# Reversal of Anticoagulation Effect of Dabigatran with Idarucizumab, for Thrombolysis in Acute Ischemic Stroke: Inimicus Inimico Amicus

Sir,

A 38-year-old doctor presented to us with an acute ischemic stroke (AIS) of 4 h duration. He was a known case of systemic lupus erythematosus with triple positive antiphospholipid antibody syndrome (APS) with persistent high titers of anticardiolipin, lupus anticoagulant, and beta-2 glycoprotein antibodies for the past 4 years. He had a history of ischemic stroke with mild left hemiparesis 2 years earlier and deep vein thrombosis of the left leg 1 year earlier. For his secondary APS, he had been started on Dabigatran 150 mg BD [Pradaxa™ {Boehringer Ingelheim}] and was taking it regularly. On examination, he was conscious and had a

prominent motor aphasia without buccofacial apraxia or dysphagia. He also had a mild right hemiparesis. A CT angiogram showed left M3 branch occlusion with essentially normal brain parenchyma. As he was not a candidate for mechanical thrombectomy and he was close to the end of the rtPA time window, he was administered Idarucizumab 5 g IV [Praxbind™ {Boehringer Ingelheim}] as two consecutive bolus infusions of 2.5 g each, over 10 min at 260 min from the time of onset. At the end of the infusion (270 min), rtPA 90 mg was initiated (9 mg bolus + 81 mg infusion over 1 h for a body weight of 110 kg). The infusion was completed uneventfully and an MRI brain after 24 h showed a left frontal opercular infarction without hemorrhagic transformation [Figure 1]. At 24 h, he was commenced on low molecular weight heparin followed by Warfarin, after a rheumatology opinion. A repeat CT brain on day 5 showed no further changes. He made a steady recovery and was discharged on day 6 with minimal word finding difficulty.

Dabigatran etexilate is a non-vitamin K antagonist oral anticoagulant agent (NOAC) or direct oral anticoagulant. It is indicated to reduce systemic embolic events in patients with nonvalvular atrial fibrillation as well as in venous thromboembolism.[1] Dabigatran is a competitive reversible nonpeptide antagonist of thrombin (an enzyme that converts fibrinogen to fibrin). The newly formed cross-linked fibrin monomers activate factor XIII and accelerate further thrombin production via the activation of factors V and VIII with a procoagulant effect. Conversely, thrombin also has an anticoagulant effect in the coagulation cascade by activating platelets and protein C. Most of the actions of thrombin are inhibited by Dabigatran etexilate. It is a fast acting agent with an onset of action of 30 minutes and has a duration of anticoagulation of 24–36 h. The NOACs [Dabigatran (a direct thrombin inhibitor) or Apixaban, Rivaroxaban, Edoxaban (Factor Xa inhibitors)] offer noninferior efficacy and a good safety profile compared to the conventional vitamin K antagonists (VKA) such as Warfarin or Acenocoumarol. Their greatest advantages are that they do not need regular laboratory monitoring of their anticoagulant effect (different from the VKAs), dose adjustment is simpler, and they have fewer drug or food interactions. Nevertheless, their anticoagulant effects can be tested by the diluted thrombin time (dTT), thrombin time (TT), or ecarin clotting time. Although the activated partial thromboplastin time (aPTT) can be used, it has a weaker correlation with Dabigatran levels or its anticoagulant effects. These tests were not feasible in our patient due to the lack of time and logistical constraints.

Idarucizumab was designed as a specific reversal agent for patients treated with Dabigatran who developed life threatening or uncontrolled bleeding or required emergency surgery. It is a humanized monoclonal antibody fragment (Fab) that rapidly reverses the anticoagulant effect of Dabigatran and normalizes dTT and/or ECT in 88–98% of patients within minutes of idarucizumab infusion. This Fab has 300 times the affinity for Dabigatran than the NOAC has for thrombin. Additionally, the Fab-Dabigatran complex is a very stable complex that potently reverses the anticoagulant effect of Dabigatran by almost 100% in 4 h.[2]

Thrombolytic treatment with IV recombinant tissue plasminogen activator (rtPA) was initially contraindicated in patients taking a NOAC. However, as the use of Dabigatran has increased exponentially, the contrarian situation necessitating its reversal in patients with an AIS, requiring iv rtPA has also correspondingly increased. There is now, data that Idarucizumab can be used safely to reverse Dabigatran effect before rtPA administration in AIS.[3]

To our knowledge, this is the first reported case from India, of Dabigatran reversal with Idarucizumab in AIS followed by iv rtPA administration, although there is a report of Apixaban reversal.[4] Our report adds to the safety profile of Dabigatran reversal in this situation. Although Idarucizumab is expensive (approximately Rs 77,000/- for 5 g), it was provided gratuitously and promptly from the local distributor as the patient was taking the innovator product and had registered online via their "Pradaxa care and support Program." A patient who was instead, taking a biosimilar of Dabigatran would have to pay the "plena pretium" or full price. Hence, all clinicians should be aware of this therapeutic option in patients taking Dabigatran and

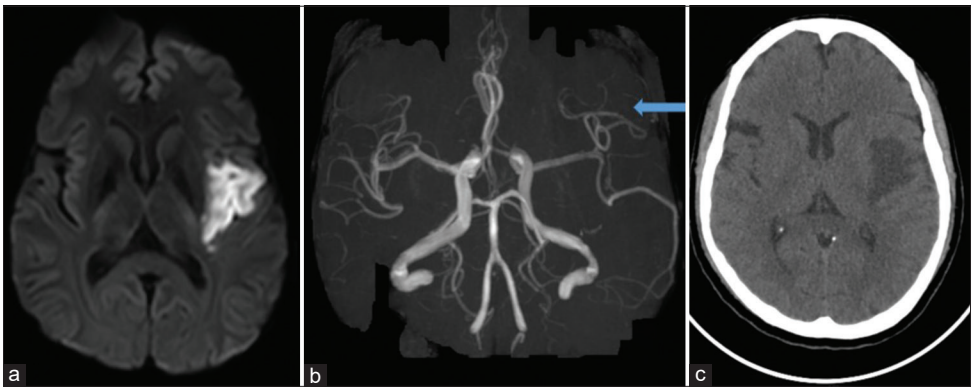


**Figure 1:** Panel a: DWMRI axial sequence showing left MCA opercular infarction. Panel b: MRA shows left MCA branch occlusion (blue arrow). Panel c: CT brain at 24 h showing completed left MCA opercular infarction without hemorrhagic transformation

specifically the "gratuitous" offer of Idaricizumab on those taking the innovator product.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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