Usefulness of initial plasma dabigatran concentration to predict rebound after reversal

Major bleeding occurs in about 4% of patients treated with direct oral anticoagulants.[1] Following the RE-VERSE AD trial, idarucizumab administered as a single 5g IV dose has been licensed for the management of patients with life-threatening bleeding or in case of urgent surgery/procedures while on treatment with dabigatran etexilate.[2] The 5g dose was calculated to reverse the total body load of dabigatran that was associated with the 99th percentile of the dabigatran levels measured in the phase III study RE-LY. However, since idarucizumab commercialization, several case studies[3,4] as well as the complete analysis of RE-VERSE AD,[5] highlighted several cases of patients either having required a second dose of idarucizumab, or with a rebound effect of plasma dabigatran levels (in 114 of 497 patients in complete RE-VERSE AD study). Herein, the authors defined reappearance as an increase of the dabigatran plasma concentration above the 20ng/mL threshold of detection after reversal. In RE-VERSE AD, these reappearances were associated with recurrent or continued bleeding in 10 patients with overt, uncontrollable, or life-threatening bleeding; among which 3 required an additional dose of idarucizumab. In RE-VERSE AD phase III study, the protocol did not include dabigatran measurement before administration of the antidote to guide clinical follow up; plasma samples were collected before and after injection and analyzed post hoc. Initial and post reversal dabigatran measurement would indeed be important for any physician deciding upon the proper use of idarucizumab.[6] Since we think that "no testing" before reversal is questionable, our objective was to identify a patient profile with rebound after reversal.

Thus, the aim of our study was to analyze clinical and biological data reported in literature to date. We also present 10 new cases referred to our center (Table 1). To improve patient follow up after reversal and idarucizumab use in our daily practice, we analyzed the impact of initial dabigatran plasma concentrations on the incidence of rebound.

The study included 33 cases of patients found in literature between December 1th 2015 and February 1st 2017, and 10 cases referred to our institution (European Hospital Georges Pompidou, Paris, France), of which 7 received idarucizumab for serious bleeding and 3 for required surgery or other emergent invasive procedure (Table 1 and *Online Supplementary Figure S1*). We collected clinical and biological data from all patients. In our study, dabigatran plasma concentrations were analyzed when determined using the specific diluted thrombin time (TTd) assay, as reported in RE-VERSE AD. Patients

Table 1. Clinical and biological characteristics of the patients referred to our institution for idarucizumab injection.

Case	1	2	3	4	5	6	7	8	9	10
Age (year)	88	61	88	91	87	88	88	81	83	75
Sex	M	M	M	F	F	F	M	M	M	M
Weight (Kg)	60	85	NA	58	77	43	64	61	73	57
Hemoglobin (g/L)	66	NA	54	65	66	100	81	132	142	NA
CHA_2DS_2-VASc	6	2	4	5	5	4	5	5	2	2
ClCr* (ml/min)	45.1	113	NA	26.3	17	31	16	16	33	32
Dose of dabigatran etexilate	150 BID	150 BID	NA	110 BID	110 BID	110 BID	110 BID	75 BID	110 BID	NA
Indication for dabigatran etexilate	NVAF	NVAF	NVAF	NVAF	NVAF	NVAF	NVAF	NVAF	NVAF	NVAF
Indication for idarucizumab infusion	Gastro-intestinal bleeding	Intracranial bleeding	Gastro-intestinal bleeding	Gastro-intestinal bleeding	Gastro-intestinal bleeding	Gastro-intestinal bleeding	Gastro-intestinal bleeding	Laparotomy	Coloscopy	Aortic and mitral valve replacement
Dabigatran at baseline (ng/ml, unbound)	159	NA	215	239	764	520	602	1014	388	NA
Dabigatran reappearance	No	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Time post-reversion (h)	–	NA	58	42	61	49,5	13	28	10	NA
Concentration (ng/ml)	–	NA	NA	30	294	40	104	97	361	NA
TT(s)	–	NA	38	NA	>150	76	99	41.89	66.88	NA
Evolution	Favorable outcomes	Favorable outcomes	Died	Favorable outcomes	Favorable outcomes	Favorable outcomes	Favorable outcomes	Died	Favorable outcomes	Cardiac tamponade 11 days afte

In the patient cases referred to our institution, there were two deaths. Patient #3 died of a cardiac arrest seven days after dabigatran reversal. Patient #8, who received two injections of idarucizumab after his first laparotomy due to dabigatran rebound, died 4 hours following second surgical laparotomy from multi-organ failure. None of these deaths was directly attributed to dabigatran related bleeding. NA, non-available; ClCr, creatinine clearance; NVAF, non-valvular atrial fibrillation; TT, thrombin time. *= estimated with Cockcroft-Gault equation.

from published cases and cases referred to our institution formed the Reported case Group and were compared to RE-VERSE AD patients.[5] Of the 33 cases from literature, 3 were excluded because patients received idarucizumab for deliberate dabigatran overdose and/or without bleeding or urgent invasive procedures needed. Seven other patients were excluded because they had an indication of thrombolysis for ischemic stroke. A total of 23 cases from literature were therefore analyzed in addition to the 10 cases from our institution (Table 1). The characteristics of the 33 patients are described in Table 2. In all published cases, measurement of dabigatran plasma concentrations was considered with a specific method if it was carried out with dTT and/or Ecarin tests.[6] For the patients reported from our institution, dabigatran plasma concentration was determined using the Hemoclot® Thrombin Inhibitor (HTI) assay (dTT, Hyphen BioMed, France) with the STA-R® coagulometer (Stago, France) or the ACL TOP 700 CTS coagulometer (Werfen Group, Kirchheim bei Munchen, Germany). The group of patients with severe bleeding included 13 published cases and 7 cases referred to our institution (Table 1). The patients' general characteristics were similar to those from the Group A of RE-VERSE AD (Table 2). The median hemoglobin concentration of the reported cases was of 75.5g/L. Median value for creatinine clearance (CrCl) was of 34.7 ml/min in the reported case group and 50.8 ml/min in RE-VERSE AD Group A. Bleeding types are reported in table 2.

The group of patients who required urgent surgery or invasive procedures included 10 published cases and 3 cases referred to our institution. The patients' general characteristics were similar to those of the RE-VERSE AD trial (Table 2). The median value of the CrCl was 33 ml/min in the Reported case Group and 56 ml/min in RE-VERSE AD Group B (patients who required surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required). All procedures are reported in Table 2.

In the Reported case Group with serious bleeding, the median baseline dabigatran plasma concentration was 455 ng/ml (range 50 to 3337 ng/ml) and was higher than in the Group A of RE-VERSE AD (110 ng/ml). All patients but one received a single 5g infusion of idarucizumab; indeed, one patient in the reported case group received 2 doses of 5g idarucizumab associated with hemodialysis due to end-stage renal disease.[7] A reappearance of dabigatran plasma concentration was observed in 10 patients (50% of the reported cases). One patient (5%) had an early rebound (<12 hours), and 9 (45%) had a late rebound (>12 hours).

In the Reported case Group of patients who required urgent surgery or invasive procedure, the median baseline dabigatran concentration (209 ng/ml, range 84 to 1014) was also higher than in Group B of RE-VERSE AD (73.6 ng/ml). All patients received a first infusion of 5g idarucizumab. Two patients in the reported case group received 2 and 3 injections, respectively.[8] In four reported cases, 6 reappearances were observed; three patients had one rebound after a single idarucizumab infusion whilst one patient had 3 rebounds after each injection.[8] Two reappearances of dabigatran plasma concentrations were described as early and 4 as late. In the entire Reported case Group, 22 (66.6%) patients had an initial measure of circulating dabigatran with dTT whilst 11 (33.3%) had non-specific haemostasis tests (prothrombin time, activated partial thromboplastin time, thrombin time or thromboelastographic methods). Sixteen of the 33 patients (48.5%) had a measure of dabigatran plasma concentrations by specific methods before and after idarucizumab injection.[3,8-12] One of these patients had 3 idarucizumab injections.[8] We noticed 14 (77.7%) reappearances of plasma dabigatran between 7h and 61h after idarucizumab infusion,[3,8,9,10] whilst 4 (22.2%) had no rebound effect.[3,11,12] At baseline, median creatinine plasma levels or CrCl (*data not shown*) of patients with or without reappearance did not significantly differ. Median dabigatran plasma concentration at baseline of patients without rebound effect (139 ng/ml; range: 108-176) was significantly lower than in patients with reappearances (495 ng/ml; range 215 to 3337.3; P=0.0035, Figure 1). According to the population studied (Figure 1), we noticed that an initial dabigatran plasma concentration above 200ng/ml could discriminate patients with a rebound risk. Thus, initial concentration of dabigatran before reversal could allow us to predict a rebound and its potential clinical consequences. The "no testing" attitude before reversal is questionable. In our study, median plasma dabigatran concentrations were higher than in RE-VERSE AD. International Society of Thrombosis and Haemostasis (ISTH) recommendations[13] and the French Working Group on Perioperative Hemostasis (GIHP)[14,15] do not clearly recommend dabigatran level determination before reversal in case of life-threatening bleeding. Thus, our objective was not to decide who needs to receive idarucizumab or not, but to understand who might have a rebound and potential non-surgical or surgical bleeding owing to significant circulating dabigatran reappearance after reversal. If patients are no longer bleeding, this rebound after reversal is probably not clinically relevant. However, in patients who do not have controlled bleeding after a first idarucizumab infusion, or in patients who need a powerful neutralization such as in cerebral bleeding or in thrombolysis for stroke, this cutoff could help anticipating the need for subsequent injections. Dabigatran reappearance is indeed likely due to a shift back from extravascular dabigatran into plasma in response to the concentration gradient occurring after

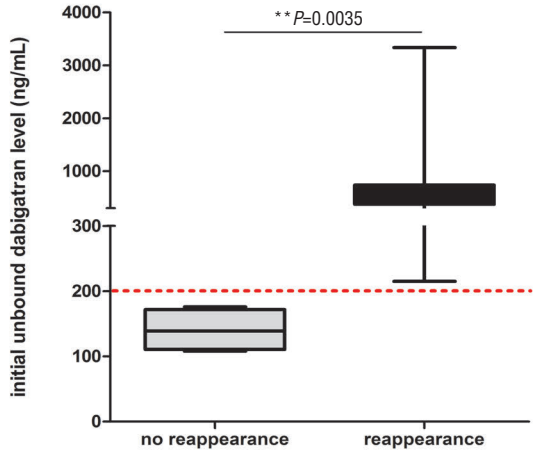

Figure 1. Initial plasma dabigatran concentrations of patients with or without dabigatran concentration rebound after idarucizumab injection. Sixteen of the 33 patients in the Reported case Group had a specific measure of dabigatran plasma concentrations by diluted thrombin time before and after idarucizumab injection At baseline, patients with no rebound had a significant lower median of dabigatran plasma concentration (139 ng/ml; range: 108-176) than patients with rebound (495 ng/ml; range: 215-3337.3; P=0.0035; non-parametric Mann-Whitney tests.).

Table 2. Clinical and biological characteristics of patients receiving idarucizumab for serious bleeding, or for urgent procedures/surgery in comparison with the Phase III trial RE-VERSE AD trial Group A and Group B, respectively.

Characteristics	Patients receiving idarucizumab for serious bleeding Phase III trial (Groupe A) n= 301	 Reported case Group n=20
Age (year) – Median (Range)	79 (24-96)	79.5 (58-96)
Male sex (%)	172 (57.1)	11 (55)
Weight (Kg) - Median (Range)	74 (35-231)	62 (42-163)
Hemoglobin g/L – Median (Range)	NA	75.5 (39-137)
CHA_2DS_2-VASc - Median (Range)	NA	3.5 (1-6)
ClCr (ml/min) - Median (Range)*	50.8 (6.1-216.9)	34.7 (16-113)
Indication of dabigatran etexilate - no (%)		
NVAF	288 (95.7)	20 (100)
VTE	5 (1.7)	0 (0)
Type of bleeding - no (%)**		
Intracranial	98 (32.6)	4 (20)
Trauma-related	78 (25.9)	2 (10)
Gastro intestinal	137 (45.5)	12 (60)
Other***	88 (55.1)	2 (10)
Baseline unbound dabigatran - ng/ml		
Median (Range)	110 (NA)	455 (50.0-3337.3)
Characteristics	**Patients receiving idarucizumab for urgent procedures Phase III trial (Groupe B) n= 202**	** Reported case Group n=13**
Age (year) – Median (Range)	77 (21-96)	77 (59-85)
Male sex (%)	102 (50.5)	10 (82.8)
Weight (Kg) - Median (Range)	77 (39-169)	59 (50-73)
CHA_2DS_2-VASc - Median (Range)	NA	3 (1-5)
ClCr (ml/min) - Median (Range)	56 (7.9-198.7)	33 (16-99)
Indication of dabigatran etexilate - no (%)		
NVAF	190 (94)	13 (100)
VTE	4 (2)	0 (0)
Type of procedure - no (%)		
Cardiovascular condition	37 (18.3)	7 (53.9)
Abdominal condition or infection	49 (24.3)	4 (30.7)
Skin condition	6 (3.0)	1 (7.7)
Central nervous system condition	17 (8.4)	1 (7.7)
Baseline unbound dabigatran - ng/ml		
Median (Range)	73.6 (NA)	209 (84-1014)

NA: non-available; ClCr: creatinine clearance; NVAF: non-valvular atrial fibrillation; VTE,: venous thromboembolism; *= estimated with Cockcroft-Gault equation. **Patients may have had more than one type of bleeding. ***Other bleedings are intramuscular, retroperitoneal, intrapericardial, intraarticular, intraocular and other bleeding or not identified in RE-VERSE AD study.

neutralization. This study has limitations. Firstly, it is based on spontaneous cases and not on data from a randomized study, and therefore prospective registers are still needed. Secondly, biological follow up of dabigatran plasma concentrations was not standardized. Thirdly, our population mainly consisted of gastrointestinal bleeding (GIB, 60%). Dabigatran reversal in most cases allowed endoscopy, mechanical and/or surgical local hemostasis to stop bleeding without increasing the bleeding risk due to dabigatran itself. There is no clue as to whether the GIB population will show different pharmacokinetic of dabigatran reversal.

To optimize management and follow up of patients with active bleeding, dabigatran reappearance regarding initial dabigatran level should be prospectively analyzed to confirm these preliminary observations suggesting a cut-off of 200 ng/ml for which further idarucizumab administrations would be needed. Indeed, it could allow physicians to anticipate potential postoperative or non surgical bleeding and/or subsequent injections of the antidote.

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