

Idarucizumab for dabigatran reversal in patients with atrial fibrillation undergoing emergency surgery for acute aortic syndrome

To the Editor The recent European Heart Rhythm Association (EHRA) practical guidelines on the use of non-vitamin-K oral anticoagulants in patients with nonvalvular AF recommend administration of idarucizumab for life-threatening bleeding or prior to emergency surgery in dabigatran-treated patients.¹ At the end of 2015, idarucizumab, a monoclonal antibody fragment that binds dabigatran with high affinity, was approved for use in Europe. In the context of the European guidelines,¹ we would like to present our experience with the use of the specific reversal agent in everyday practice, indicating the important role of idarucizumab in the setting of surgery that cannot be delayed.

Dabigatran etexilate (dabigatran), a direct thrombin inhibitor, is commonly used for stroke prevention in patients with atrial fibrillation (AF),² who can experience serious perioperative bleeding if the procedure is performed while on anticoagulation.

Acute aortic syndromes (AASs) are a common cause for emergency cardiac surgery associated with high mortality and morbidity. The REVERSE AD trial³ has shown that idarucizumab is efficacious in dabigatran reversal, and it was used in a single patient with aortic dissection (AD) in this trial. According to the study protocol, idarucizumab was administered preoperatively. We used idarucizumab intraoperatively in 2 dabigatran-treated patients with Stanford type A AAS.

An 83-year-old man with a history of ascending aortic aneurysm (AAA) complicated with AAS in form of Stanford type A intramural hematoma, was taking dabigatran due to AF (2×110 mg/d; last dose intake on the day of surgery). Comorbidities were chronic kidney disease (stage 3 CKD), arterial hypertension, prior ischemic stroke, peripheral arterial disease, and peptic ulcer disease. The diagnosis was confirmed with contrast-enhanced computed tomography. Preoperative laboratory findings, including dabigatran concentrations based on dilute thrombin time, are presented in [TABLE 1](#). According to the Papworth Bleeding Risk Score, the bleeding risk was high (4 points).⁴

Immediate surgery in cardiopulmonary bypass (CPB) and deep hypothermia was performed. The patient was transferred to the operating room directly from the admission unit, after 66 minutes needed for transthoracic echocardiography and preoperative laboratory workup. Dabigatran intake did not delay any part of cardiosurgical management. A supracoronary ascending aortic and hemiarch replacement procedure was successfully performed. Following CPB cessation, idarucizumab was administered (5 g IV, in 1 infusion of 5-minute duration). A total of 12 units of platelet concentrate and 3 units of fresh frozen plasma were administered in the operating room. The control level of dabigatran immediately upon intensive care unit admission was below 32 ng/ml. Three units of packed red blood cells were transfused. Moderate perioperative bleeding was observed⁵ and drainage volumes were low (390 ml after 24 hours).

During the postoperative course, the patient required diuretic treatment and intensive pulmonary rehabilitation. The postoperative course was complicated with pneumonia which resolved after antibiotic treatment. Anticoagulation with warfarin was initiated, and on postoperative day 8, the patient was discharged to a local hospital for further management. On postoperative day 30, the follow-up was uneventful.

Another patient, a 76-year-old man with Stanford type A AD, anticoagulated with dabigatran (2×110 mg/d; last intake on the day preceding the day of surgery) for paroxysmal AF was admitted to our institution in May 2016 for emergency surgery. His other risk factors were stage 2 CKD and arterial hypertension. We confirmed the diagnosis of AAA and AD with computed tomography, and the preoperative laboratory findings are presented in [TABLE 1](#). Also in this patient, the bleeding risk was high (3 points in the Papworth Bleeding Risk Score).⁴

Immediate surgery was executed using the same protocol (time from hospital admission until admission to the operating room was 98 minutes, there was no delay due to dabigatran therapy).

TABLE 1 Preoperative laboratory findings in patients with acute aortic syndrome and receiving dabigatran treatment (reference ranges are given in brackets)

Patient, sex/age, y	RBC (4.2–6.0 × 10 ⁶ /μl)	HGB (14.0–18.0 g/dl)	HCT (40.0%–54.0%)	PLT (140–440 10 ³ /μl)	APTT (25.9–36.6 sec)	INR (0.9–1.3)	Creatinine (62–106 μmol/l)	eGFR (>60 ml/min/1.73 m ²)	Baseline dabigatran level, ng/ml
M/83	3.36	10.4	31.2	129	77.8	1.74	264	19	209
M/76	5.31	15.3	47.3	115	48.3	1.46	185	30	84

Dabigatran levels were measured using the Hemoclot thrombin inhibitor assay (HYPHEN BioMed, Neuville-sur-Oise, France), as described elsewhere.⁸ Baseline dabigatran level (during dabigatran treatment): 61–143 ng/ml.

Abbreviations: APTT, activated partial thromboplastin time; eGFR, estimated glomerular filtration rate; HCT, hematocrit; HGB, hemoglobin; INR, international normalized ratio; M, male; RBC, red blood cells; PLT, platelets

Upon opening of the pericardium, massive cardiac tamponade was apparent; however, a supra-coronary ascending aortic and hemiarch replacement procedure was successfully performed. Idarucizumab was administered after CPB termination (5 g IV, in 1 infusion of 5-minute duration), and the control level of dabigatran was 36 ng/ml in the operating room. Severe low cardiac output syndrome has developed upon CPB cessation. A total of 10 units of platelet concentrate, 3 units of fresh frozen plasma, and 2 units of packed red blood cells were administered in the operating room, before chest closure, and massive inotropic support was required (epinephrine, 1 μg/kg/min; norepinephrine, 0.83 μg/kg/min; dobutamine, 10 μg/kg/min; milrinone, 0.42 μg/kg/min). Although intraoperative transesophageal echocardiography revealed normal aortic valve function and appropriately de-aired left ventricle, severe cardiogenic shock developed and resistant hypotension was observed. Mechanical circulatory support was not feasible. Despite the treatment, the patient expired directly following the end of the procedure, in the operating room, without any apparent bleeding.

Our current report demonstrates that idarucizumab effectively reverses dabigatran in the setting of emergency cardiac surgery for AAS in patients with high plasma drug levels. One patient had a completely favorable outcome, and the other died due to heart failure. However, no major bleeding was observed in any of the presented cases, despite high preoperative bleeding risk (3–4 points in the Papworth Bleeding Risk Score) and high preoperative levels of dabigatran. Only blood product transfusions were needed, but no activated prothrombin complex concentrate or recombinant factor VII were necessary. Importantly, treatment with dabigatran did not delay any part of the cardiosurgical management, as idarucizumab was readily available on site.

The REVERSE AD trial³ demonstrated that idarucizumab rapidly and completely reverses dabigatran levels (in most patients they dropped by 99% and remained low for at least 12 hours; in some cases, an increase in dabigatran levels was observed after this time, probably secondary to drug redistribution from peripheral circulation); however, in individuals requiring an operation, it was administered before the surgery.

Our approach was slightly different, as a result of cardiac surgery-specific procedural characteristics. During an open heart surgery, coagulation is blocked anyway with heparin, and internal CPB suction is used to prevent blood loss. The rationale behind the choice of the idarucizumab administration timepoint was to provide the patient with dabigatran-free coagulation for as long postoperatively as possible. Dabigatran levels returned to normal in both cases. In the first patient, postoperative drainage was low, and bleeding was assessed as moderate—not more pronounced than in any other patient with AAS.

The important issue of necessary dabigatran treatment adjustment in individuals with renal failure warrants a comment, as both our patients suffered from CKD. The Cockcroft–Gault formula for creatinine clearance (CrCl) was employed in the RELY trial⁶ for the assessment of dabigatran eligibility and dosing. In AF patients aged 80 years or older, it has been demonstrated that 15% were ineligible for dabigatran based on CrCl of less than 30 ml/min, but the same patients would have been eligible if the Modification of Diet in Renal Disease (MDRD) formula had been applied for the calculation of estimated glomerular filtration rate (eGFR); for those younger than 80 years, 5% would have received too high a dose of dabigatran.⁷ Thus, some patients (whose renal function is assessed based on eGFR with the MDRD formula) probably receive dabigatran despite excluding CKD or receive too high a dose. Furthermore, during CKD exacerbation, dabigatran should be stopped if there is any suspicion that the patient might need urgent surgery (as in a patient with known severe aortic dilation). That notwithstanding, our report demonstrates that salvage with idarucizumab is a bail-out option even in an dabigatran-overtreated individual with CKD exacerbation, who requires emergency cardiac surgery. No such option is available for patients treated with rivaroxaban or apixaban yet.

In our second patient, the fact of dabigatran intake was discovered after patient admission, during the emergency anesthesia workup. Emergency medicine personnel should be trained to obtain the information on dabigatran use and last intake from any patient with known AF and to pass this information to the tertiary care center. This approach is supported by the recent EHRA

guidelines.¹ Idarucizumab should be available in any tertiary cardiac and trauma center, where patients treated with dabigatran are likely to be managed. All physicians should be made aware which centers have idarucizumab at their disposal, and this information should be available at all times at any blood bank countrywide.

In conclusion, our report demonstrates that idarucizumab can facilitate successful cardio-surgical treatment with a satisfactory hemostasis in the setting of AAS, in a patient treated with dabigatran. We believe that in the setting of cardiac surgery, the administration of idarucizumab intraoperatively (not preoperatively) is safe. The dose of 5 g IV in a rapid infusion administered upon CPB cessation may be a good therapeutic choice.

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REFERENCES

- 1 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary-Revision 1. *Eur Heart J.* 2016. [Epub ahead of print].
- 2 Undas A, Pasiński T, Windyga J, et al. Practical aspects of new oral anticoagulant use in atrial fibrillation. *Pol Arch Med Wewn.* 2014; 124: 124-135.
- 3 Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015; 373: 511-520.
- 4 Vuytsteke A, Pagel C, Gerrard C, et al. The Papworth Bleeding Risk Score: a stratification scheme for identifying cardiac surgery patients at risk of excessive early postoperative bleeding. *Eur J Cardiothorac Surg.* 2011; 39: 924-930.

5 Dyke C, Aronson S, Dietrich W et al. Universal definition of perioperative bleeding in adult cardiac surgery. *J Thorac Cardiovasc Surg.* 2014; 147: 1458-63 e1.

6 Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361: 1139-1151.

7 Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J.* 2013; 34: 2094-2106.

8 Czubek U, Góralczyk T, Zalewski J, et al. Monitoring of anticoagulant effects of dabigatran in everyday practice: first experience in 32 Polish patients. *Pol Arch Med Wewn.* 2014; 124: 487-489.