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SYSTEMATIC REVIEW

Idarucizumab in Dabigatran-Treated Patients with Acute Ischemic Stroke Receiving Alteplase: A Systematic Review of the Available Evidence

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Abstract

Background and Purpose Current guidelines do not recommend the use of intravenous recombinant tissue plasminogen activator in patients with acute ischemic stroke who receive direct oral anticoagulants. While the humanized monoclonal antibody idarucizumab can quickly reverse the anticoagulant effects of the thrombin inhibitor dabigatran, safety data for subsequent tissue plasminogen activator treatment are sparse. Here, we review current knowledge about dabigatran reversal prior to systemic reperfusion treatment in acute ischemic stroke.

Methods We performed a systematic review of all published cases of intravenous tissue plasminogen activator treatment following the administration of a dabigatran antidote up to June 2017 and added five unpublished cases of our own. We analyzed clinical and radiological outcomes, symptomatic post-thrombolysis intracranial hemorrhage, and other serious systemic bleeding. Additional endpoints were allergic reaction to idarucizumab, and venous thrombosis in the post-acute phase.

Results We identified a total of 21 patients (71% male) with a median age of 76 years (interquartile range 70–84). The median National Institute of Health Stroke Scale score at baseline was 10 ($n = 20$, interquartile range 5–11) and 18/20 patients (90%) had mild or moderate stroke severity. The time from symptom onset to start of tissue plasminogen activator was 155 min ($n = 18$, interquartile range 122–214). The outcome was unfavorable in 3/19 patients (16%). There was one fatality as a result of a symptomatic post-thrombolysis intracranial hemorrhage, and two patients experienced an increase in the National Institute of Health Stroke Scale compared with baseline. One patient had a recurrent stroke. No systemic bleeding, venous thrombosis, or allergic reactions were reported.

Conclusion Experience with idarucizumab administration prior to tissue plasminogen activator treatment in acute ischemic stroke is limited. Initial clinical experience in less severe stroke syndromes and short time windows seems favorable. Larger cohorts are required to confirm safety, including bleeding complications and the risk of thrombosis.

Key Points

Idarucizumab is a monoclonal antibody fragment that quickly reverses the anticoagulant effects of dabigatran.

Experience for dabigatran reversal with the aim of intravenous tissue plasminogen activator treatment in acute ischemic stroke is limited.

We summarize 16 published cases and five of our own unpublished cases of systemic thrombolysis in acute ischemic stroke following the administration of idarucizumab.

Initial real-life experience for idarucizumab in less severe stroke syndromes and short time windows seems favorable.

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1 Introduction

1.1 Stroke Prevention in Atrial Fibrillation

Atrial fibrillation (AF) is a major and continuously increasing cause of acute ischemic stroke (AIS) [1]. Until recently, vitamin K antagonists have been the only treatment option for the prevention of stroke and systemic embolization arising from AF. The use of vitamin K antagonists (warfarin, phenprocoumon, and acenocoumarol) for non-valvular AF has been decreasing in favor of direct oral anticoagulants (DOACs) [2]. In fact, DOACs (apixaban, edoxaban, dabigatran etexilate, and rivaroxaban) are preferentially used because of their favorable risk–benefit profile. Four randomized, controlled, phase III trials supported the approval of these drugs, which individually demonstrated non-inferiority to warfarin for stroke prevention in non-valvular AF [3–6]. Each year, approximately 1–2% of patients with non-valvular AF are expected to develop AIS despite treatment with DOACs [7, 8]. Thrombolytic treatment with intravenous (i.v.) recombinant tissue plasminogen activator (tPA) is contraindicated in patients taking a DOAC.

1.2 Dabigatran and Treatment with Tissue-Plasminogen Activator in Acute Ischemic Stroke

Dabigatran etexilate is a prodrug of dabigatran. Dabigatran inhibits the function of thrombin, which stabilizes clots by catalyzing the conversion of fibrinogen to fibrin [9]. Severe hemorrhagic complications, similar to those seen with vitamin K antagonists, can be anticipated in the context of tPA treatment in patients receiving anticoagulation treatment with dabigatran, and, in fact, a case of fatal intracerebral hemorrhage has been reported among seven tPA-treated patients also receiving dabigatran [10, 11]. Drug labeling suggests a 48-h gap following the last intake of dabigatran, or at least the elapse of two half-lives since the most recent dose [12, 13]. The use of tPA may be justified if the patient had not taken dabigatran for the previous 12 h, and anticoagulation assays are consistent with an absence or a very low level of dabigatran activity [14]. Normal kidney function is a prerequisite in both situations. Determination of dabigatran serum concentrations, however, is not possible at many centers in a reasonable time frame, and the absolute safety margins for tPA treatment have not been established yet.

Traditional tests of coagulation, including International Normalized Ratio and activated partial thromboplastin time (aPTT), have somewhat limited reliability in measuring the anticoagulant effects of dabigatran. As normal thrombin time (TT, <38 s) and aPTT (<37 s) exclude the significant anticoagulant effect by dabigatran, some authors would allow i.v. thrombolysis in such scenarios [15].

1.3 Reversal of Anticoagulant Effect of Dabigatran for Thrombolysis in Acute Ischemic Stroke

Idarucizumab has been approved as a specific antidote of dabigatran. This antibody fragment demonstrated prompt and durable reversal of the anticoagulant effects of dabigatran in animal studies, and in phase I studies of young and elderly individuals, as well as in renally impaired volunteers [16, 17]. The standard dose of 5 g of this humanized antibody fragment completely reverses the biological activity of dabigatran within a few minutes. It has primarily been developed for the reversal of anticoagulant effects of dabigatran for emergency surgery and life-threatening bleeding [18]. Whether idarucizumab could be used to safely perform systemic thrombolysis with tPA has not been evaluated in clinical trials so far. Of importance, additional questions such as the efficacy of tPA after antagonization of dabigatran, the risk of intracerebral and systemic bleeding, as well as the potential occurrence of procoagulant effects need to be answered [19]. In addition, the significance of potential adverse reactions including hypokalemia, delirium, constipation, pyrexia, and pneumonia in AIS needs to be established [20]. Since the approval of idarucizumab for the management of bleeding complications related to dabigatran use, there have been case reports of off-label use in the context of i.v. thrombolysis in AIS. Here, we review the current evidence by analyzing all published cases and our additional five unpublished cases of patients with AIS who received tPA after reversal of dabigatran with idarucizumab.

2 Materials and Methods

2.1 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: adult patients (age $\geq$18 years) with acute-onset focal neurological deficits suggestive of AIS; receiving treatment with dabigatran (110 or 150 mg twice a day); and the administration of idarucizumab prior to treatment with tPA. The exclusion criterion was the a final diagnosis of a stroke mimic.

2.2 Search Strategy

The literature review was performed via a comprehensive search on MEDLINE, SCOPUS, and Web of Science databases up to 12 June, 2017. We used the following terms and keywords: 'ischemic stroke', 'stroke', 'brain

infarction', 'thrombolysis', 'thrombolysis therapy', 'thrombolytic therapy', 'recombinant tissue plasminogen activator', 'rtPA', 'tPA', 't-PA', 'alteplase', 'new oral anticoagulant', 'NOAC', 'DOAC', 'direct thrombin inhibitor', 'DTI', 'pradaxa', 'dabigatran', 'idarucizumab', and 'praxbind', with different Boolean operators. All English abstracts and full texts of the relevant articles were studied. We also manually searched reference lists of the retrieved articles to identify additional sources.

2.3 Quality Assessment and Data Extraction

No additional rating of the quality was performed because the publications were entirely case reports. Cases were also included if minimum reporting standards were available from the report. These included patient age, National Institutes of Health Stroke Scale (NIHSS) score at baseline, and at least one of the following criteria: (1) determination of dabigatran serum concentrations on admission; (2) time from last dabigatran intake to laboratory examination; or (3) time from symptom onset to tPA administration. Stroke severity was classified using the NIHSS total score. The categories were mild (1–4), moderate (5–15), moderate to severe (16–20), and severe (21–42).

2.4 Outcome and Assessment of Complications

Unfavorable outcome was defined as an increase of the NIHSS score or death. We considered symptomatic intracerebral hemorrhage (sICH) and systemic bleeding as major complications. We applied the National Institutes of Neurological Disorders and Stroke tPA trial definition of sICH [21]. Additional endpoints were allergic reaction to idarucizumab, recurrent stroke, and venous thrombosis during the post-acute phase. We noted the occurrence of infections and other findings attributed to idarucizumab.

2.5 Own Case Series

We reviewed the medical records of consecutive patients who developed AIS while taking dabigatran at our department before 12 June, 2017. The data collected included baseline demographics, clinical findings, coagulation parameters upon admission, imaging parameters, clinical course, and approach to secondary prevention. We added patients to the analysis if i.v. tPA treatment had been performed after reversal of the anticoagulant effect of dabigatran with the use of idarucizumab. No patient consent was required for reporting in accordance with Austrian national regulations. This was confirmed by the local ethics committee (Ethikkommission für das Bundesland Salzburg; 415-EP/73/750-2017).

2.6 Statistical Analysis

Continuous variables are presented as median with interquartile range (IQR). GraphPad Prism Version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analyses.

3 Results

3.1 Systematic Review

A total of 13 eligible papers, reporting on 16 patients, were identified based on the inclusion and exclusion criteria [9, 22–34]. A national case collection from Germany comprising 19 cases (58% women) was not included as minimum reporting standards for this systematic review were not met [35]. For matter of completeness, major findings of that publication are shown in Table 1.

3.2 Own Case Series

We identified five patients fulfilling the inclusion criteria. Details of these patients are reported in Table 2 (patients 1–5). Additional information can be obtained upon e-mail request to the corresponding author.

3.3 Pooled Analysis

3.3.1 Clinical Details

An analysis was performed on 21 cases (71% male); details of each patient are shown in Table 2. The median age was 76 years (IQR 70–84). Information on stroke severity at baseline was available for 20 patients, with a median NIHSS score of 10 (IQR 5–11). Most patients (90%) had mild ($n = 4$) or moderate ($n = 14$) stroke severity. The remaining two patients were classified as having "moderate to severe" ($n = 1$) or severe ($n = 1$) stroke.

Seven patients were treated with 150 mg twice daily, 11 patients with 110 mg twice daily, and one with 150 mg once daily of dabigatran. No information on dabigatran dose was available in two cases. Details on the last dabigatran intake were available in 14 patients (71%), ranging from 45 min to 17 h. Intake was within the last 6 h in ten cases (67%), and beyond 6 h in four cases (33%). Dabigatran serum concentrations were determined in 11 patients (52%). The median dabigatran concentration was 74 ng/mL (IQR 43–172.2). Symptom onset to the start of tPA time was reported in 18 patients, with a median of 155 min (IQR 122–214).

Table 1 Demographic, laboratory, and imaging characteristics of 21 patients with acute ischemic stroke receiving tissue plasminogen activator (tPA) treatment following dagbiatran reversal with idarucizumab

	Age/sex	Dabigatran dosage (mg, twice daily)	Dabigatran intake[a] (h)	Dabigatran serum concentration (ng/mL)	r-tPA adm. from onset (min)	TT (s)[b]	aPTT (s)[c]	tPA Dabigatran dosage (mg)	Baseline NIHSS	Follow-up imaging	Outcome (NIHSS)	Hypersensitivity/vascular event/infection	Dabigatran re-established (days)
Patient 1 (current case 1)	88/F	110	4:30	202.4	160	–	71	54	10	No demarcation	1	-/-/-	1 (apixaban)
Patient 2 (current case 2)	67/M	150	5:38	183.7	247	–	77	50	4	No demarcation	0	-/-/-	1
Patient 3 (current case 3)	84/M	150 once daily	7:04	31.4	133	–	84	72	10	No demarcation	2	-/-/urinary infection	2 (2 × 110 mg)
Patient 4 (current case 4)	85/M	110	–	43	95	–	36	77	7	No demarcation	2	-/-/-	2
Patient 5 (current case 5)	82/M	110	–	172.2	123	–	52	80	18	Left MCA	7	-/-/-	–
Patient 6 (Mutzenbach et al.[23])	68/M	110	0:45	34.1	110	–	34	70	3	Left PCA	3	-/-/-	3
Patient 7 (Berrouschot et al.[22])	76/M	110	1:00	–	150	218	73.3	69	11	No demarcation	1	-/-/-	1
Patient 8 (Schäfer et al.[24])	67/F	150	4:00	–	90	130	–	60	10	Deep MCA	–	-/-/-	–
Patient 9 (Kafke et al.[25])	75/F	110	–	90	120	>150	35.5	67	7	Pons and thalamus	18	-/-/pneumonia	Change to rivaroxaban planned after 3–4 weeks
Patient 10 (Gawehn et al.[9])	75/M	110	9:30	–	–	66.8	39	–	5	–	–	-/-/-	1
Patient 11 (Schulz et al.[26])	76/M	110	9:00	–	170	72.2	–	72	11	PCA	4	-/-/-	–
Patient 12 (Ng et al.[27]) first	85/M	–	17:00	–	167	>60	–	–	30	Symptomatic hemorrhage	Died on day 4	-/-/-	See outcome
Patient 13 (Ng et al.[27]) second	46/M	–	1:00	–	178	–	–	–	5	Left MCA	18	-/contralateral stroke 30 h later/-	–

Table 1 continued

	Age/sex	Dabigatran dosage (mg, twice daily)	Dabigatran intake[a] (h)	Dabigatran serum concentration (ng/mL)	r-tPA adm. from onset (min)	TT (s)[b]	aPTT (s)[c]	tPA Dabigatran dosage (mg)	Baseline NIHSS	Follow-up imaging	Outcome (NIHSS)	Hypersensitivity/vascular event/infection	Dabigatran re-established (days)
Patient 14 (Cappellari et al.[28])	75/F	150	1:30	74	225	–	–	64	4	–	0	-/-/-	–
Patient 15 (Turine et al.[29])	85/F	110	4:15	–	303	112	32.2	49.5	17	Left and right MCA	0	-/-/-	1
Patient 16 (Facchinetti et al.[31])	78/F	150	5:00	74	240	–	1.69 (ratio)	64	4	Right MCA	0	-/-/-	5
Patient 17 (Vosko et al.[30]) 1st	78/M	110	–	–	–	>150	–	0.6 mg/kg	–	–	0	-/-/-	–
Patient 18 (Vosko et al.[30]) second	84/M	110	–	79	–	129	41.6	–	9	–	4	-/-/-	–
Patient 19 (von Wovern et al.[32])	78/F	150	–	–	125	–	49	–	11	–	0	-/-/-	Day 1 or 2
Patient 20 (Tireli et al.[33])	71/M	150	0:30	–	137	–	62	–	6	No demarcation	0	-/-/-	–
Patient 21 (Bissig et al.[34]	69/M	150	–	74	210	–	39.2	–	12	Left MCA	1	-/-/-	–

aPTT activated partial thromboplastin time, *F* female, *M* male, *MCA* middle cerebral artery, *NIHSS* National Institute of Health Stroke Scale, *PCA* posterior cerebral artery, *r-tPA adm.* intravenous recombinant tissue plasminogen activator administration, *TT* thrombin time, – not done, not available or not reported

[a] Dabigatran intake before laboratory testing

[b] Normal value range <20 s

[c] Normal value range <34 s

Table 2 German national case series of 19 patients with acute ischemic stroke treated with tissue plasminogen activator (tPA) following dabigatran reversal with idarucizumab

	Age/sex	Dabigatran dosage (mg, twice daily)	Dabigatran intake[a] (h)	Dabigatran serum concentration (ng/mL)	r-tPA adm. from onset (min)	TT (s)[b]	aPTT (s)[c]	tPA Dabigatran dosage (mg)	Baseline NIHSS	Follow-up imaging	Outcome (NIHSS)	Details of course	Dabigatran re-established (days)
Patient 22 (German series case 1)	75/M	110	–	–	–	66.8	38	–	5	No demarcation	1	–	1
Patient 23 (German series case 2)	40/F	110	–	–	–	69.1	24.3	–	12	–	1	–	7 (VKA)
Patient 24 (German series case 3)	83/M	110	–	–	–	45.4	34.6	–	4	–	2	–	8
Patient 25 (German series case 4)	76/M	110	–	–	–	218	73	–	11	–	1	–	3
Patient 26 (German series case 5)	67/F	150	–	–	–	129.8	26	–	10	–	8	–	10 (apixaban)
Patient 27 (German series case 6)	86/F	110	–	–	–	–	34.6	–	5	–	2	–	1
Patient 28 (German series case 7)	86/F	110	–	–	–	–	45	–	12	–	2	–	Edoxaban
Patient 29 (German series case 8)	58/F	150	–	–	–	87.5	35.8	–	3	–	–	–	3 (argatroban)
Patient 30 (German series case 9)	85/M	150	–	–	–	19.2	25.9	–	17	–	Died on day 5	Pneumonia, DVT and PE	See outcome
Patient 31 (German series case 10)	78/F	110	–	–	–	>150	35.6	–	7	–	18	Deterioriation on day 1	21 (no details)
Patient 32 (German series case 11)	84/F	110	–	–	–	>150	59	–	5	–	2	–	1
Patient 33 (German series case 12)	77/M	110	–	–	–	>150	69	–	6	–	0	–	1
Patient 34 (German series case 13)	85/M	150	–	–	–	–	48	–	7	–	1	–	7

Table 2 continued

	Age/sex	Dabigatran dosage (mg, twice daily)	Dabigatran intake[a] (h)	Dabigatran serum concentration (ng/mL)	r-tPA adm. from onset (min)	TT (s)[b]	aPTT (s)[c]	tPA Dabigatran dosage (mg)	Baseline NIHSS	Follow-up imaging	Outcome (NIHSS)	Details of course	Dabigatran re-established (days)
Patient 35 (German series case 14)	78/F	110	–	–	–	–	84	–	7	–	1	–	2
Patient 36 (German series case 15)	84/F	110	–	–	–	–	25.6	–	14	–	14	–	2
Patient 37 (German series case 16)	77/M	110	–	–	–	–	43.6	–	4	–	1	–	2
Patient 38 (German series case 17)	54/M	150	–	–	–	24.1	26.1	–	11	–	2	–	1
Patient 39 (German series case 18)	89/F	110	–	–	–	–	38.9	–	5	–	2	–	8
Patient 40 (German series case 19)	90/F	110	–	–	–	>120	37	–	7	–	3	–	7

aPTT activated partial thromboplastin time, *DVT* deep vein thrombosis, *F* female, *M* male, *NIHSS* National Institute of Health Stroke Scale, *PE* pulmonary embolism, *r-tPA adm* intravenous tissue plasminogen activator administration, *TT* thrombin time, *VKA* vitamin K antagonists, – not done, not available or not reported

[a] Dabigatran intake before laboratory testing

[b] Normal value range <20 s

[c] Normal value range <34 s

3.3.2 Coagulation Parameters

The standard coagulation parameters reported were APTT and TT, performed in 14 and 8 cases, respectively. Both values were reported in five cases. In all patients who had their TT measured, this was above the normal range (<20 s). The aPTT was not prolonged in 1/14 patients (normal, <34 s). Ecarin time was not given for any patients. Further information about coagulation parameters is shown in Table 2.

3.3.3 Clinical and Radiological Course

The NIHSS score on admission was reported in all but one patient. The median NIHSS score was 10 (IQR 5–11). We classified disease severity as "minor" in 4, "moderate" in 14, and "moderate to severe" and "severe" in one each. Thus, mild and moderate cases comprised 90% of our series. Clinical follow-up was available in 19 of 21 patients. We calculated a median score of 1. We found that 13 survivors had an improved short-term course (72%), the median decline was 7 points (IQR 4–9.5) in the NIHSS score. Unfavorable outcome was detected in three cases (3/19, 16%); two patients had a higher NIHSS score on follow-up (patients 9 and 13), and one patient died (patient 12).

Information on follow-up neuroimaging was present for 16 patients. Imaging findings consistent with AIS were present in nine patients (56%), and no obvious hypodense infarct was found in six patients (38%). In one patient, a large hemispheric infarct with significant hemorrhage and mass effect was detected on day 1 (patient 12). The hemorrhage was rated as sICH; this patient died on day 4 following further neurological deterioration. Another patient sustained a contralateral stroke 30 h after dabigatran reversal and thrombolysis (patient 11).

3.3.4 Other Study Endpoints and Findings

One patient was treated with antibiotics after developing pneumonia (patient 7). No events of hypersensitivity to idarucizumab or deep vein thrombosis were reported. Resumption of treatment with a DOAC was reported in 11 patients. In most patients ($n = 7$, 64%), dabigatran was restarted on day 1 or 2. In two patients, apixaban or rivaroxaban was chosen instead. We identified high-grade carotid artery stenosis as the etiology of AIS in one of our patients (patient 5). This patient remained on weight-adapted, low-weight molecular heparin until carotid artery surgery on day 3.

4 Discussion

We analyzed real-world experience with tPA treatment in 20 patients after neutralization of the anticoagulant effects of dabigatran with idarucizumab. We emphasize that this cohort comprised only relatively few patients with moderate-to-severe stroke severity (10%). In addition, most patients were treated within an early time window (a median of 155 min from symptom onset). Additionally, coagulation tests indicated high dabigatran concentrations only in a few cases (3/11, 27%). With these limitations, our data imply that reversal of dabigatran with idarucizumab before i.v. thrombolysis may be feasible in clinical practice, and could therefore be considered in patients with AIS taking dabigatran. Moreover, with a clinical improvement in 72% of the patients, and a median decrease of 7 NIHSS points, our analysis suggests that i.v. tPA maintains its effectiveness. The overall safety aspects can only be partly commented on and larger studies should examine the occurrence of sICH, recurrent infarction, and thrombosis.

Management of stroke including intracerebral hemorrhage and AIS under DOAC therapy is a major healthcare issue, as prescription rates for non-valvular AF and additional indications steadily increase [1, 36]. Indeed, as observed in the various clinical trials, these drugs do not exclude the occurrence of embolic brain infarcts [37]. Pfeilschifter and co-workers estimated that 1% of all patients with AIS presenting within the window of opportunity for tPA would currently be on DOACs [19]. While i.v. tPA has become a standard of care for the treatment of AIS, this approach for reperfusion therapy is currently contraindicated by guidelines in patients on DOACs. Thus, idarucizumab administration prior to i.v. thrombolysis in AIS may be a treatment option in patients taking dabigatran.

Here, we corroborate the report by Kermer and co-workers who retrospectively studied 19 patients from different German centers with the idarucizumab-tPA approach [35]. They concluded that idarucizumab should be considered in cases where ischemic stroke occurs in patients undergoing dabigatran therapy. The German patient series was not included in this narrative review, as details required for further analysis were not reported. The median age in the German cohort was 78 years (IQR 67–86), with a median NIHSS score on admission of 7 (IQR 5–11). The NIHSS score improved in 15/19 patients by a median of 5 points. Two patients had unfavorable outcomes; one died from pneumonia, deep vein thrombosis, and bilateral pulmonary embolism; the other patient deteriorated neurologically 1 day after admission with an NHISS score increasing from 7 to 18. Their patients were

slightly older (German cohort median 78 vs. 76 years) and were less severely affected (median 7 vs. 10 NIHSS points). Patients with unfavourable outcomes were reported in both series, including cases with thrombotic events such as recurrent stroke, deep vein thrombosis, and pulmonary embolism.

There is a theoretical possibility that idarucizumab promotes a pro-coagulant state, or even interferes with tPA action. Interim data from the RE-VERSE study revealed that 5/90 patients developed thrombotic events [18]. The occurrence was late (beyond 72 h) in four patients, including one patient who experienced deep vein thrombosis and pulmonary embolism 2 days after reversal. Notably, a left-atrial thrombus was detected in one patient 9 days after treatment with idarucizumab. None of the patients in the RE-VERSE study received antithrombotic treatment during the period when these adverse events occurred. Notably, a late plasma dabigatran concentration surge, as observed in 22 patients in the RE-VERSE study, which most likely results from the redistribution of extravascular dabigatran into the intravascular compartment, needs to be taken into account. The relevance of this potentially detrimental process in the setting of tPA and AIS needs to be evaluated in upcoming studies.

The findings of our analysis are also important from a laboratory perspective. Kate and co-workers set a threshold for potentially safe dabigatran concentrations at less than 10 ng/mL [15]. The median dabigatran concentration in our study was 74 ng/mL, and in four patients was less than 50 ng/mL. Concentrations below 50 ng/mL are considered subtherapeutic [38, 39]. The anticoagulant effect of DOACs is initiated immediately after oral intake, and is strongly related to their plasma concentrations [40]. Thus, the relatively low serum concentrations in a few patients are likely to have increased, possibly peaking during ongoing i.v. tPA treatment, if not neutralized by idarucizumab. In addition, renal function is crucial when considering the anticoagulant properties of DOAC such as dabigatran, which is predominantly cleared via the kidney [41].

In warfarin-treated patients, the selection for potential thrombolysis candidates is based on International Normalized Ratio values. For dabigatran, ecarin time, TT, and aPTT may be used as point-of-care methods if dabigatran concentrations cannot be determined [19]. Again, Kate and co-workers suggested thresholds for TT (<38 s) or aPTT (<37 s) when i.v. tPA treatment might be performed safely [15]. Using this algorithm, i.v. tPA treatment without antagonization of dabigatran-related anticoagulant activity would have only been considered in one patient (patient 6). Our data, however, also confirm the dilemma that the relationship of aPTT prolongation and dabigatran concentrations is not linear [40]. For instance, the apparently "normal" aPTT in patient 5 was associated with a dabigatran serum concentration of 90 ng/mL. A comparative analysis of TT and aPTT vs. dabigatran was not possible as both values were only reported in five patients.

Another challenge in clinical practice is when to re-start treatment with DOACs after an ischemic event. In the absence of clinical trials, the 1–3–6–12-day rule was proposed in 2013 for patients with non-valvular AF. Briefly, anticoagulation could be started in patients with a transient ischemic attack after 1 day, with minor stroke (NIHSS score <8) after 3 days, a moderate stroke (NIHSS score 8–16) after 6 days, and severe stroke (NIHSS score >16) after 12 days [42]. We demonstrate that this recommendation is implemented in clinical routine, with the majority of the patients having been restarted on DOAC treatment on day 1 or 2. Interestingly, dabigatran was not reintroduced in all patients, and alternative DOACs were considered. This might also indicate that in some cases a direct Factor Xa inhibitor function, and thus a different mode of action, was preferred.

This study has limitations imposed by the limited number of patients and the retrospective study design. Further, the heterogeneity of the cases, missing data, and inhomogeneous endpoints hindered comparability. Further studies and patient registries (e.g., the Registry of Acute Stroke Under Novel Oral Anticoagulants-Prime (RASUNOA-Prime), ClinicalTrials.gov: NCT02533960) are needed to confirm the findings in our cohort.

5 Conclusion

Administration of tPA after reversing dabigatran activity with idarucizumab in AIS might be feasible, and seems to be effective and safe in less severe stroke syndromes in an early time window. These findings need to be corroborated in larger cohorts within the entire spectrum of ischemic stroke subtypes, as well as longer time windows of i.v. tPA treatment and in the presence of various medical comorbidities.

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Compliance with Ethical Standards

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