### Title

Acute Stroke Despite Dabigatran Anticoagulation Treated with Idarucizumab and Intravenous Tissue Plasminogen Activator




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**[a Case Report for the Journal of Stroke and Cerebrovascular Diseases]**

**TITLE:** Acute stroke despite dabigatran anticoagulation treated with idarucizumab and intravenous tissue plasminogen activator

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**RUNNING TITLE:** Use of IV-tPA after reversal of dabigatran

## ABSTRACT

Dabigatran is a direct thrombin inhibitor used to reduce the risk of stroke in patients with nonvalvular atrial fibrillation. For patients who present with an acute stroke despite dabigatran therapy, clinical data on the use of intravenous tissue plasminogen activator (IV-tPA) is limited. There is an anticipated increased risk of symptomatic intracranial hemorrhage (sICH) when using IV-tPA in patients on dabigatran therapy. In 2015, the humanized monoclonal antibody fragment idarucizumab was approved for rapid (minutes) reversal of anticoagulant effects of dabigatran. Dabigatran reversal with idarucizumab before administration of IV-tPA might reduce the risk of sICH. We report a case of a 69-year-old stroke patient on dabigatran for paroxysmal atrial fibrillation who presented with an initial NIH stroke scale (NIHSS) of 12. There was no early evidence of ischemic stroke or hemorrhage on head computed tomography, and coagulation studies implied therapeutic dabigatran levels. After controlling blood pressure, dabigatran was reversed with idarucizumab, and IV-tPA was administrated beginning 197 min after he was last seen at his baseline. Subsequent brain magnetic resonance imaging showed two punctate infarcts in the left temporal lobe and occipital lobe with no evidence of hemorrhage. The patient was discharged with an NIHSS of 1. Telephone follow-up two months later indicated he was at his pre-stroke baseline, except for a complaint of worsened short-term memory. Idarucizumab reversal of dabigatran may reduce the risk of sICH and should be considered for acute stroke patients arriving in the IV-tPA time window.

A 69-year-old man with a history of hypertension, diabetes, and nonvalvular atrial fibrillation (NVAF) treated with dabigatran 150 mg twice daily was brought to our emergency department after waking from a nap with slurred speech and “confusion”. He scored 12 on the NIH stroke scale (NIHSS), with findings of expressive aphasia, left gaze preference, right neglect, dysarthria, ataxia, down-beat nystagmus, and baseline leg weakness (pre-stroke modified Rankin Scale (mRS) of 3). A head computed tomography (CT) scan showed no signs of bleeding or hyperacute ischemia. Initial labs showed a therapeutic dabigatran level (74 ng/mL) [1], an international normalized ratio of 1.12, and an activated partial thromboplastin time (aPTT) of 39.2 s. After obtaining consent, we administered 5 grams of idarucizumab [2,3], then infused intravenous tissue plasminogen activator (IV-tPA) within 3.5 hours of symptom onset. Clinical improvement was noted 30 minutes later. Magnetic resonance imaging (MRI) 4.5 hours later showed two punctate ischemic strokes in the medial left temporal lobe and occipital lobe (Figure 1). Head CT at 24 hours post-IV-tPA showed no evidence of hemorrhage. He was discharged with an NIHSS of 1 for mild residual dysarthria. Telephone follow-up two months later supported return to his pre-stroke neurological baseline (mRS of 3) except perhaps for worsened short-term memory.

Dabigatran reduces stroke risk in patients with NVAF. Those patients who nevertheless have an ischemic stroke may not be offered IV-tPA due to the risk of symptomatic intracranial hemorrhage [4]. Risk stratification is complicated by dabigatran’s non-linear effects on available rapid coagulation assays including prothrombin time, activated clotting time, and aPTT, which are elevated at high dabigatran levels, but normal at still-therapeutic drug levels [1,5]. Intravenous idarucizumab was approved in 2015 to reverse the anticoagulation effects of dabigatran, normalizing coagulation assays including thrombin time (TT) and aPTT within 10 minutes [2,3]. Rapid clearance of idarucizumab (<7% remains after 6 hours) allows low levels of extravascular dabigatran to return to the blood, explaining a slow rise in aPTT and TT from 4 to 24 hr [2], which is an important consideration during the 24 hours of intensive monitoring after IV-tPA.

This is the second published case of idarucizumab pre-treatment before IV-tPA [6], and the first case for which MRI identifies ischemic areas and reassures against post-tPA hemorrhage therein (Fig.1). Although outcomes in both cases were good –consistent with other cases of carefully-selected patients given IV-tPA without idarucizumab [7,8] – more studies are needed to determine whether this represents a new therapeutic paradigm.

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**FIGURE 1**

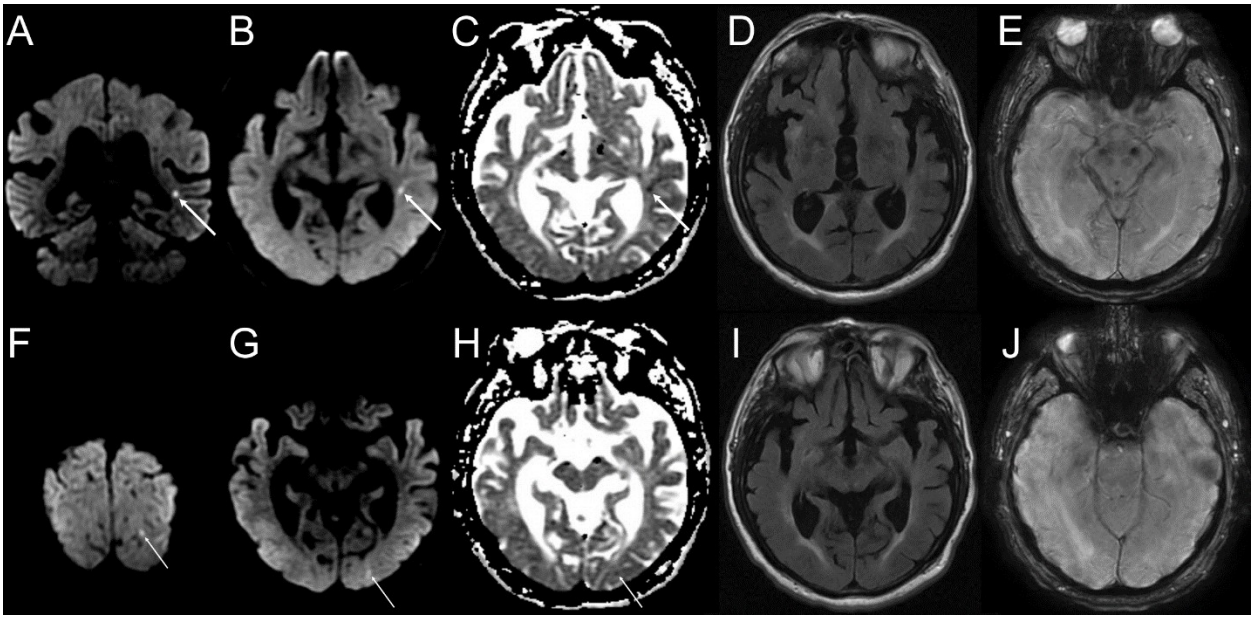


**FIGURE 1 LEGEND**

*MR images acquired eight hours after symptom onset showing puncta of restricted diffusion consistent with acute embolic strokes.* Two hyperintense punctate lesions were identified in diffusion-weighted coronal (panels A and F) and axial (panels B and G) images. Axial maps of apparent diffusion coefficient confirmed that there was restricted diffusion at the two sites; one in the medial left temporal lobe (thick arrow in panels A-C), and one in the left occipital lobe (thin arrow in panels F-H). $T_2$-weighted fluid-attenuated inversion recovery (FLAIR; panels D and I) and susceptibility-weighted angiography (SWAN; panels E and J) images through the infarct locations are also provided; due to acquisition differences the slice location is non-identical to the images sensitized to diffusion. Note that 8 hours after symptom onset the strokes are not yet visible on FLAIR images. Importantly there is no evidence of hemorrhage in these post-IV-tPA SWAN images – a sequence that is extremely sensitive for hemorrhage detection.