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Reversing dabigatran effect with idarucizumab to enable intravenous thrombolysis in patients with acute ischaemic stroke — a single centre experience

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ABSTRACT

Introduction. Our study analysed the safety and effectiveness of idarucizumab in enabling intravenous thrombolysis (IVT) in dabigatran-treated patients with acute ischaemic stroke (AIS).

Clinical rationale for the study. New oral anticoagulants (NOAC), including dabigatran, are the first-choice treatment option for preventing ischaemic stroke in patients with non-valvular atrial fibrillation (AF). However, a significant percentage of AF patients develops AIS despite NOAC treatment. According to current guidelines, treatment with IVT is contraindicated in patients who have received NOAC within the last 48 hours. Idarucizumab is a fragment of a monoclonal antibody that reverses the anticoagulation effect of dabigatran. The latest research shows that it can enable safe and successful IVT in patients with recent dabigatran intake, but more data is needed to confirm the safety and effectiveness of such treatment.

Material and methods. Our study included dabigatran-treated patients who received idarucizumab to allow AIS treatment with IVT in the University Hospital in Kraków (Poland) from December 2018 to June 2023. We gathered data on their past medical history, stroke severity, course of treatment and outcomes as defined by modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) scores at discharge. A good functional outcome was defined as mRS 0–2 points at discharge.

Results. This observational study included 19 patients (13 male and six female) with a median age of 74 (IQR = 13) years. In all patients (100%), the reason for dabigatran treatment was AF. A good functional outcome after treatment (mRS 0–2) was achieved in 68.4% of patients, but mRS was already ≥ 3 points before stroke onset in three (15.8%) patients. Haemorrhagic transformation of stroke occurred in three (15.8%) patients, including symptomatic intracranial haemorrhage in two (10.5%). The mortality rate was 5.3%.

Conclusions and clinical implications. Our study results are in line with previous research on this topic, showing that IVT after idarucizumab can be successfully administered and is reasonably safe in dabigatran-treated patients with AIS.

Keywords: acute ischaemic stroke, intravenous thrombolysis, idarucizumab, dabigatran, new oral anticoagulants

Introduction

Acute ischaemic stroke (AIS) is the most common form of stroke, and is an important cause of death and disability worldwide [1]. Early treatment with reperfusion therapies (intravenous thrombolysis, IVT; and/or mechanical thrombectomy, MT) is crucial for improving the prognosis [2].

New oral anticoagulants (NOAC) including dabigatran have been proven to prevent stroke in patients with nonvalvular atrial fibrillation (AF) [3], but a significant percentage of AF patients develop AIS despite NOAC treatment [4]. According to current guidelines, treatment with IVT is contraindicated in patients who have received NOAC within the last 48 hours [5].

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Idarucizumab is a fragment of a monoclonal antibody that binds with dabigatran. Its application has been proven to be safe and effective in rapidly reversing dabigatran's anticoagulation effect in patients with uncontrolled bleeding or requiring emergency surgery or urgent procedures [6]. There is growing evidence that idarucizumab can be safely used in patients with AIS to reverse dabigatran's effect for enabling IVT. Current ESO guidelines state that the evidence is so far insufficient to make a recommendation for or against using idarucizumab and IVT in patients with AIS who have taken dabigatran within the last 48 hours, although in the expert consensus statement most group members suggested that this form of treatment should be preferred over no IVT [5].

Clinical rationale for study

More data is needed to establish the safety and effectiveness of idarucizumab in enabling thrombolytic treatment of AIS in dabigatran-treated patients. We here present a single centre report from Poland concerning outcomes of dabigatran-treated AIS patients who received idarucizumab to allow treatment with IVT.

Material and methods

This observational study is a retrospective analysis of medical documentation of patients hospitalised in the University Hospital in Kraków (Poland) from December 2018 to June 2023. Based on the documentation of patients included in studies: *Identification and clinical validation of biomarkers for long-term outcome after cerebral ischaemia* (Jagiellonian University Bioethics Committee approval number KBET/1072.6120.118.2020) and *Molecular genetics of age-related diseases of the nervous system - a bank of genetic material and clinical data* (Jagiellonian University Bioethics Committee approval number KBET/54/B/2007), we identified patients treated with idarucizumab to enable thrombolytic treatment of AIS over this period. The abovementioned studies include all AIS patients hospitalised in our centre, and the study group represents all AIS patients who have received idarucizumab for enabling IVT in our clinic to date. We did not include patients who had received idarucizumab and IVT in another centre, before being transferred to our hospital. The decision regarding idarucizumab administration was made individually for each patient according to his or her clinical situation and the current guidelines and expert consensuses as updated during the analysed time (2018–2023).

From the documentation of this selected group of patients, we gathered data concerning their age, biological sex, and relevant comorbidities: 1. arterial hypertension (diagnosed in previous medical history and/or antihypertensive treatment prior to stroke onset and/or aystolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at least in two different measurements after the first three days of hospitalisation); 2. atrial fibrillation (diagnosed in previous medical history or during hospitalisation based on electrocardiograms); 3. coronary artery disease (based on medical documentation, available electrocardiograms and/or laboratory data); 4. carotid artery atherosclerosis (intima-media complex thickening or presence of atherosclerotic plaques, with stenoses > 50% considered haemodynamically significant); 5. stroke or transient ischaemic attack (TIA) in previous medical history; 5. diabetes or prediabetes (diagnosed according to ESC criteria [7]); 6. dyslipidaemia (defined as a cholesterol level > 5.2 mmol/L or use of cholesterol–lowering treatment); 7. peripheral artery disease (presence of atherosclerotic plaques in arteries other than coronary and cerebral confirmed by ultrasound during hospitalisation or in previous medical history); 8. history of smoking during the last 15 years; and 9. obesity (BMI > 30 kg/m^2).

We noted functional disability before stroke onset (assessed using modified Rankin Scale, mRS) and neurological deficit at admission (assessed using National Institutes of Health Stroke Scale, NIHSS). We noted the reason for dabigatran treatment, which dose was used, when the last dose was taken, and what was the patient's compliance to treatment (as non-compliant we classified patients who had missed any dabigatran dose within the week preceding the stroke). We analysed time from stroke onset to hospital admission (time to admission, TTA) as well as time from admission to the start of intravenous thrombolysis (door-to-needle time, DTN). Ischaemic lesion size was estimated using perfusion computed tomography (CT) analysis with iRAPID software [8]. We noted whether or not thrombolytic treatment was followed by mechanical thrombectomy (MT), and if so, what was the radiological effect of the reperfusion (assessed with modified thrombolysis in cerebral infarction scale, mTICI). If present, we classified haemorrhagic transformation of the stroke using the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) definitions [9]. Symptomatic intracranial haemorrhage was defined as haemorrhagic transformation of stroke causing a worsening of neurological condition > 4 points in NIHSS score or resulting in mortality within 22-36 hours post-treatment. We gathered data concerning in-hospital mortality and the percentage of patients needing transfer to the intensive care unit (ICU). Short term outcome was measured by mRS and NIHSS score at discharge. A good functional outcome was defined as mRS 0–2 points at discharge.

Statistical analysis of the gathered data was performed using Imago Pro 8.0. We presented categorical data as counts and percentages, and continuous data as median and interquartile range (IQR).

Results

This study included 19 patients who developed AIS while being treated with dabigatran and who received idarucizumab to enable intravenous thrombolysis. The individual patient characteristics are set out in Table 1.

Table 1. Individual characteristics of included patients

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
1.	77, F	Atrial fibrillation Arterial hypertension History of stroke Atherosclerosis of carotid arteries	1	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Left cerebral hemisphere	68	135	22	CBF < 30% = 0 mL Tmax > 6 s = 81 mL Mismatch volume = 81 mL	1 (TICI = 3)	NIHSS = 2 mRS = 1
2.	68, F	Atrial fibrillation Arterial hypertension Coronary artery disease Atherosclerosis of carotid arteries Smoking	0	Atrial fibrillation	2 × 150 mg	12–24 h	No information	Right cerebral hemisphere	110	155	17	CBF < 30% = 25 mL Tmax > 6 s = 124 mL Mismatch volume = 99 mL	1 (TICI = 3)	NIHSS = 2 mRS = 1
3.	63, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Atherosclerosis of carotid arteries Obesity	0	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Right cerebral hemisphere	108	155	6	CBF < 30% = 0 mL Tmax > 6 s = 33 mL Mismatch volume = 33 mL	0	NIHSS = 1 mRS = 1
4.	83, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries Coronary artery disease	0	Atrial fibrillation	2 × 150 mg	12–24 h	Non compliance	Right cerebral hemisphere	169	255	7	CBF < 30% = 0 mL Tmax > 6 s = 95 mL Mismatch volume = 95 mL	0	NIHSS = 3 mRS = 1
5.	79, F	Atrial fibrillation Arterial hypertension Diabetes mellitus Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease History of stroke Smoking	1	Atrial fibrillation	2 × 110 mg	12–24 h	Non compliance	Left cerebral hemisphere	94	188	9	CBF < 30% = 9 mL Tmax > 6 s = 44 mL Mismatch volume = 35 mL	0	NIHSS = 2 mRS = 1

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
6.	38, M	Atrial fibrillation Arterial hypertension Smoking	0	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Left cerebral hemisphere	46	100	6	CBF < 30% = 13 mL Tmax > 6 s = 57 mL Mismatch volume = 44 mL	1 (TICI = 3)	NIHSS = 0 mRS = 0
7.	79, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease History of stroke	0	Atrial fibrillation	2 × 110mg	0–12 h	Full compliance	Right cerebral hemisphere	192	255	20	CBF < 30% = 0 mL Tmax > 6 s = 83mL Mismatch volume = 83 mL	0	NIHSS = 1 mRS = 0
8.	70, M	Atrial fibrillation Arterial hypertension Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease History of stroke	1	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Left cerebral hemisphere	102	155	5	CBF < 30% = 0 mL Tmax > 6 s = 79 mL Mismatch volume = 79 mL	0	NIHSS = 2 mRS = 1
9.	84, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries Peripheral atherosclerosis	3	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	143	225	9	CBF < 30% = 0 mL Tmax > 6 s = 15 mL Mismatch volume = 15 mL	0	NIHSS = 3 mRS = 3
10.	72, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease Smoking	0	Atrial fibrillation	2 × 150 mg	0–12 h	Full compliance	Left cerebral hemisphere	53	112	4	CBF < 30% = 0 mL Tmax > 6 s = 53 mL Mismatch volume = 53 mL	0	NIHSS = 0 mRS = 0

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
11.	61, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease History of stroke Smoking	0	Atrial fibrillation	2 × 150 mg	0–12 h	Full compliance	Right cerebral hemisphere	166	260	11	CBF < 30% = 0 mL Tmax > 6 s = 50 mL Mismatch volume = 50 mL	0	NIHSS = 0 mRS = 0
12.	81, F	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease	1	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	81	160	7	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = 0 mL	0	Deceased
13.	69, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease History of stroke	0	Atrial fibrillation	2 × 150 mg	24–48 h	Non compliance	Brainstem stroke	85	130	12	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = 0 mL	0	NIHSS = 10 mRS = 4

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
14.	80, M	Atrial fibrillation Arterial hypertension Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Smoking Obesity	0	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	36	142	20	CBF < 30% = 0 mL Tmax > 6 s = 93 mL Mismatch volume = 93 mL	0	NIHSS = 4 mRS = 1
15.	74, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease	0	Atrial fibrillation	2 × 150mg	0–12 h	No information	Right cerebral hemisphere	68	160	8	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = 0 mL	0	NIHSS = 6 mRS = 2
16.	83, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries History of stroke	0	Atrial fibrillation	2 × 110 mg	0–12 h	No information	Left cerebral hemisphere	178	238	7	CBF < 30% = 0 mL Tmax > 6 s = 68 mL Mismatch volume = 68 mL	1 (TICI = 3)	NIHSS = 2 mRS = 1
17.	86, F	Atrial fibrillation Arterial hypertension Diabetes mellitus Atherosclerosis of carotid arteries History of stroke Obesity	3	Atrial fibrillation	2 × 110 mg	12–24 h	Non compliance	Brainstem stroke	95	135	7	CBF < 30% = 0 mL Tmax > 6 s = 18 mL Mismatch volume = 18 mL	0	NIHSS = 1 mRS = 4

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
18.	63, F	Atrial fibrillation Arterial hypertension Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease History of stroke	3	Atrial fibrillation	2 × 150 mg	12–24 h	No information	Right cerebral hemisphere	65	143	10	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = 0 mL	0	NIHSS = 0 mRS = 3
19.	70, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries	0	Atrial fibrillation	2 × 150 mg	0–12 h	No information	Right cerebral hemisphere	154	180	1	CBF < 30% = 4 mL Tmax > 6 s = 71 mL Mismatch volume = 67 mL	1 (TICI = 3)	NIHSS = 27 mRS = 5

CBF — cerebral blood flow; IVT — intravenous thrombolysis; mRS — modified Rankin scale; NIHSS — National Institutes of Health Stroke Scale; Tmax — time to maximum

The patients were aged between 38 and 86 with a median age of 74 (IQR 68–81) years. Thirteen (68.4%) were male. The most common cardiovascular risk factors were atrial fibrillation (AF) and arterial hypertension (AH), present in all patients (n = 19; 100%). Eighteen (94.7%) patients had concomitant internal carotid artery atherosclerosis (intima-media complex thickening or presence of atherosclerotic plaques) with haemodynamically significant stenosis (> 50%) present in four (21.1%) patients. Coronary artery disease was present in 11 (57.9%), previous stroke or transient ischaemic attack (TIA) in nine (47.4%), diabetes or prediabetes in eight (42.1%), dyslipidaemia in eight (42.1%), peripheral artery disease in seven (36.8%), history of smoking in six (31.6%), and overweight or obesity in three (15.8%) patients. The dependence level assessed with mRS before stroke onset was 0 in 12 (63.2%), 1 in 4 (21.1%), and 3 in 3 (15.8%) patients.

In all patients (n = 19; 100%), the reason for dabigatran treatment was AF. Dabigatran dose was 2 × 150 mg in 12 (63.2%) and 2 × 110 mg in seven (36.8%) patients. Thirteen (68.4%) patients took the last dose of dabigatran within 0–12 hours, 5 (26.3%) patients within 12–24 hours and one (5.3%) patient within 24–48 hours before admission. Six (31.6%) patients took dabigatran on a regular basis, eight (42.1%) were noncompliant, and in five (26.3%) the compliance was unknown. APTT result before idarucizumab administration was available in 14 patients. It ranged from 22.4 to 48.7 seconds (median = 35.1, IQR 29.2–40.8), with the upper normal limit for our hospital laboratory diagnostics department being 36 seconds.

In six (31.6%) patients, the ischaemic lesion was located in the left cerebral hemisphere, in 11 (57.9%) in the right cerebral hemisphere, and in two (10.5%) in posterior circulation territory. The neurological deficit at admission assessed with NIHSS ranged from 1 to 22 points (median 8, IQR 6–12). Median of ischaemia volume assessed with perfusion CT analysis using iRAPID software was 53 ml (IQR 15–81 mL), with median of irreversible ischaemic changes volume being 0 ml (IQR 0–0) and median of penumbra volume being 50 mL (IQR 15–81).

TTA ranged from 36 to 192 minutes (median = 95, IQR 68–154). DTN ranged from 26 to 106 minutes (median = 63, IQR = 47–86). Five (26.3%) patients were additionally treated with MT, and in all of them full reperfusion was achieved (mTICI = 3).

Haemorrhagic transformation of stroke occurred in three (15.8%) patients, with sICH occurring in two (10.6%) patients. Using definitions from SITS-MOST, in one patient the haemorrhage was classified as HI1 (small petechiae along the margins of the infarct), in one as PH2 (local or intra-ischemic confluent hematoma > 30% of the infarcted area with a substantial space-occupying effect), and in one as PHr2 (large confluent haematoma located remotely from the actual infarct(s), with substantial space-occupying effect). One patient (PHr2) was treated with only IVT, and two others (HI1 and PH2) with both IVT and MT.

Table 2. Summary of results

Personal information	
Age [median (IQR)]	74 (IQR 68–81)
Male sex [n (%)]	13 (68.4%)
mRS before stroke onset [n (%)]	
— 0 points	12 (63.2%)
— 1 points	4 (21.1%)
— 3 points	3 (15.8%)
Cardiovascular risk factors	
Arterial hypertension [n (%)]	19 (100%)
Atrial fibrillation [n (%)]	19 (100%)
Carotid artery atherosclerosis [n (%)]	18 (94.7%)
— significant stenosis [n (%)]	4 (21.1%)
Coronary artery disease [n (%)]	11 (57.9%)
Previous stroke/TIA [n (%)]	9 (47.4%)
Diabetes/prediabetes [n (%)]	8 (42.1%)
Dyslipidaemia [n (%)]	8 (42.1%)
Peripheral artery disease [n (%)]	7 (36.8%)
History of smoking [n (%)]	6 (31.6%)
Overweight/obesity [n (%)]	3 (15.8%)
Dabigatran treatment	
Reason for dabigatran treatment	
AF [n (%)]	19 (100%)
Dabigatran dose [n (%)]	
2 × 150 mg	12 (63.2%)
2 × 110 mg	7 (36.8%)
Last dose of dabigatran before admission [n (%)]	
< 12 hours	13 (68.4%)
12–24 hours	5 (26.3%)
24–48 hours	1 (5.3%)
Compliance [n (%)]	
Full compliance	6 (31.6%)
Non-compliance	8 (42.1%)
Unknown	5 (26.3%)
Stroke localisation	
Left cerebral hemisphere [n (%)]	6 (31.6%)
Right cerebral hemisphere [n (%)]	11 (57.9%)
Posterior circulation territory [n (%)]	2 (10.5%)
Stroke severity	
NIHSS [median (IQR)]	8 (IQR 6–12)
Total ischaemia volume [median (IQR)]	53 (IQR 15–81) mL
Infarct volume [median (IQR)]	0 (IQR 0–0) mL
Penumbra volume [median (IQR)]	50 (IQR 15–81) mL
Disease course	
TTA [median (IQR)]	95 (IQR 68–154) minutes
DTN [median (IQR)]	63 (IQR 47–86) minutes
MT [n (%)]	4 (21.1%)
Full reperfusion (mTICI = 3)	4 (100%)
Complications	
Haemorrhagic transformation	
Total [n (%)]	3 (15.8%)
sICH	2 (10.5%)
HI1	1 (5.3%)
PH2	1 (5.3%)
PHr2	1 (5.3%)
Transfer to ICU [n (%)]	1 (5.3%)
Death [n (%)]	1 (5.3%)
Functional outcome	
NIHSS [median (IQR)]	2 (IQR 0.75–3.25)
mRS at discharge [median (IQR)]	1 (IQR 1–3)
mRS 0 [n (%)]	4 (21.1%)
mRS 1 [n (%)]	8 (42.1%)
mRS 2 [n (%)]	1 (5.3%)
mRS 3 [n (%)]	2 (10.5%)
mRS 4 [n (%)]	2 (10.5%)
mRS 5 [n (%)]	1 (5.3%)
mRS 6 [n (%)]	1 (5.3%)

AF — atrial fibrillation; DTN — door-to-needle time; ICU — intensive care unit; IVT —intravenous thrombolysis; mRS — modified Rankin scale; NIHSS — National Institutes of Health Stroke Scale; TIA — transient ischaemic attack; TTA — time to admission

One patient (5.3%), with PHr2 haemorrhage, died during hospitalisation. In the remaining 18 patients, the NIHSS score at discharge ranged from 0 to 27 (median = 2 points, IQR 0.75–3.25), and median mRS score at discharge was 1 point (IQR 1–3). A good functional outcome (mRS 0–2) was achieved in 13 (68.4%) patients, but it is worth noting that among the remainder mRS was already 3 points before stroke onset in three patients. One patient (5.3%), with PH2 haemorrhage, needed temporary transfer to the ICU. In 12 (63.2%) patients, dabigatran was continued in the secondary prophylaxis of stroke. Four patients (21.1%) were given a different NOAC instead, and two (10.5%) were discharged with deferred anticoagulation due to persistence of intracranial haemorrhage.

Results are summarised in Table 2.

Discussion

NOACs (including dabigatran) are the first-choice treatment option for preventing ischaemic stroke in patients with non-valvular AF [10]. However, despite being treated, each year 1–2% of patients with AF receiving NOAC will develop AIS [11]. According to different studies, 20–36% of AIS in patients with AF occur despite anticoagulation therapy with

NOAC or vitamin K antagonists. This may result from other comorbidities (aetiology of stroke other than cardioembolic), non-compliance, inappropriate dosage or, in the most challenging situation, even despite sufficient anticoagulation and with no other cause [4].

As the number of patients with AF receiving NOACs is increasing, the number of AIS patients with preceding NOAC treatment is also growing [12]. Current European Stroke Organisation (ESO) guidelines recommend that IVT should not be used in patients who have received NOAC within the last 48 hours (or more, if their renal function is impaired) [5]. With early reperfusion therapy being the key factor for improving prognosis of patients with AIS [2], a need for antidotes reversing NOAC effect to enable IVT treatment has emerged.

Idarucizumab is a fragment of a humanised monoclonal antibody that binds with dabigatran and then quickly (within minutes) reverses its anticoagulation effect [13]. A dose of 2×2.5 g (5 g in total) administered intravenously was approved for dabigatran reversal in 2015 [14]. Currently, the use of idarucizumab for enabling IVT in dabigatran-treated patients with AIS is allowed based on expert consensuses included, among others, in ESO guidelines [5] and Polish Neurological Society guidelines [15].

So far, many case reports [16–44] and some case series including 2-80 dabigatran-treated AIS patients who have received idarucizumab for enabling IVT [45–56] have been published, with their results pointing towards the safety and effectiveness of such a procedure.

There have been descriptions of idarucizumab application before IVT treatment of stroke due to rare aetiologies, such as antiphospholipid antibody syndrome in the course of systemic lupus erythematosus [57]. A case series from Australia showed successful implementation of idarucizumab treatment before IVT in a prehospital setting in a mobile stroke unit [58]. A case series from Australia and New Zealand showed the safety of idarucizumab for allowing IVT not only with alteplase, but also tenecteplase [59]. Although bad outcomes have also been reported [60–62], current data shows that enabling IVT in dabigatran-treated AIS patients seems to be generally safe and efficient.

A systematic review by Frol et al. including 251 AIS patients who received idarucizumab to enable IVT showed the rates of haemorrhagic transformation, symptomatic intracranial haemorrhage, and mortality to be 7.6%, 3.6%, and 8.4% respectively, which was similar to previous studies concerning IVT-treated AIS patients without preceding anticoagulation [63]. Mortality rate was higher than haemorrhagic transformation of stroke. Other causes of death included malignant media infarct and pulmonary embolism [46].

A multicentre study with systematic review and meta-analysis by Romoli et al. showed that 39 IVT-treated patients after dabigatran reversal with idarucizumab had an insignificantly higher risk of symptomatic intracerebral haemorrhage and death, but their functional outcome was comparable to IVT-treated AIS patients without preceding use of anticoagulants. The rates of haemorrhagic transformation, sICH and mortality in the idarucizumab-treated group were 23.1%, 10.3% and 17.9% respectively. Good functional outcome (mRS 0–2) was reached in 64.1% of patients [64].

Another study comparing idarucizumab-treated AIS patients who subsequently received IVT to patients treated with IVT with no prior anticoagulation showed better improvement (measured using NIHSS) and better functional outcome (measured using mRS) in the idarucizumab-treated group, with a similar frequency of complications [65]. The incidence of thromboembolic events after idarucizumab uptake also seems to be low — a recent systematic review with meta-analysis including 3,602 patients found it to be 2% [66].

The findings of our study accord with the results of previous research on this topic. The incidence of haemorrhagic transformation was 15.8% with symptomatic intracranial haemorrhage in two (10.5%) patients. The mortality rate was 5.3% and, in our study group, associated only with secondary haemorrhagic transformation of stroke. A good functional outcome was achieved in the majority of patients (68.4%), but, as mentioned before, within the remainder mRS was already ≥ 3 points before stroke onset in three (15.8%) patients.

Our study has some limitations, the most important being its retrospective character and the lack of a control group. We did not gather data on patients with AIS on dabigatran who were not treated with idarucizumab and IVT.

Clinical implications/future directions

The results of our study align with previous research on the safety and effectiveness of idarucizumab in enabling IVT in patients with AIS receiving dabigatran. They also provide reassurance that IVT after idarucizumab is a reasonable option for patients with AIS receiving dabigatran who are not eligible to MT.

More multicentre, prospective, cohort studies are required. Future research should also focus on the reasons why patients treated with NOAC go on to develop AIS, with the aim of more successful prevention of thromboembolic events in this group.

Article information

Data availability statement: *Our data can be shared with other scientists, if needed.*

Ethics statement: *Jagiellonian University Bioethics Committee approval numbers for the study are KBET/54/B/2007 and 1072.6120.118.2020.*

Authors' contributions: *E.W., K.S. — data aquisition, statistical analysis, draft writing and revision; P.W. — data acquisition; A.S. — conceptualisation, data aquisition, draft revision, supervision.*

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