



Idarucizumab Pharmacology as Dabigatran Antidotes: Mechanism of action, pharmacokinetics, efficacy and safety (A Literature Review)

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ABSTRACT

Atrial Fibrillation (AF) is a common abnormal heart rhythm, responsible for a high rate cardiovascular and cerebrovascular morbidity and mortality. The prevalence of AF in the general population is about 3%. Stroke patients with AF have a high mortality rate of 50% in a year, compared to stroke patients without AF as 27%. Dabigatran etexilate is an oral thrombin inhibitor had been approved for stroke prevention and treatment in nonvalvular atrial fibrillation and venous thromboembolism (VTE). Since dabigatran usage results in haemorrhage, an antidote is highly needed during this emergency. Dabigatran etexilate is prospective antidote for idarucizumab. Idarucizumab and its metabolite, acylglucuronide, has a high affinity to both free and thrombin-bound dabigatran. Idarucizumab neutralize anticoagulant effect of dabigatran by binding stoichiometric complex with 1:1 molar ratio. Idarucizumab and dabigatran interaction have a very fast on-rate and a slow off-rate resulting in a stable complex which elicits its effect in a few minutes. Idarucizumab reverse dabigatran effects in a few minutes by forming reactive stable complex. Some studies on efficacy and safety Idarucizumab as an antidote in healthy and renal disorders patients pointed that Idarucizumab could be well tolerated. There was no severe adverse event, dose-dependent event, drop-out due to an adverse event, and no relevant clinical findings were reported for a vital sign, physical examination, electrocardiogram, cardiac telemetry, or laboratory parameters, after dabigatran use as an antidote.

1. Introduction

Atrial Fibrillation (AF) is a common abnormal heart rhythm, responsible for a high rate of cardiovascular and cerebrovascular morbidity and mortality. AF is generally classified according to the duration of a single episode. In particular, episodes that end spontaneously or with intervention within 7 days of onset are classified as paroxysmal AF, whereas those that last more than 7 days or more than 12 months are defined as persistent AF.¹ Stroke is the most serious and terrible complication of AF, related to its long-term disability, high mortality, and high healthcare cost.² AF-related stroke is mostly cardio embolic. The prevalence of cardio embolic strokes ranged between 15-20% of all ischemic strokes. Stroke patients with AF have a high mortality rate up to 50% in one year, compared to stroke patients without AF which is 27%.¹ The prevalence of AF in the general population is about 3% adjusted for age worldwide (> 20 years), as estimated in the Global Burden of Disease Study, 2010, was 5.96 per 1,000 in men and 3.73 per 1,000 in women, including around 33 million people.³ Whereas nonvalvular atrial fibrillation (NVAF) is generally associated with older age (70% of NVAF patients aged 65 to 85 years and 10% > 80 years) and several concurrent acute and chronic health conditions. For this reason, it is estimated that NVAF patients have a 4-fold increased odds of having a higher risk of thromboembolic events due to NVAF. However elderly patients appear to be relatively less likely to receive adequate oral anticoagulation (OAC) compared to younger patients.⁴

For decades, vitamin K antagonist (VKA) such as warfarin is the only oral agent used for long-term anticoagulant. Since warfarin adverse events and interactions with other drugs inhibit its therapeutic anticoagulant effect, it should be routinely monitored. The emergence of Novel Oral Anticoagulant (NOACs), dabigatran, followed by edoxaban, rivaroxaban, and apixaban, have altered the status of warfarin as the only one anticoagulant.⁵ Although both VKA and NOACs have a risk of bleeding, NOACs shown to have a lower risk of bleeding with a similar efficacy on atrial fibrillation patients compared to VKA.^{6,7,8} NOACs do not require routine monitoring such as the use of warfarin, but laboratory measurement of blood levels or anticoagulant activity may be helpful during an emergent bleeding situation. A meta-analysis from three RCTs including 44,563 patients showed that NOACs safety is superior to warfarin in VTE and atrial fibrillation treatment.⁹ With an advantageous safety profile, by reducing the risk of intracranial hemorrhage, NOACs become a promising alternative replacing warfarin.¹⁰

Dabigatran etexilate, a non-vitamin K oral anticoagulant, is an oral thrombin inhibitor that had been approved for stroke prevention in nonvalvular atrial fibrillation patients and also has a role in venous thromboembolism (VTE) prevention and treatment in the US and Europe in 2010.¹¹ Even though dabigatran side effect is not as strong as warfarin, a severe hemorrhage could be happened due to dabigatran. In some circumstances, commonly available coagulation tests such as activated partial thromboplastin time (aPTT), prothrombin time, and thrombin time (TT) can provide a qualitative assessment of

the presence or absence of anticoagulant effects. On arrival five hours after dabigatran intake, aPTT was 75 s (normal 25–37 s) and PT was 26 s (normal 9–12.5 s).¹² The standard thrombin time (TT) assay is highly sensitive to the presence of dabigatran, but aPTT sensitivity assay is limited. For accurate quantitative measurements of dabigatran concentration, diluted thrombin time (dTT) tests using dabigatran calibrators are recommended. The ecarin clotting time (ECT) test provides a direct measurement of dabigatran activity but is not routinely available. If an assessment of low dabigatran plasma concentrations is needed (for example, in perioperative settings), chromogenic ecarin (ECA), as well as dTT and ECT tests, can be used.^{13, 14} Furthermore, since dabigatran use can result in hemorrhage and might lead to immediate intervention or surgery, a specific reversal agent (antidote) is highly needed to improve patient management during this emergency.¹⁵ A specific reversal agent for dabigatran is Idarucizumab.^{14, 16}

Idarucizumab is a humanized monoclonal antibody fragment that acts as a specific reversal agent for dabigatran¹⁷, which received accelerated approval by the U.S. Food and Drug Administration in October 2015 and the European Medicines Agency in November 2015.^{18, 19} Idarucizumab binds to dabigatran with a high affinity and specificity in a 1:1 molar ratio and quickly reverse its anticoagulant activity.^{12, 20, 21} An *in vitro* and *ex vivo* study found that Idarucizumab immediately turns the prolonged coagulation parameters of dabigatran back to its normal range.^{18, 22} Relevant coagulation parameters are TT, aPTT, dTT, and ECT.²³ Immediately after the first bolus of idarucizumab, the aPTT and PT were 26 s and 11 s, whereas dTT assessed by liquid chromatography, dropped from 643 ng/mL to <1 ng/mL, respectively, consistent with complete reversal.¹² Although the previous study showed that Idarucizumab is effectively reverse the coagulant effect, its impact and safety are not clearly stated. This literature review tries to explore the impact of Idarucizumab pharmacological aspects including mechanism of action, pharmacokinetics, and safety as dabigatran antidote...

2. Discussion

Atrial Fibrillation

Atrial fibrillation (AF) is characterized by high-frequency atrial excitation that results in disynchronous atrial contraction and irregular ventricular contraction.²⁴ While AF can arise without any structural or electrophysiologic abnormalities, epidemiological association studies had to identify many comorbid conditions. Some of them had been shown to cause structural and histopathological changes causing a unique AF substrate or atrial cardiomyopathy.²⁵

Atrial fibrillation (AF) risk factors (figure 1) are fibrosis, inflammation, and molecular or cellular changes that result in atrial structural and histopathological changes. Such changes increase susceptibility to AF. Furthermore, persistent AF can induce electric and structural remodeling which causing AF persistence. AF can also lead to the development of additional risk factors that alter the atrial substrate. Finally, AF is related to stroke, venous

thromboembolism (VTE), Congestive Heart Failure (CHF), and myocardial infarct.²⁵

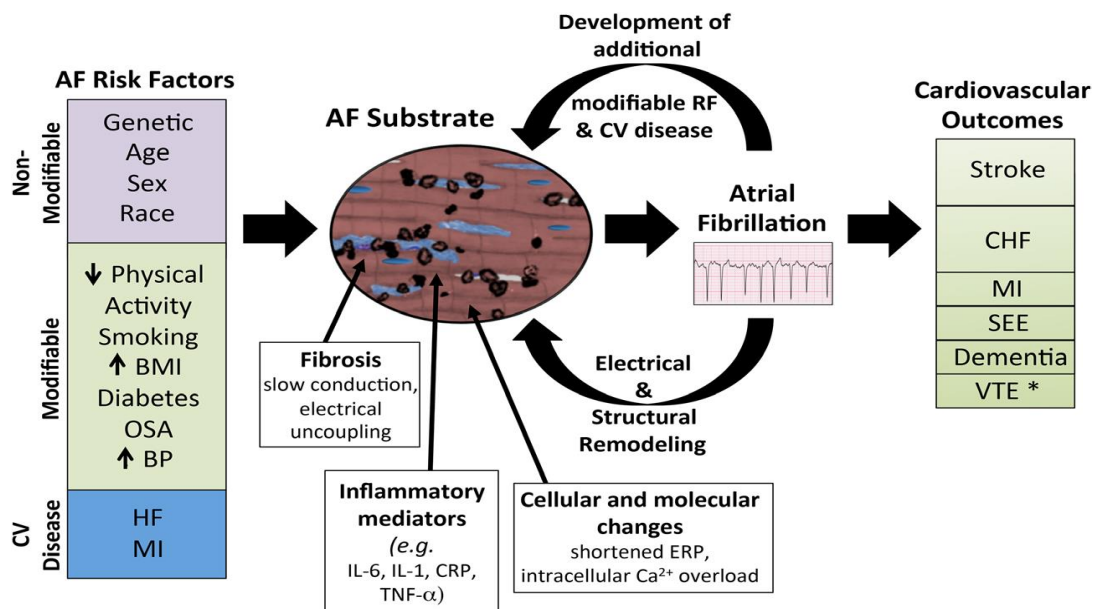


Figure 1. Atrial fibrillation (AF) risk factors (RFs) induce structural and histopathology changes to the atrium characterized by fibrosis, inflammation, and cellular and molecular changes. Such changes increase susceptibility to AF. Persistent AF further induces electric and structural remodeling that promotes perpetuation of AF. AF also may lead to the development of additional AF risk factors that further alters the atrial substrate. Finally, AF is associated with several clinical outcomes.²⁵

Abbreviation: VTE, venous thromboembolism, BMI, body mass index; ERP, effective refractory period; HF, heart failure; IL, interleukin; MI, myocardial infarction; OSA, obstructive sleep apnea; SEE, systemic embolism event; TNF, tumor necrosis factor; and VTE, venous thromboembolism.²⁵

Three atrial remodelling forms during atrial fibrillation (AF) development are electrical, contractile, and structural remodelling. Electrical remodelling is a consequence of high atrial level, including the shortening of atrial myocytes refractory period and the deceleration of atrial conduction. Contractile remodelling, mainly due to calcium handling disturbance cause atrial mechanical dysfunction which may be temporary or develop into irreversible dysfunction. Structural remodelling is characterized by atrial myocytes alteration in the interstitial, and also extracellular matrix composition alteration and fibrotic tissue deposition. Impaired contractility is caused by local cell physiologic changes and also from atrial myocytes structural remodelling.^{26, 27}

Mechanism action of Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment that can neutralize anticoagulant effect from dabigatran by binding to free and thrombin-bound dabigatran and its metabolite, acylglucuronide, to form a stoichiometric complex with 1:1.¹⁸ Idarucizumab affinity to dabigatran is ≈ 350 times higher than dabigatran and thrombin.^{23, 28} Once the dabigatran became a complex with Idarucizumab (figure 2), the anticoagulant effects, both from the free dabigatran, thrombin-bound dabigatran, or its metabolite, are neutralized. Idarucizumab and dabigatran interaction have a very fast on-rate (milliseconds) and a slow off-rate, in line with its high affinity bound. This cause Idarucizumab and dabigatran make a stable complex with a

few dabigatran separations from them.¹⁸

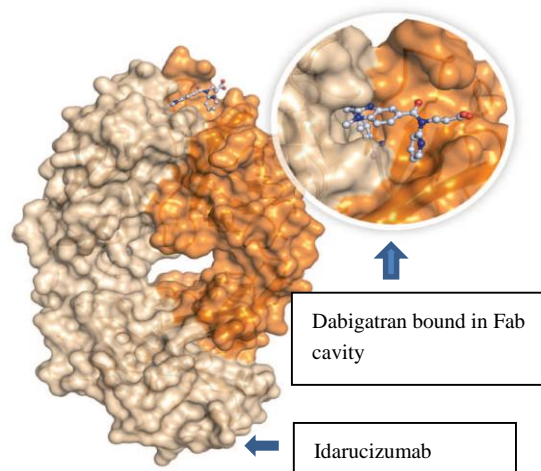


Figure 2.Surface description of X-ray crystallography of dabigatran bound to idarucizumab. Inset, A zoom into the cavity formed by the light interface (orange) and heavy chains of the fragment antigen-binding into which the benzamidine moiety of dabigatran fits. Fab indicates fragment antigen-binding.¹⁸

Dabigatran is a hydrophilic molecule with a low molecular weight and distribution volume ≈1 L/kg which make dabigatran can freely move from blood to the extravascular compartment. In the plasma, when Idarucizumab binds to dabigatran, the unbound dabigatran

concentration is reduced. The unbound dabigatran will maintain their balance by moving from the extravascular compartment to the plasma, where they are bound by Idarucizumab. This process continues until all dabigatran are bound by Idarucizumab and their anticoagulant activity are neutralized (Figure 3).¹⁸

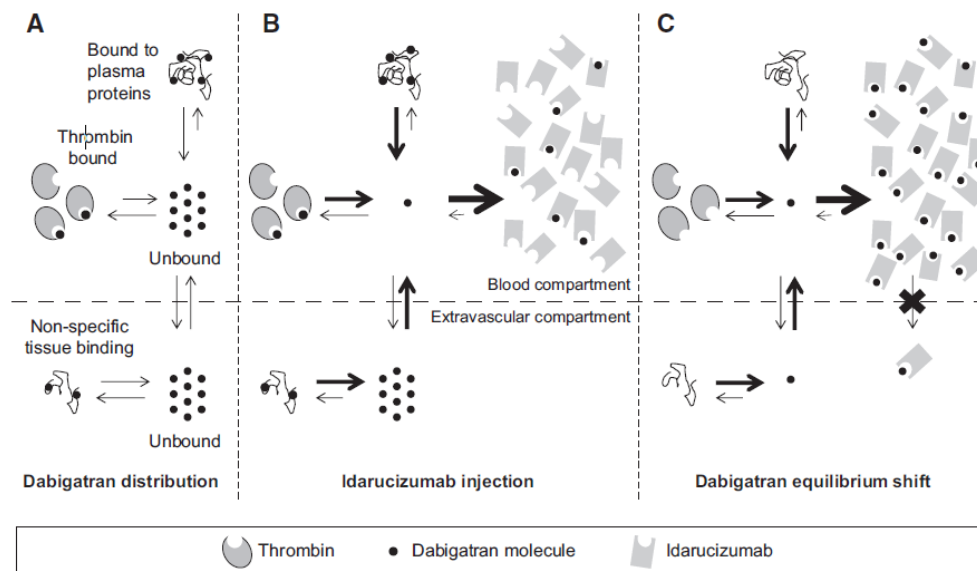


Figure 3. Dabigatran distribution alteration after Idarucizumab administration. **A**, Dabigatran circulation balance between plasma and extravascular compartment. Only the unbound dabigatran which can bind the thrombin and inhibit coagulation. **B**, Idarucizumab quickly binds to dabigatran in the plasma and alter their balance. Extravascular compartment dabigatran move to the plasma and detached from thrombin (larger arrow). **C**, Because of the high affinity of Idarucizumab to dabigatran, thrombin can be feed and start triggering the coagulation.¹⁸

Idarucizumab is specific to dabigatran and free from thrombin or their substrate. Idarucizumab doesn't activate the platelet or facilitate the shifting from thrombin to fibrin. So, there is only a little chance of getting an adverse effect.²⁹ In the animal and volunteers, Idarucizumab didn't promote or attenuate thrombin generation, suggesting that it has no intrinsic anticoagulant or procoagulant effects.¹⁸

Dosage form

Idarucizumab is available as an instant solution and packed as two glass bottles, each bottle contains 2.5 grams Idarucizumab at 50 mg/mL concentration. It can be administered quickly because it doesn't need any reconstitution. It is stored at the fridge (2 – 8°C) and stable for the next 24 months.²³ Before it is opened, it can be stored in the room temperature for 48 hours if stayed in the original package and protected from light or only for 6 hours if exposed to the light. It can be administered as 2 consecutive intravenous boluses (each 2.5 g) or as 2 consecutive intravenous drips (each 2.5 g) within more than 5 – 10 minutes. Parallel administration with another intravenous infusion at the same site or mixed with another drug are not recommended.^{19, 28}

Pharmacokinetic Aspect

Idarucizumab time of peak concentration (T_{max}) is 5 minutes after intravenous administration. The peak concentration (C_{max}) and total exposure (AUC) proportionally increase along with the dose.^{22,28} Idarucizumab volume distribution at steady state condition is similar to blood volume ≈0.06 L/kg and mostly found in

plasma, volume distribution at terminal phase is about 17.6 – 37.9 liter for Idarucizumab dose ≥ 600 mg.^{22,30} Idarucizumab is absorbed and degraded in the proximal renal tubules or excreted in the urine, about 32.1 – 38.9%, as its unchanged. The total clearance is ranged from 36.9 up to 47.1 mL/minutes. In renal disorder patients, the clearance rate is lower than normal patients. Patients with CrCl between 60 - <90 mL/minutes, the total clearance is 32.8 mL/minutes and at CrCl between 30 - <60 mL/minutes, the total clearance is 25.7 mL/minutes.^{28,30} This cause the Idarucizumab concentration in the plasma is increased. In the healthy subjects, Idarucizumab exposure, as defined by the area under the curve, increases up to 43.5% and 83.5% in the subjects with mild to moderate renal disorder. But, as patients with renal disorder tend to have increased plasma dabigatran concentration, higher Idarucizumab exposure will be advantageous.¹⁵

The initial half life is faster, from 39 – 54 minutes but the terminal half life for ≥600 mg Idarucizumab is ranged from 4.5 – 8.1 hours. In the subjects with normal renal function, Idarucizumab plasma concentration declines biphasically with quick initial half life, 45 minutes, and only 4% from the peak concentration that left in the plasma after 4 hours. This is associated with observed Idarucizumab renal excretion, particularly at the urine collection in the first 4 hours. Despite the relatively short half time, Idarucizumab binds all dabigatran in the plasma and extravascular compartment in several minutes as the unbound dabigatran plasma concentration is quickly falling. In the absence of dabigatran, idarucizumab had no effect on coagulation

parameters.³⁰ Idarucizumab plasma concentration can be detected within 16 hours after 1 g Idarucizumab IV administration and 24 hours after administration a higher dose.¹⁹

Efficacy and Safety

Idarucizumab usage is allowing early and safe intervention in most patients. Pollack, et al conducted RE-VERSE AD research to investigate Idarucizumab efficacy and safety in patients treated with dabigatran who experience serious bleeding or need immediate intervention. This research found that Idarucizumab normalized 88 – 98% patients test result. This effect was achieved in several minutes. The unbound dabigatran concentration remains below 20 nano gram per milliliter within 24 hours in 79% patients.¹⁵ A study about Idarucizumab efficacy and safety using some RCTs conducted by Glund, et al in healthy patients and patients with renal disorder found that Idarucizumab was well tolerated and there was no severe or serious adverse event, dose-related event, and drop out due to adverse drug event observed.^{20,22,30} A similar study by Pollack, et al also reported the same result about Idarucizumab safety and supported dabigatran usage in an emergency. In patients with open bleeding evaluated at the first 24 hours, the average time for the bleeding to stop was 2.5 hours. Idarucizumab administration allowed surgery or intervention in 197 from 202 patients, the mean time to start the procedure was 1.6 hours, and 95% of patients were having a normal or slightly abnormal hemostatic condition during the procedure.²¹

Some studies about Idarucizumab adverse event found that there was no relevant clinical finding were reported for vital sign, physical examination, electrocardiogram, cardiac telemetry, or laboratory parameters. Relly Paul et al in the original article reported that among 35 patients in one group that observed their hemostasis, the abnormalities could be restored within 11.4 hours. And among 36 patients in the other group who underwent a procedure, normal intraoperative hemostasis was reported in 33 patients. Mild and moderate abnormal hemostasis was reported in 2 patients and 1 patient respectively. A thrombotic event occurred within 72 hours after Idarucizumab administration in patients who anticoagulants had not been re-initiated.¹⁵ While other studies regarding adverse event after Idarucizumab administration observed in 5 people (placebo (n: 2), Idarucizumab (n: 3) reported some adverse events including headaches (n: 2), erythema (n: 1), and migraines (n: 1), and in the placebo group, extremity pain (n: 1) and chest and upper abdominal pain (n: 1).²⁰

3. Conclusion

Idarucizumab can reverse the effects of dabigatran anticoagulants in a few minutes by forming a stable complex. Some studies on efficacy and safety Idarucizumab as an antidote in healthy and renal disorders patients pointed that Idarucizumab could be well tolerated. There was no severe adverse event, dose-dependent event, drop-out due to an adverse event, and no relevant clinical findings were

reported for vital sign, physical examination, electrocardiogram, cardiac telemetry, or laboratory

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