with renal impairment, the half-lives of both dabigatran and idarucizumab are prolonged [1,16]. No adjustment of timing of re-initiation of dabigatran is necessary in these patients.

The interim results supported the rapid approval of idarucizumab by both the FDA and the European Medicines Agency. The target population mirrored the inclusion criteria and administration used in RE-VERSE AD. The study will be complete in 2016 after the enrollment of 500 patients worldwide [25]. Clinical use of idarucizumab will ensue in parallel to study enrollment, and there will doubtless be varying protocols governing access to the reversal agent in the emergency care setting.

2. Conclusions

Use of idarucizumab will be unusual in the clinical setting if it is used per label and as it is being used in RE-VERSE AD: only in those situations in which emergency reversal is clinically warranted. Most DOAC-related bleeding does not require reversal; most invasive procedures in anticoagulated patients can be safely delayed until the anticoagulant effect has diminished. The exceptions–true surgical emergencies, intracranial hemorrhage, exsanguinating gastrointestinal bleeds, multiple trauma with hemorrhagic shock–are dramatic but rare. The usual measures to support and stabilize dabigatran-treated patients with controllable hemorrhage of bleeding concerns should still be followed, reserving idarucizumab for refractory cases (Fig. 2).

Further clinical experience will be required to determine the frequency of a need for repeated doses of idarucizumab. Given the overwhelming nature of the 5-g dose (with respect to dabigatran levels measured in the Randomized Evaluation of Long-term anticoagulation therapY [RE-LY] trial), this should be unusual and should be considered only when pathologic bleeding persists or recurs after initial reversal, or if a second urgent/emergent procedure is required and clotting studies suggest a recurrent dabigatran effect. It is anticipated that there will
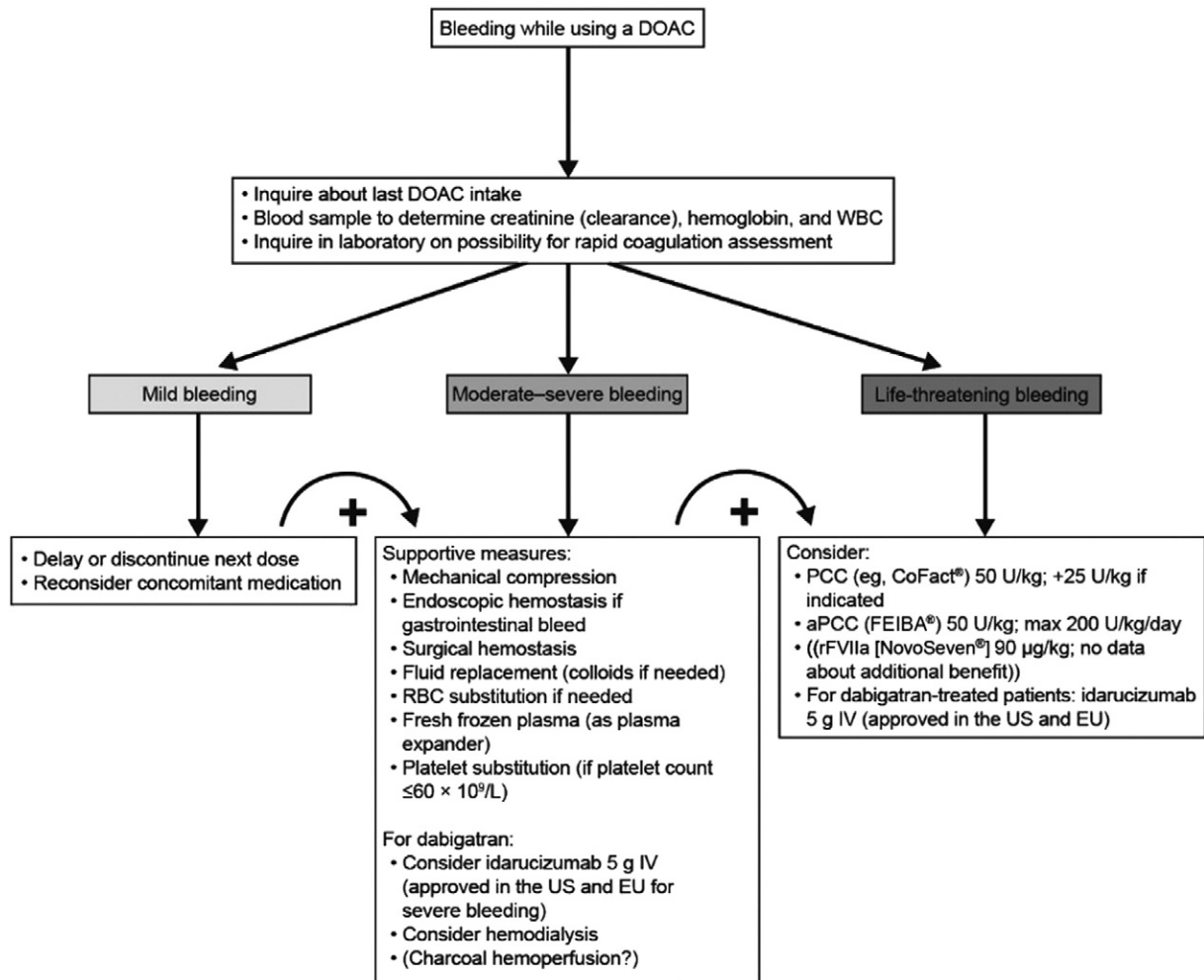
Fig. 2. Management of bleeding in patients taking direct oral anticoagulants (DOACs). Possible therapeutic measures in case of minor or severe bleeding in patients on DOAC therapy. Based on van Ryn et al. [8] Adapted with permission of Oxford University Press from Heidbuchel et al. [5] aPCC = activated prothrombin complex concentrate; IV = intravenous; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; RBC = red blood cell count; WBC = white blood cell count.

be broad and deep interest in the clinical use of the drug and the outcomes achieved.

References

[1] Boehringer Ingelheim Pharmaceuticals, Inc.. Pradaxa (dabigatran etexilate mesylate) U.S. prescribing information. Available at: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. [Accessed February 9, 2016].

[2] Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764–72.

[3] Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342–52.

[4] Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709–18.

[5] Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467–507.

[6] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

[7] Bristol-Myers Squibb Company. Coumadin (warfarin sodium) prescribing information. Availabe at: http://packageinserts.bms.com/pi/pi_coumadin.pdf. [Accessed February 9, 2016].

[8] van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilatea novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116–27.

[9] Stangier J, Stähle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet 2008;47:47–59.

[10] Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol 2007;64:292–303.

[11] Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol 2012;87(Suppl. 1):S141–5.

[12] Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: current status and future potential. Arterioscler Thromb Vasc Biol 2015;35:1736–45.

[13] Liesenfeld KH, Gruenenfelder F, Clemens A. Enhanced elimination of dabigatran: identifying the appropriate patient for the use of continuous venovenous hemodialysis instead of intermittent hemodialysis-A simulation analysis. J Clin Pharmacol 2016;56:597–608.

[14] Liesenfeld KH, Staab A, Hartter S, Formella S, Clemens A, Lehr T. Pharmacometric characterization of dabigatran hemodialysis. Clin Pharmacokinet 2013;52:453–62.

[15] Honickel M, Braunschweig T, van Ryn J, et al. Prothrombin complex concentrate is effective in treating the anticoagulant effects of dabigatran in a porcine polytrauma model. Anesthesiology 2015;123:1350–61.

[16] Boehringer Ingelheim Pharmaceuticals, Inc.. Praxbind prescribing information. U.S. Food and Drug Administration. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. [Accessed October 20, 2015].

[17] Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. Blood 2013;121:3554–62.

[18] Glund S, Stangier J, Schmohl M, et al. 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. Lancet 2015;386:680–90.

[19] Glund S, Moschetti V, Norris S, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. Thromb Haemost 2015;113:943–51.

[20] Reilly PA, van Ryn J, Grottke O, et al. Idarucizumab, a specific reversal agent for dabigatran: mode of action, pharmacokinetics and pharmacodynamics, and safety and efficacy in phase 1 subjects. Am J Emerg Med 2016;34:26–32.

[21] Pollack Jr CV, Reilly PA, Bernstein R, et al. Design and rationale for RE-VERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost 2015;114:198–205.

[22] Glund S, Stangier J, van Ryn J, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, doubleblind, crossover phase Ib study [e-pub ahead print]. Clin Pharmacokinet 2016. http://dx.doi.org/10.1007/S40262-016-0417-0.

[23] Grottke O, Honickel M, van Ryn J, ten Cate H, Rossaint R, Spronk HM. Idarucizumab, a specific dabigatran reversal agent, reduces blood loss in a porcine model of trauma with dabigatran anticoagulation. J Am Coll Cardiol 2015;66:1518–9.

[24] Avecilla ST, Ferrell C, Chandler WL, Reyes M. Plasma-diluted thrombin time to measure dabigatran concentrations during dabigatran etexilate therapy. Am J Clin Pathol 2012;137:572–4.

[25] Pollack Jr CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511–20.

[26] Boehringer Ingelheim, Inc.. Reversal of dabigatran anticoagulant effect with idarucizumab (NCT02104947). Available at: www.clinicaltrials.gov/ct2/show/NCT02104947?term=idarucizumab&rank=1. [Accessed February 9, 2016].

[27] Pollack C, Reilly PA, Verhamme P, et al. Initial results of the RE-VERSE AD trial: idarucizumab reverses the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions. J Thromb Haemost 2015;13:85, 85.

[28] U.S. Food and Drug Administration. FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm. [Accessed February 9, 2016].

[29] European Medicines Agency. EPAR summary for the public, Praxbind. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003986/WC500197464.pdf. [Accessed February 9, 2016].

[30] Boehringer Ingelheim (Canada) Ltd./Ltée. Interim sub-group analysis shows the reversal agent idarucizumab* enables rapid initiation of emergency surgery in dabigatran-treated patients. Available at: www.boehringer-ingelheim.ca/en/news/press_releases/2015/09Sept2015.html. [Accessed February 9, 2016].

[31] Pollack Jr CV, Reilly PA, Eikelboom J, et al. Reinitiation of antithrombotic therapy after emergency procedures or after an uncontrolled or life threatening bleeding event. Initial experience from the RE-VERSE AD trial. Circulation 2015;132(Suppl. 3):A16418.