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CASE REPORT
*Cardiovascular surgery*

# Hemostatic protocol and risk-reduction surgery for treating coronary artery disease with aortic stenosis in a patient with combined coagulation factor VIII and XI deficiency: a case report

**Sayaka Honda[1], Yusuke Shimahara [1]*, Yushi Chikasawa[2], and Hitoshi Ogino[1]**

[1]Tokyo Medical University, Department of Cardiovascular Surgery, Tokyo, Japan; and [2]Tokyo Medical University, Department of Laboratory Medicine, Tokyo, Japan

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**Background** Cardiac surgery remains a significant challenge in patients with coagulation factor VIII (FVIII) deficiency, especially in those with multiple factor deficiencies.

**Case summary** A 79-year-old man with combined FVIII and factor XI (FXI) deficiency was admitted for heart failure treatment. Transthoracic echocardiography revealed aortic stenosis (AS) with decreased left ventricular ejection fraction (LVEF) of 40%, mean aortic pressure gradient of 21 mmHg, and aortic valve area of 0.58 $cm^2$. Coronary angiography revealed significant triple-vessel disease. The patient had multiple comorbidities, including diabetic end-stage renal disease treated with hemodialysis and liver cirrhosis (Child–Pugh score of A). Considering the high surgical risk, a two-stage treatment strategy was developed: the first with off-pump coronary artery bypass grafting (CABG), and the second with transcatheter aortic valve implantation if AS symptoms were significant after CABG. A perioperative hemostatic protocol by the author's heart team was used to appropriately replenish recombinant FVIII concentrates and fresh frozen plasma. The target preoperative and postoperative FVIII coagulation activity values were set at 80–100% and 60–80%, respectively, whereas the target perioperative FXI coagulation activity value was set at 30–45%. Off-pump CABG without aortic manipulation was completed without bleeding events. Transthoracic echocardiography conducted 20 months postoperatively revealed LVEF of 65% and mean aortic pressure gradient of 31 mmHg. The patient leads a normal life 21 months after surgery.

**Discussion** The hemostatic protocol and risk-reduction surgery provided satisfactory surgical results in a patient with significant coronary artery disease and AS, high-surgical-risks, and combined FVIII and FXI deficiency.

**Keywords** Factor VIII deficiency • Factor XI deficiency • Coronary bypass grafting • Aortic stenosis • Perioperative hemostatic management • Case report

**ESC Curriculum** 4.2 Aortic stenosis • 3.1 Coronary artery disease • 7.5 Cardiac surgery

## Learning points

- In the hemostatic protocol for off-pump coronary artery bypass grafting, the target preoperative and perioperative FVIII:C values were set at 80–100% and 60–80%, respectively, whereas the target perioperative FXI:C value was set at 30–45%.
- The hemostatic protocol and risk-reduction surgery provided satisfactory surgical results in a patient with significant coronary artery disease and aortic stenosis, high-surgical-risks, and combined FVIII and FXI deficiency.

* Corresponding author. Tel: +81 3 3342 6111, Email: shimahamomaon@gmail.com
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# Introduction

Coagulation factor VIII (FVIII) deficiency called hemophilia A is a recessive X-linked bleeding disorder,[1] whereas factor XI (FXI) deficiency called hemophilia C is less common and has a distinguished autosomal inheritance pattern when compared to X-linked FVIII deficiency.[2] Age-associated cardiovascular comorbidities are increasing in those patients because coagulation factor deficiencies cannot protect against atherosclerotic development.[3] When hemophilia patients undergo a cardiac surgery, they are exposed to a high risk of excessive perioperative bleeding because coagulopathy is exacerbated by heparin administration, sternal and anastomotic site bleeding, clotting factor dilution, and use of cardiopulmonary bypass with or without hypothermia.[4] Although those patients require appropriate perioperative coagulation management, a specific protocol has not been established and only a few studies have reported hemophilia patients undergoing cardiac surgery.[5] In addition, the therapeutic strategy for coronary artery disease and concomitant aortic stenosis (AS) remains a matter of discussion in those patients with multiple comorbidities. To our best knowledge, this report describes the first patient who underwent cardiac surgery and had combined FVIII and FXI deficiency with multiple comorbidities.

# Timeline

| Date | Patient profile, examinations, events | |
|---|---|---|
| April. 2021 | Patient: A 79-year-old man (dry weight, 50.0 kg; height, 154 cm) | |
| | Admission to cardiac care unit with a complaint of dyspnea | |
| | Comorbidities (listed below) | |
| | 1. Factor VIII (FVIII:C of 20% at diagnosis) and XI deficiencies | |
| | 2. Type 2 diabetes (Insulin) | |
| | 3. Diabetic end-stage renal failure hemodialysis without anticoagulation three times per week supplement with 1500 IU of a third-generation recombinant FVIII concentrate (Advate®) after hemodialysis | |
| | 4. Liver cirrhosis (Child-Pugh score of A, Hepatitis C, hepatectomy in 2013) | |
| | 5. Thrombocytopenia | |
| | 6. Moderate stenosis of bilateral internal carotid arteries | |
| | 7. Hypothyroidism | |
| | TTE | low-flow low-gradient aortic stenosis with a decreased LVEF of 40% |
| | Cardiac CT | Traced aortic valve area of 0.58 $cm^2$ |
| | | Reduced left ventricular contractility with hypertrophic muscle |
| | Coronary angiography | Stenotic lesions in the proximal LAD, circumflex and RCA |
| | | Syntax score of 37. |
| May. 2021 (POD 0) | Aortic no-touch off-pump CABG (3 distal anastomoses) | |
| | Extubation (5 h after surgery) | |
| POD 1 | Total chest tube output | 400 mL within 12 h after surgery |
| POD 2 | Removal of chest tubes (total chest tube output of 700 mL within 36 h after surgery) | |
| | Resuming of hemodialysis without anticoagulation | |
| POD 5 | Left thoracentesis | |
| POD 6 | Transfer to general ward | |
| POD 7 | Right thoracentesis | |
| POD 14 | Cardiac CT | patent all grafts |
| POD 30 | TTE | LVEF of 51% with a mean transaortic pressure gradient of 18 mmHg |
| POD 39 | Discharge from hospital | |
| | No antiplatelet therapy after surgery | |
| | Postoperative follow-up by cardiologists, hematologists, and cardiovascular surgeons | |
| 14 months | TTE | Preserved LVEF of 60% with a mean transaortic pressure gradient of 32 mmHg |
| 20 months | TTE | Preserved LVEF of 65% and a mean transaortic pressure gradient of 31 mmHg |
| 21 months | Normal life without any heart failure symptoms | |

Continued

Continued

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CRP, c-reactive protein; CT, computed tomography; FVIII:C, factor VIII coagulation activity; FXI:C, factor XI coagulation activity; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PT-INR, international normalized ratio; RCA, right coronary artery; SAVR, surgical aortic valve replacement; STS, the society of thoracic surgeons; TTE, transthoracic echocardiography; WBC, white blood cell.

# Case presentation

A 79-year-old man with combined FVIII and FXI deficiency presented with dyspnea and was admitted to the cardiac care unit for heart failure treatment in 2021. The lower leg edema was observed, and a systolic murmur was audible on the aortic and neoaortic area. X-ray revealed lung consolidation and bilateral pleural effusion. Transthoracic echocardiography (TTE) revealed low-flow low-gradient AS with a decreased left ventricular ejection fraction (LVEF) of 40% and mean aortic pressure gradient of 21 mmHg (*Table 1*). Blood examination revealed decreased platelet counts (69 000/μL), prolonged activated partial thromboplastin time (APTT) (100 s), and normal fibrinogen value (359 mg/dL) and prothrombin time-international normalized ratio (0.85). FVIII and FXI activity (FVIII:C and FXI:C, respectively) values were markedly decreased (42.0% and 1.3%, respectively). The patient had multiple comorbidities: diabetes (hemoglobin A1c of 7.6%), diabetic end-stage renal disease treated with hemodialysis since 2017, liver cirrhosis with Child–Pugh score of A caused by hepatitis C virus, and hepatectomy-treated hepatic cancer in 2013. The patient received hemodialysis without anticoagulation three times per week and was always supplemented with 1500 IU of a third-generation recombinant FVIII concentrate (Advate®, Takeda Pharmaceutical Co., Ltd., Osaka, Japan) after hemodialysis. Coronary angiography revealed significant triple-vessel disease (*Figure 1*). Cardiac computed tomography (CT) revealed tricuspid aortic valve with calcium scoring of 2689 Agatston unit and traced AVA of 0.58 $cm^2$ (*Figure 2*). The patient's predicted risk of mortality for coronary artery bypass grafting (CABG) with surgical aortic valve replacement of the Society of Thoracic Surgeons and EUROSCORE II were high at 22% and 19%, respectively. Considering the high surgical risk, the authors' heart team developed a two-stage treatment strategy: the first with off-pump CABG, and second with transcatheter aortic valve implantation (TAVI). TAVI was planned if an AS symptom was significant after CABG.

A perioperative hemostatic protocol by the heart team was intended to replenish a third-generation recombinant FVIII concentrate (Advate®, Takeda Pharmaceutical Co., Ltd., Osaka, Japan) and fresh frozen plasma (FFP) (*Figure 3*). The target preoperative and perioperative FVIII:C values were set at 80–100% and 60–80%, respectively,[6] whereas the target perioperative FXI:C value was set at 30–45%.[7]

**Table 1 Transthoracic echocardiography data**

| | Before surgery | Early after surgery | 21 months after surgery |
|---|---|---|---|
| LV end-diastolic diameter, mm | 50.0 | 42.0 | 45.0 |
| LV end-systolic diameter, mm | 42.0 | 34.0 | 29.0 |
| LV ejection fraction, % | 40.0 | 51.0 | 65.0 |
| Stroke volume index, mL/m$^2$ | 30 | 33 | 35 |
| Aortic stenosis | | | |
| Peak velocity | 2.9 | 2.9 | 3.7 |
| Mean transaortic pressure gradient, mmHg | 21.0 | 18.0 | 31.0 |
| Aortic valve area (continuity equation), cm$^2$ | 0.58 | 0.78 | 0.70 |
| Aortic regurgitation | Mild | Mild | Mild |
| Mitral regurgitation | Mild | Mild | Mild |
| Tricuspid regurgitation | Mild | Mild | Mild |

LV, left ventricular.

Under general anesthesia, the saphenous vein (SV) was endoscopically harvested using the Vasoview Hemopro 2 device (Getinge, Gothenburg, Sweden). After the median sternotomy, the bilateral internal thoracic arteries (ITA) were harvested using a skeletonized technique. First, the *in situ* left ITA was individually anastomosed to the left anterior descending artery. Then, the *in situ* right ITA was extended by the SV in an end-side fashion anastomosis. The SV was sequentially anastomosed to the posterolateral and posterodescending arteries with the elevation of the left ventricular (LV) apex. The patient's hemodynamics was stable during off-pump CABG despite having low-flow low-gradient AS. The activated clotting time, APTT, fibrinogen, platelet, FVIII:C, FXI:C, and clot viscoelasticity by TEG$^R$6 s (Haemonetics Corporation, Boston, MA, USA) were measured to evaluate the hemostatic capability (*Figure 4*). Continuous FFP transfusion was performed during the surgery, resulting in the total transfusion volume of 1440 mL and the FXI:C value of 44% at the end of surgery. Advate® was continuously infused between heparin and protamine administration at the scheduled infusion rate, resulting in the FVIII:C value of 67% at the end of the surgery. Platelet concentrate transfusion of 600 mL was performed after protamine administration. TEG$^R$6 s revealed quantitative and qualitative deficiency of coagulation factors and platelets before median sternotomy, and canceled heparin effect and sufficient platelet and fibrinogen function after protamine administration. The absence of bleeding tendency was observed during the surgery. The total transfusion volume of red blood cell concentrate was 1400 mL to maintain a blood hemoglobin concentration >9.0 g/dL. The intraoperative blood loss was 500 mL. The patient was extubated 5 h after the surgery, and hemodialysis treatment without anticoagulation was resumed on POD 2. Advate® of 2000 IU and FFP of 480 mL were administered every day until POD 7. Cardiac CT performed 14 days postoperatively revealed excellent patent grafts (*Figure 2*). The patient did not receive the antiplatelet drug after surgery. After discharge, the patient received same treatment of Advate® before surgery. Twenty months postoperatively, TTE revealed LVEF of 65% and mean transaortic pressure gradient of 31 mmHg (*Table 1*) continues leads a normal life without any heart failure symptoms 21 months postoperatively.

## Discussion

Combined FVIII and FXI deficiency is an extremely rare disorder and is called the first group of Familial Multiple Coagulation Factor

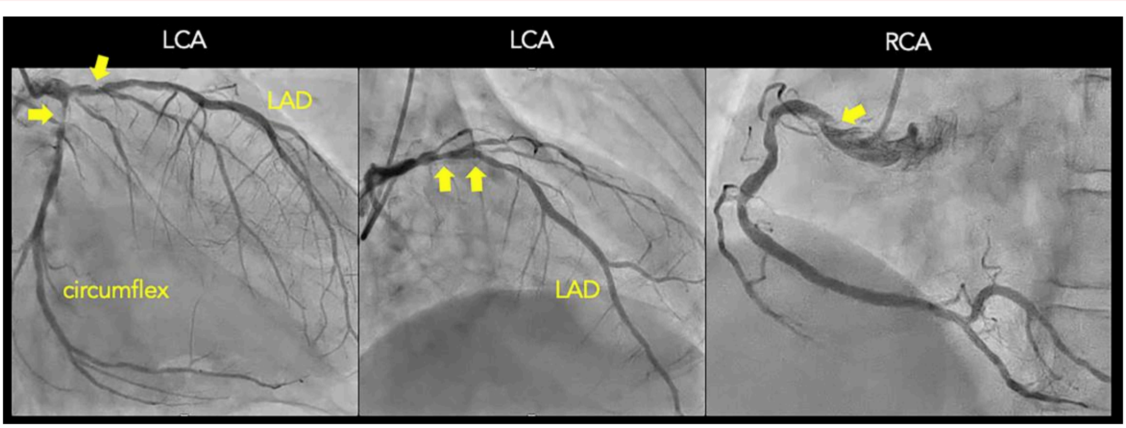


**Figure 1** Coronary angiography. Arrows indicate stenotic lesions. The percent diameter stenosis of left anterior descending artery, circumflex artery, and right coronary artery lesions were 70%, 80%, and 75%, respectively. LAD, left anterior descending artery; LCA, left coronary artery; RCA, right coronary artery.

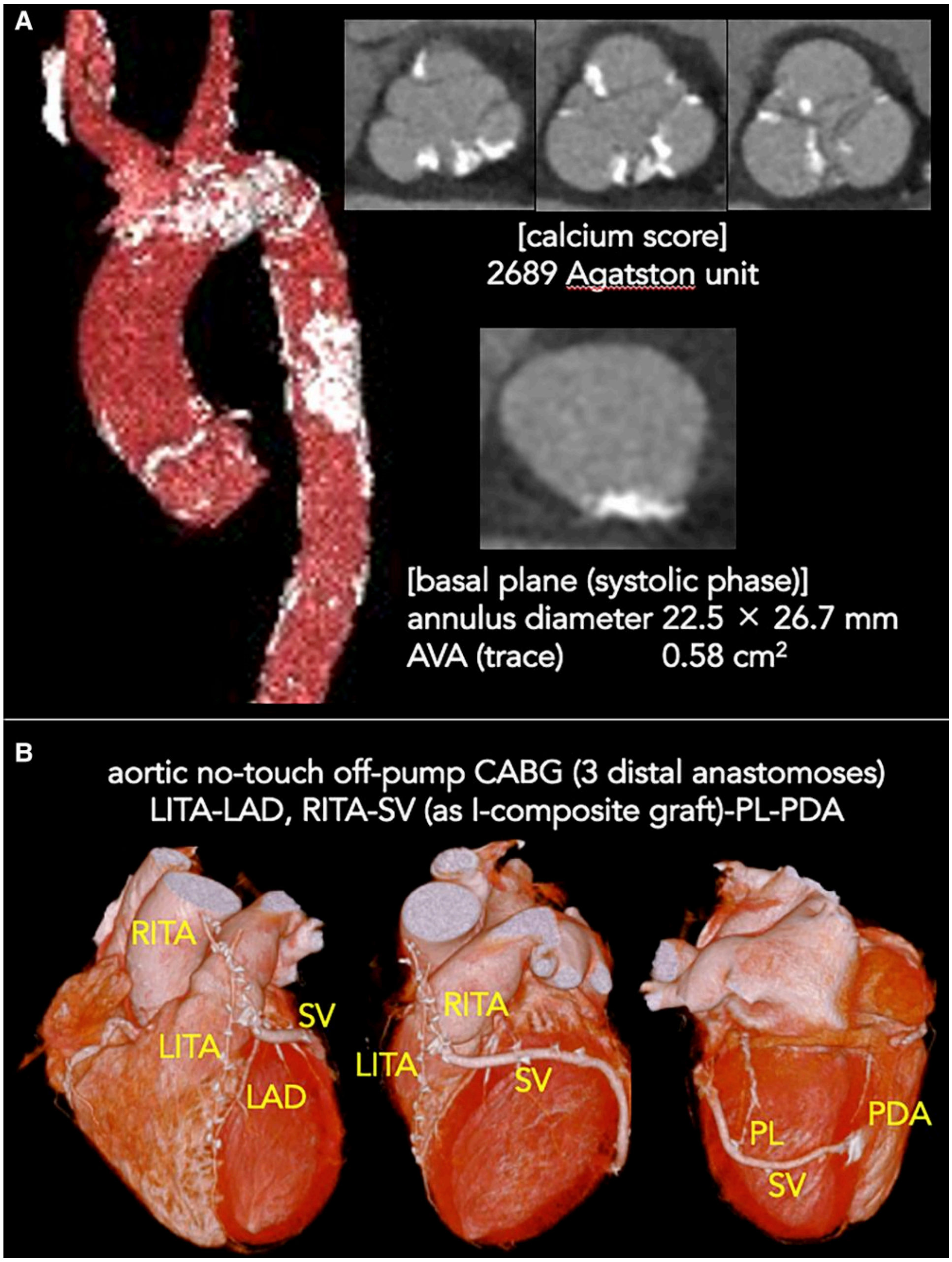


**Figure 2** Cardiac computed tomography. *A*) Preoperative cardiac computed tomography. *B*) Postoperative cardiac computed tomography. All grafts were patent. AVA, aortic valve area; CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LITA, left internal thoracic artery; PDA, posterior descending artery; PL, posterolateral branch; RITA, right internal thoracic artery; SV, saphenous vein.

Deficiencies, which was only reported in 10 male and one female patient and were not related to a surgery.[8,9] Although the bleeding tendency of FXI deficiency is generally mild, severe intractable bleeding may be provoked by the combined effect of FVIII deficiency perioperatively. The present coagulation management for off-pump CABG based on the protocol achieved perioperative target levels of the FVIII:C and FXI:C values. By contrast, excess administration of clotting factor concentrates or FFP may increase the cost, side effects of those plasma products, and thromboembolic events including a graft occlusion. A replenishment of the FVIII:C value up to 140% did not provide any additional hemostatic benefit,[10] whereas the normalization of FXI:C value >70% is not recommended because of a thromboembolic risk.[11] In this patient, as the FVIII:C and FXI:C values were checked point by point, excess administration of those clotting factors was prevented. Although Nordic hemophilia guidelines[12] recommend the use of tranexamic acid combined with factor replacement 3–4 times daily for 7–10 days after a major surgery, it was not used for the patient because of the absence of bleeding tendency.

Dual antiplatelet therapy is recommended after CABG to improve SV graft patency.[13] However, the patients did not receive any antiplatelet therapy postoperatively because the combined clotting factor deficiency and additional comorbidities associated with bleeding tendency (liver cirrhosis,

| Variables | | POD -1 | POD 0 | | | | | POD 1–7 |
|---|---|---|---|---|---|---|---|---|
| | | | Before surgery | During surgery Heparin | | Protamine | After surgery | |
| Advate® | Scheduled dose (IU) | 1,500 | 2,000 | | 2.7 /kg/h | | 1,000 | 1,000 or 2,000 / day |
| FVIII:C target value (%) | | 80–100 | | | | | 60–80 | |
| FFP | Scheduled dose (mL) | 2,400 | | 960 or 1440 | | | | 480 / day |
| FXI:C target value (%) | | 30–45 | | | | | | |
| PC | Scheduled dose (mL) | | | | | 500 | Based on platelet count | |
| Platelet target value (× $10^3$/μL) | | > 50 | | | | | | |
| RBC | Scheduled dose (mL) | | Based on hemoglobin level | | | | | |
| Hemoglobin target value (g/dL) | | | > 9.0 | | | | | > 10.0 |
| Hemodialysis without anticoagulation | | Ultrafiltration volume* 4,500 mL | | | | | | Resuming on POD 2 (3 times per week) |

**Figure 3** Perioperative hemostatic and hemodialysis protocol. A single dose of Advate®, a rate of continuous infusion of Advate®, and a transfusion volume of fresh frozen plasma (FFP) were determined based on the patient's *in vivo* recovery of Advate® and FFP (0.84 and 0.54 IU/dL per IU/kg, respectively). *In hemodialysis one day before surgery, the ultrafiltration volume was greater than usual to remove extra fluid caused by FFP replenishment (2400 mL). FFP, fresh frozen plasma; FVIII:C, factor VIII activity; FXI:C, factor XI activity; ICU, intensive care unit; PC, Platelet concentrate; POD, postoperative day; RBC, red blood cell concentrate.

| Variables | Ad | POD -1 | | POD 0 | | | | | | POD | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Before surgery | During surgery | Heparin | | Protamine | After surgery | 1 | | 2 | | 3 | 4 | 5 | 6 | 7 |
| ACT (s) | | | | | | 181 | 250 | 168 | | | | | | | | | | |
| Advate® infusion (IU) | | 1,500 | | 2,000 | | | 2.7 IU/kg/h (135) | | 1,000 | | 1,000 | 1,000 | 1,000 | 2,000 | 2,000 | 2,000 | 2,000 | 2,000 |
| FVIII:C (%) | 42 | | 109 | 51 | 118 | 72 | 69 | 67 | 60 | 71 | 51 | 52 | 54 | | | | | 81 |
| FFP transfusion (mL) | | 2,400 | | | 1,440 | | | | 480 | 480 | | 480 | | 480 | 480 | 480 | 480 | 480 |
| FXI:C (%) | 1.5 | | 55 | 40 | | 33 | 18 | 44 | 47 | 41 | | 25 | | | | | | 24 |
| APTT (s) | 100 | 32 | | 39 | | 35 | 94 | 35 | 34 | 45 | 46 | 52 | 51 | 53 | 51 | 45 | 38 | 49 |
| Fibrinogen (mg/dL) | 359 | 374 | | 409 | | 279 | 280 | 273 | 302 | 374 | 414 | 505 | 516 | 494 | 533 | 533 | 395 | 470 |
| PC transfusion (mL) | | | | | | | 600 | | | | | | | | | | 400 | |
| Platelet count (× $10^3$ μL) | 69 | 53 | | 66 | | | 59 | 104 | 110 | 83 | 94 | 84 | 74 | 61 | 69 | 68 | 51 | 100 |
| Hemodialysis | | ↔ | | | | | | | | | | ↔ | | ↔ | | | ↔ | |

**Figure 4** Hemostatic and hemodialysis protocol-based perioperative management. ACT, activated clotting time; Ad, admission; APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; FVIII:C, factor VIII activity; FXI:C, factor XI activity; ICU, intensive care unit; PC, Platelet concentrate; POD, postoperative day; RBC, red blood cell concentrate.

hemodialysis, and advanced age) were deemed to be effective in protecting against graft thrombosis. Consequently, no heart failure symptom was observed, all grafts were patent as detected by postoperative cardiac CT, and LV contractility improved as revealed by TTE 20 months postoperatively. A close clinical follow-up by a heart team, including cardiologists, hematologists, and cardiovascular surgeons, may be necessary to achieve favorable postoperative outcomes in such hemophilia patients.

In this patient, although CABG with concomitant surgical AVR was considered to be a standard definitive surgery, the surgical risk including serious bleeding was higher than that with isolated CABG or TAVI. In the TAVI era, off-pump CABG with concomitant TAVI is a less invasive feasible option for those patients with a high-risk status.[14] However, given the unprecedented bleeding risk by multiple coagulation factor deficiencies, hemodialysis, and liver cirrhosis, the surgical risk of this new alternative procedure was still higher than that of isolated CABG if the AS did not have a considerable effect on hemodynamic instability perioperatively. As the heart team deemed the patient's hemodynamics tolerant during and after isolated CABG based on the relatively low pressure gradient and aortic valve calcium score.[15] Consequently, the patients endured CABG and has not yet received TAVI because of the absence of AS-related symptom.

In conclusion, the hemostatic protocol and staged risk-reduction surgery provided satisfactory surgical results in a patient with significant coronary artery disease and AS, high-surgical-risks, and combined FVIII and FXI deficiency.

# Lead author biography

Sayaka Honda is a medical trainee at Tokyo Medical University (Tokyo, Japan) and will be surgical resident from 2023. Her research interests include risk-reduction staged surgery for the treatment of coronary artery disease and aortic stenosis, off-pump coronary artery bypass surgery using multiple arterial grafts, cardiac surgery based on preoperative planning based on cardiac CT.

# Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** Written consent for the submission and publication of this case report and accompanying images and text was obtained from the patient in line with the COPE guidelines.

**Conflict of interest:** None declared.

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## Data availability

The data underlying this article are available in the article and in its online *Supplementary material*.

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