

## Emergency Cardiac Surgery for Acute Type A Aortic Dissection on Apixaban

### INTRODUCTION

Difficulties of warfarin usage and the convenience of Direct-Acting Oral Anticoagulant (DOAC) have changed the anticoagulation strategy.<sup>1</sup> Vitamin K antagonists are being increasingly altered to DOAC therapy for suitable clinical settings. In near future, surgeons will more frequently perform emergency operations for patients on DOACs therapy. This will eventually bring in an excessive risk of postoperative bleeding following emergency cardiac surgery. Cardiopulmonary bypass (CPB)-induced coagulation defects become more remarkable in aortic dissection cases, as fibrin degradation products and D-dimer levels increase.<sup>2</sup> For this reason, bleeding management of the patients on factor Xa inhibitors is even more difficult in these cases. Apixaban, with a rapid onset of action and a half-life of 8-14 hours, is one of the most frequently used factor Xa inhibitors.<sup>3</sup> It is used twice a day 5 mg or 2.5 mg; the dose is adjusted according to weight and kidney function. For elective surgery, cessation is recommended 2-3 days before the procedure. In urgent cases, waiting up to 24 hours, if possible, reduces bleeding complications. Residual anticoagulant activity decreases 50% at 12 hours and below 25% at 24 hours after drug cessation.<sup>4</sup> In some case reports, activated prothrombin complex concentrate 25 IU/kg could reverse the anticoagulant effect of apixaban.<sup>5</sup> Nevertheless, there is no consensus and clear guidelines on reversal management. We present a patient with acute type A aortic dissection on apixaban, needing emergency cardiac surgery. The discussion addresses Apixaban's pharmacokinetics and key points of emergency cardiac surgery on Apixaban.

### CASE REPORT

A 67-year-old woman, on apixaban 5 mg bid due to paroxysmal atrial fibrillation (AF) was admitted to the intensive care unit (ICU) from another center for type A aortic dissection. Contrast-enhanced computed tomography images revealed the type A dissection that involved the entire aorta extending bilaterally to the external iliac arteries (Figure 1). We confirmed that the patient took her last dose of Apixaban 14 hours ago. The antidote is not currently available in our country. She was obese (weight 95 kg, body mass index 37.1 kg/m<sup>2</sup>). Her past medical history revealed EVAR treatment for ruptured abdominal aortic aneurysm 18 months previously. Comorbidities were diabetes mellitus regulated with oral antidiabetics, hypertension, and morbid obesity. The blood tests showed the following results: hemoglobin: 13.5 g/dL, Htc: 45.4%, Plt: 265 × 10<sup>9</sup>/L, PTT: 16.1 s, aPTT: 29.6 s, INR: 1.4, D-dimer: 6.11 mg/L, factor X activity 20%, pH (arterial): 7.33, lactate (arterial): 5.9 mmol/L. The echocardiography revealed a moderate pericardial effusion which was 2 cm at the largest area and mildly compressing the right atrium, dissection flap in the ascending aorta and the coronary sinus, with moderate to severe aortic regurgitation. As she became hemodynamically unstable, an immediate operation was needed without any blood products ready to use.

In the operation room, pre-heparin activated clotting time was 184 minutes at the A point. Arterial cannulation was performed with 17 Fr percutaneous cannula after surgical access to the right axillary artery through the infraclavicular incision. Then, 400 U/kg heparin was administrated. The median sternotomy

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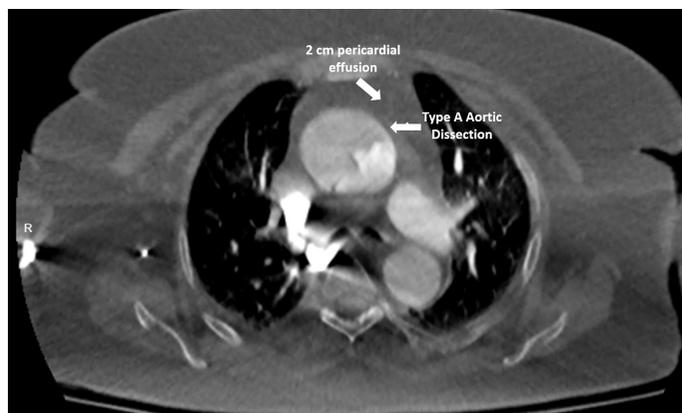
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**Figure 1. Preoperative contrast-enhanced computed tomography image, acute type A dissection with 2-cm pericardial effusion.**

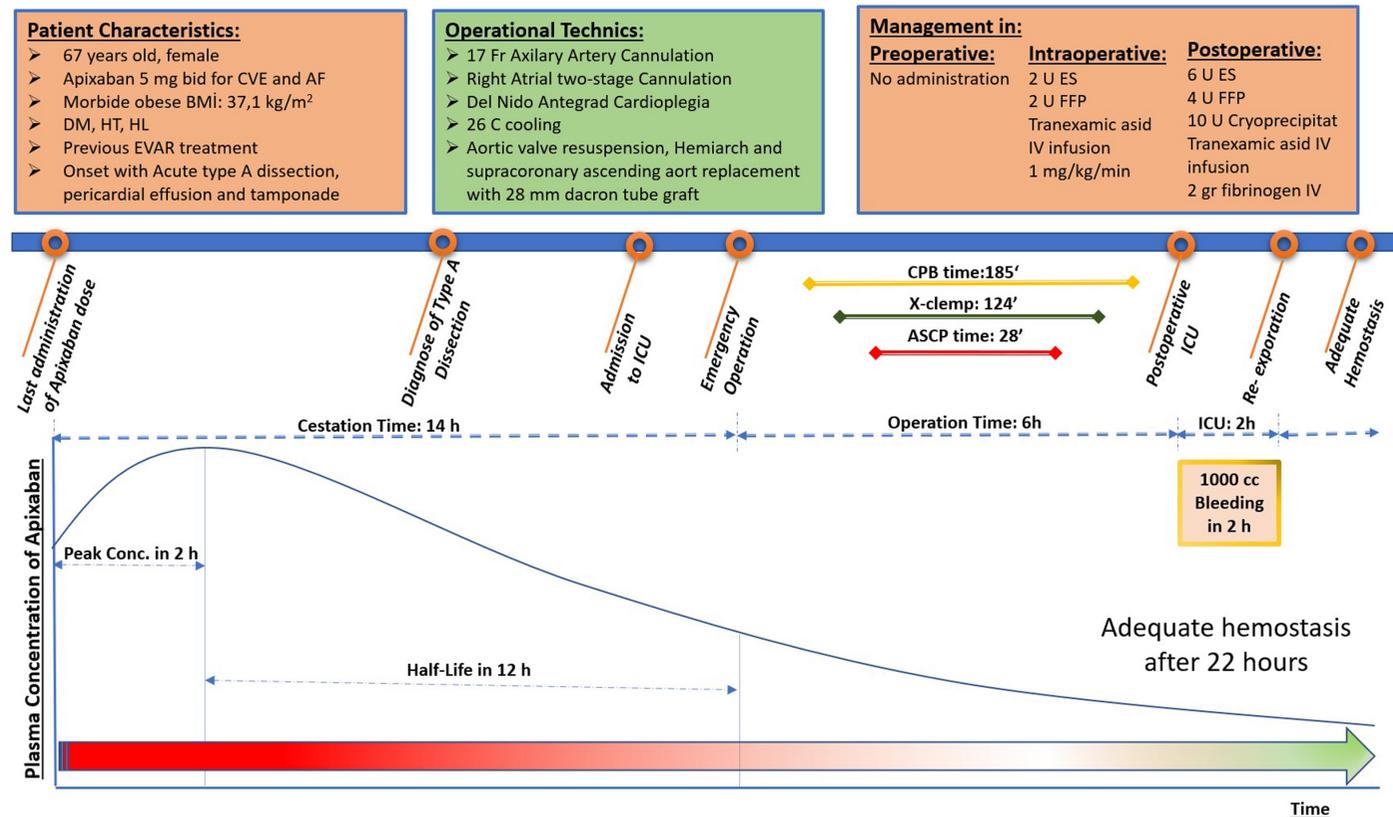
was performed. The pericardium was filled with hematoma. During the atrial venous cannulation, an aortic rupture occurred. Immediately, aortic cross-clamping was performed, the cardiopulmonary bypass (CPB) and cooling to 26°C were initiated, and cardiac arrest was established with antegrade selective Del Nido cardioplegia via coronary ostia. The aortic valve was preserved with commissural suspension stitches and neo-media reconstruction with a piece of dacron graft and the aldehyde-based glue (BioGlue, Cryolife Inc., Kennesaw, Georgia). A 28-mm dacron aortic

tube graft was anastomosed supracoronary fashion for the proximal end, and hemiarch replacement for the distal end. Cardiopulmonary bypass was terminated after rewarming, and heparin was reversed with 400 U/kg protamin. At the beginning of the operation, 1250 mg tranexamic acid was administered intravenous bolus and continued at 2 mg/kg/h. iv infusion throughout the operation. Intraoperatively, 2 units of erythrocyte suspension (ES) and 2U of fresh-frozen plasma (FFP) were transfused. The CPB time was 185 minutes, the cross-clamp time was 124 minutes, and the antegrade selective cerebral perfusion time was 28 minutes. The surgical operation was completed in 6 hours.

Intensive care unit, 6 U ES, 4 U FFP, and 10 U cryoprecipitates and 2 g fibrinogen (Haemocomplettan®) were transfused. Chest tube drainage volume reached 1000 mL in postoperative 2 hours and the patient was then taken back to the operating room for re-exploration. No surgical bleeding was found but a generalized oozing from pericardial surfaces. The patient was taken back to the ICU and definitive hemostasis was achieved 22 hours after the apixaban cessation (Figure 2). No further complications occurred, and the patient was discharged on the 12<sup>th</sup> day.

**DISCUSSION**

DOAC usage is expanding with new indications and the prescription rate is increasing worldwide. Therefore, surgeons



**Figure 2. Timeline of hemostasis management in emergency cardiac operation on apixaban. ES, erythrocyte suspension; FFP, fresh frozen plasma; CPB, cardiopulmonary bypass; X-clamp, cross clamping; ASCP, anterior selective cerebral perfusion; ICU, intensive care unit; CVE, cerebrovascular event.**

must be ready to deal with an emergency cardiac operation for DOAC-using patients. Besides, cardiovascular surgery has a high bleeding risk due to CPB and heparinization, DOAC usage increases the risk even further.

Acute aortic dissection is one of the challenging aortic emergencies as in this case. While replacing the aortic root, restoration of aortic blood flow to branches, prevention of cardiac tamponade, and fixing the true lumen, surgeons have another task to maintain the hemostasis. Cooling and rewarming at the operation disrupt the hemostasis. In addition, false lumen thrombosis begins to occur, and fibrin degradation products increase due to the consumption of coagulation factors.<sup>6</sup> In this case, preoperative factor X activity level was 20% which itself was an additional bleeding risk. Spontaneous major bleeding can occur when factor X level decreases under 10%.<sup>6</sup> Therefore, recent data reported increasing operative mortality in DOAC users undergoing emergency operations on the proximal aorta risk versus warfarin users because of the increased bleeding risk.<sup>7</sup>

Apixaban, with confirmed reliability and effectivity, is widely used in AF, thromboembolism, and stroke protection. It is one of the direct factor-Xa inhibitors. There is no recommendation for measurement of therapeutic efficacy or concentration of Apixaban with aPTT, INR, Prothrombin Time (PT), however, factor Xa assay may be used. Andexanet alfa received the US Food and Drug Administration approval for the reversal of factor Xa inhibitors in 2018, however, few countries have it for clinical use. Guidelines first recommend specific antidote usage for reversing anticoagulant effects of factor Xa inhibitors, if available, and if not activated prothrombin complex concentrates are recommended to reverse the anticoagulant effect.<sup>8,9</sup> The ROTEM could be an effective guide on blood and coagulation management in available centers.<sup>9</sup> Some recent reports suggest an extracorporeal hemadsorption treatment as an absorber to reduce plasma concentrates of DOACs.<sup>10</sup> As surgical management of bleeding, using topical hemostatic agents and sealing a bovine pericardial patch to tamponade the bleeding area were provided, these solutions could also make trouble in the necessity of re-exploration. Surgeons should weigh the benefits of this administration in an emergency cardiac operation on DOAC.

In our case, although we administered available blood products to prevent bleeding, we were not successful to avoid surgical re-exploration. Notably, it is noteworthy that hemorrhagic drainage stopped spontaneously 22 hours after drug cessation. Reoperation and re-exploration for bleeding are associated with increased mortality,<sup>11</sup> however, the patient could be discharged on the 12<sup>th</sup> day.

## CONCLUSION

The recent increasing DOAC treatment also increases the possibility of encountering patients in need of urgent surgical intervention. Many countries lack the necessary antidotes, and the use of the preparations recommended in the guidelines seems to be a viable alternative. In an emergency, there could be no time waiting for preparation or bridging. Despite all efforts to control bleeding after cardiac surgery on Apixaban, it should be kept in mind that there was a high bleeding risk; however the adequate hemostasis is maintained by time.

**Informed Consent:** Written informed consent was obtained from the patient who participated in this study and the institutional research ethics board granted approval for this case report.

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