Patients with acute ischemic stroke frequently have a history of anticoagulant use, such as for stroke prevention in atrial fibrillation; however, treatment with intravenous recombinant tissue-type plasminogen activator (r-tPA) in these patients remains controversial.1 However, even in patients receiving oral anticoagulants, there may be an indication for intravenous thrombolysis. Especially, when recent medication history or confirmatory specific coagulation tests no longer detect clinically relevant anticoagulant activity at the time thrombolysis is started. This is outlined in the prescribing information for r-tPA.2 Although guideline recommendations include a cutoff for international normalized ratio (INR) values (INR<1.7) in patients receiving vitamin K antagonists who may be considered for intravenous thrombolysis treatment,1,3,4 there are no established cutoff values for the anticoagulant effects of each of the non–vitamin K antagonist oral anticoagulants that would allow for thrombolysis with r-tPA. An alternative approach could be the rapid antagonization of the anticoagulant, thereby eliminating the anticoagulant effect to allow subsequent intravenous thrombolysis with r-tPA. Currently, among all oral anticoagulants, only dabigatran has a specific, rapidly acting, and approved antidote.5,6

We are reporting on the use of idarucizumab,7–11 a specific antidote for dabigatran, before intravenous thrombolysis with r-tPA for acute ischemic stroke treatment.

Case Report
A 76-year-old male patient was admitted to our hospital in early February 2016 around 9:30 pm with sudden-onset aphasia.

The patient had previously suffered a cardioembolic left-sided middle cerebral artery infarction in November 2013 without clinical sequelae. The suspected cause was a cardiac embolism, and the patient was diagnosed with nonvalvular atrial fibrillation. For this reason, he was started on dabigatran 110 mg BID. Arterial hypertension and diet-controlled diabetes mellitus were known relevant preexisting comorbidities. He received a pacemaker in 2012 because of symptomatic bradyarrhythmic episodes.

Key Words: anticoagulants  ■  antidotes  ■  dabigatran  ■  idarucizumab  ■  stroke
He presented in our emergency department ≈2 hours and 30 minutes after symptom onset. Neurological status showed a global aphasia, neglect to the right, and a slight brachiofacial hemiparesis pronounced in the right arm (NIHSS [National Institutes of Health Stroke Scale] 11 points). According to his wife, the patient took his last dabigatran dose around 6:00 pm, ≈1 hour before the start of symptoms.

The computed tomography (CT) scan showed the previous left-sided middle cerebral artery infarction and no early signs of infarction. The large, brain-supplying vessels were without relevant occlusion as analyzed by CT angiography.

The thrombin time was 218 seconds (normal range: 15–36 seconds), and the activated partial thromboplastin time (aPTT) was 73.3 seconds (normal range: 20–40 seconds) on admission. The remaining routine laboratory values, including creatinine clearance, were normal.

We treated the patient with an intravenous bolus of 5 g idarucizumab given for 5 minutes to antagonize the anticoagulant effect of dabigatran. Immediately afterward, intravenous thrombolysis with 69 mg r-tPA, equivalent to 0.9 mg r-tPA/kg body weight was initiated.

The next morning, the hemiparesis and neglect were almost fully regressed, and aphasia was significantly improved (NIH SS 3 points). The follow-up CT scan showed no new signs of cerebral infarction or hemorrhagic transformation (a magnetic resonance imaging was not possible because of the pacemaker). The thrombin time was 26.9 seconds and the aPTT was 26.6 seconds at follow-up.

A cardiovascular examination of the patient revealed slight atherosclerotic lesions in the brain-supplying arteries without relevant stenoses. Transthoracic and transesophageal echocardiography showed no additional evidence of a cardiac embolic source. Ultimately, nonvalvular atrial fibrillation remained the major determinant of the recurrent stroke in this patient. For this reason, we started oral anticoagulation again with an increased dabigatran dose (150 mg BID) beginning the following day.

After 7 days, the patient was discharged for early rehabilitation. Another CT scan showed no evidence of new cerebral infarction. At the time of transfer, the patient showed a slight fluid aphasia with primary anomia (NIH SS 1 point).

Discussion
For the first time, we report the successful use of idarucizumab in combination with subsequent intravenous thrombolysis using r-tPA, in an acute ischemic stroke patient receiving anticoagulation with 110 mg BID dabigatran.

Idarucizumab, a specific antidote for dabigatran, is a humanized antibody fragment (Fab fragment; Fab stands for fragment antigen binding) from the IgG1 isotype, which directly binds the thrombin inhibitor dabigatran and was approved in 2015 by the US Food and Drug Administration and European Medicines Agency for use in dabigatran-treated patients when rapid reversal of its anticoagulant effects is needed, such as in emergency surgery or urgent procedures or life-threatening or uncontrolled bleeding. These patients are also being enrolled in the currently ongoing, multicenter open-label, single-arm phase III study RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran), where efficacy and tolerability of idarucizumab is being studied in clinical practice. Thus, patients requiring thrombolysis could also be enrolled in the RE-VERSE AD study as those requiring an urgent procedure after dabigatran reversal. However, information on this particular patient population has been limited to date.

In our case, the significantly elevated aPTT and thrombin time values before the start of thrombolysis were seen ≈4 hours after the last intake and demonstrated an anticoagulant effect consistent with peak dabigatran values. Because CT angiography showed no proximal vascular occlusion, mechanical thrombectomy was not indicated in this patient. Although not specifically listed as an indication for use of idarucizumab as per labeling information, we first antagonized the anticoagulant effect of dabigatran with 5 g idarucizumab before immediately starting intravenous thrombolysis with r-tPA (see Table for details).

Idarucizumab rapidly reverses dabigatran anticoagulation and returns the patient coagulation status to their normal or baseline state. Thus, if they are undergoing a thrombotic event, which is procoagulant in nature, then thrombolysis should be initiated rapidly after dabigatran reversal. This is supported by recent data demonstrating that there are no interactions between idarucizumab and r-tPA–induced thrombolysis in human plasma in vitro. In addition, idarucizumab has no procoagulant effect, in contrast to coagulation factor concentrates, and as an antibody fragment is neutral regarding any pro- or anticoagulant effect. It only directly inhibits dabigatran, thus will not in itself further potentiate coagulation.

<table>
<thead>
<tr>
<th>Table. Extract From Prescribing Information of r-tPA and Idarucizumab</th>
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</thead>
<tbody>
<tr>
<td><strong>Alteplase</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>4.4 Special warnings and precautions for use</td>
</tr>
<tr>
<td>Patients receiving oral anticoagulant treatment:</td>
</tr>
<tr>
<td>The use of Actilyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely confirmed by appropriate test(s) of anticoagulant activity for the product(s) concerned showing no clinically relevant activity on the coagulation system (eg, INRs≤1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).</td>
</tr>
<tr>
<td>• For emergency surgery/urgent procedures.*</td>
</tr>
<tr>
<td>• In life-threatening or uncontrolled bleeding.</td>
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</tbody>
</table>

*Urgent procedures: any urgent procedure that cannot be postponed, any diagnostic, therapeutic, interventional, or pharmacological intervention (such as thrombolysis), and where rapid removal of an anticoagulatory effect of dabigatran is required, may be considered. In the RE-VERSE AD trial (Reversal Effects of Idarucizumab on Active Dabigatran; group B), no clinical restrictions were prespecified. Fab indicates fragment antigen binding.
Thus, this represents a new therapeutic paradigm. Patients effectively anticoagulated with dabigatran who were previously contraindicated for thrombolytic therapy in this situation may now receive treatment because of the ability to rapidly reverse the anticoagulant activity of dabigatran with idarucizumab. Particularly since both vitamin K antagonists, such as warfarin, and also other non–vitamin K antagonist oral anticoagulants currently have no specific reversal agent.

Although there is at to date limited clinical evidence and no specific labeling information for ischemic stroke use available, our case illustrates a potential beneficial use of idarucizumab in this specific situation.

Conclusions

Because of the increasing use of non–vitamin K antagonist oral anticoagulants, more anticoagulated acute stroke patients presenting within the time window for intravenous thrombolytic therapy will become more frequent in stroke departments. When these patients are treated with dabigatran, the anticoagulation can be antagonized with idarucizumab, thereby abruptly returning them to a status of normal hemostasis with respect to dabigatran anticoagulation. Afterward—presumably with a comparable bleeding risk to a nonanticoagulated patient—they may undergo intravenous thrombolysis with rtPA. Further studies on this emergency condition are needed to increase the level of evidence from an individual treatment to a generalized recommendation.

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Disclosures

C.C. Eschenfelder is an employee of Boehringer Ingelheim. The other authors report no conflicts.

References

Intravenous Thrombolysis With Recombinant Tissue-Type Plasminogen Activator in a Stroke Patient Receiving Dabigatran Anticoagulant After Antagonization With Idarucizumab
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