ESC European Society of Cardiology

European Heart Journal - Case Reports (2025) **9**, ytaf205
https://doi.org/10.1093/ehjcr/ytaf205

CASE REPORT
Structural intervention

Perioperative management of transcatheter aortic valve implantation in acquired von Willebrand syndrome secondary to monoclonal gammopathy: a case report

Gaia Filiberti [1,2]*†, Alessandro Giaj Levra[1,2]†, Mauro Chiarito[1,2], Bernhard Reimers[2], and Gianluigi Condorelli[1,2]

[1]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 4, Milan, Pieve Emanuele 20072, Italy; and [2]Cardio Center, IRCCS Humanitas Research Hospital, Via Alessandro Manzoni, 56, Milan, Rozzano 20089, Italy

Received 12 November 2024; revised 5 March 2025; accepted 22 April 2025; online publish-ahead-of-print 20 May 2025

Background Acquired von Willebrand syndrome (AvWS) is a rare bleeding disorder associated with conditions like monoclonal gammopathy of undetermined significance (MGUS). It results from monoclonal antibodies binding to von Willebrand factor (vWF), leading to rapid clearance of vWF and factor VIII (FVIII). Of note, any condition increasing shear stress, such as aortic stenosis (AS), can exacerbate AvWS.

Case summary We report the case of an 81-year-old man with AvWS secondary to MGUS who underwent transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. Pre-operative intravenous immunoglobulins (IVIG) were administered, which normalized FVIII and vWF levels. TAVI was performed without specific haemostatic measures other than vascular closure devices. There were no bleeding complications, and the patient was discharged without antiplatelet therapy. At one-year follow-up, he had no thrombotic or haemorrhagic events.

Discussion We report the management of a patient affected by AvWS secondary to MGUS who underwent TAVI for severe AS. IVIG were administered preoperatively to temporarily normalize coagulation, as their mechanism of action directly inhibits the increased consumption of vWF. Due to the increased bleeding risk associated with AvWS, antiplatelet therapy was not initiated upon discharge.

Keywords Case Report • Aortic stenosis • Acquired von Willebrand Syndrome • TAVI • Monoclonal Gammopathy of Undetermined Significance

ESC curriculum 4.2 Aortic stenosis • 4.10 Prosthetic valves • 8.6 Secondary prevention

Learning points

- To explore the pre- and peri-operative management of Transcatheter Aortic Valve Implantation in a patient at high risk of bleeding.
- To evaluate the management of antiplatelet therapy in patients undergoing Transcatheter Aortic Valve Implantation and at high risk of bleeding.

* Corresponding author. Tel: +39 3313880422, Email: gaia.filiberti@humanitas.it
† Gaia Filiberti MD and Alessandro Giaj Levra MD equally contributed to the article and should be considered as shared first authors.
Handling Editor: Lina Ya'qoub
Peer-reviewers: Sharipah Intan Syed Abas
Compliance Editor: Rafaella Siang

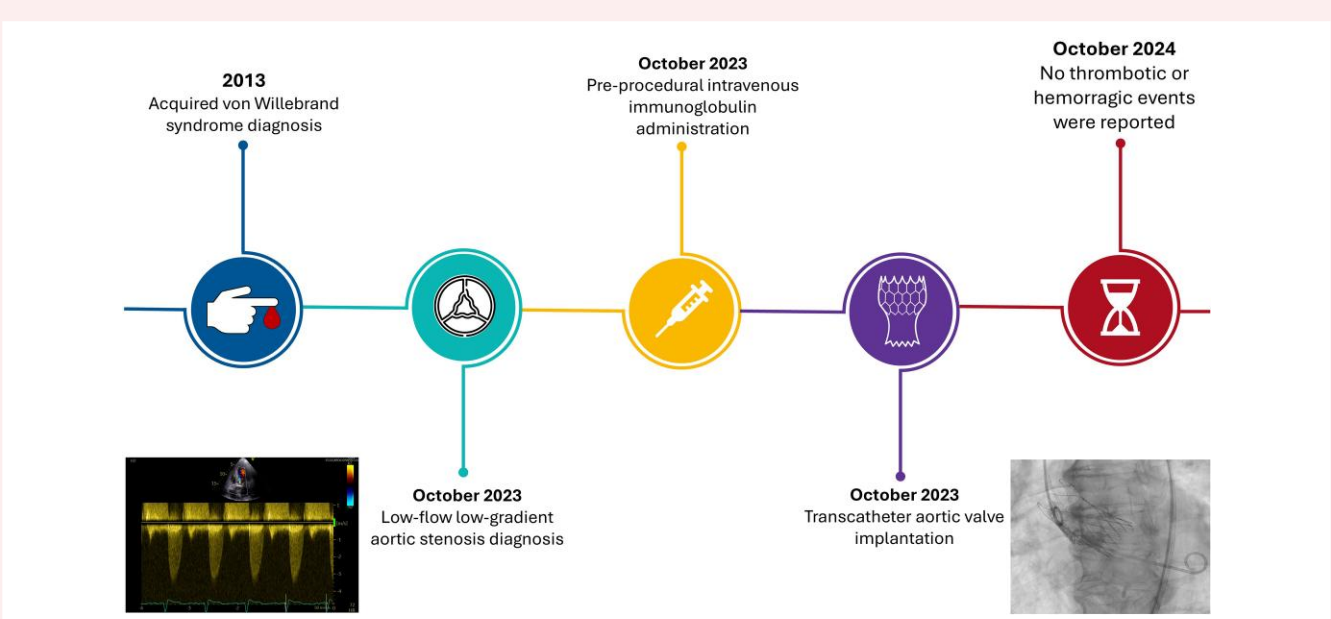
Introduction

Acquired Von Willebrand syndrome (AvWS) is a rare bleeding disorder characterized by spontaneous or surgery-induced mucosal bleeding and is often associated with haematologic conditions like monoclonal gammopathy of undetermined significance (MGUS).[1] AvWS is caused by monoclonal antibodies binding von Willebrand factor (vWF), thus accelerating the clearance of vWF and factor VIII (FVIII) or interfering with vWF function[1]. In aortic stenosis (AS), increased shear stress exacerbates AvWS by favouring the exposure of the cleavage site, and thus proteolysis, of vWF multimers[2].

Transcatheter aortic valve implantation (TAVI) is now considered the preferred treatment for AS in elderly patients over 75 years of age[3]. Indeed, TAVI results to be at least non-inferior to surgical aortic valve replacement across the spectrum of risk of patients, but it is encumbered by several possible complications, including life-threatening bleeding (15.6%) and major vascular complications (11.9%)[4]. In addition, bleeding events after TAVI are associated with increased short- and long-term mortality, prolonged hospitalization, and decreased quality of life[5]. Patients at high bleeding risk, such as those with AvWS[6], require meticulous peri-operative management, yet detailed strategies for managing this risk are poorly documented[7].

We report the peri-operative management of a patient affected by AvWS secondary to MGUS who underwent TAVI for severe AS.

Summary figure



Clinical timeline of a patient with acquired von Willebrand Syndrome and aortic stenosis, highlighting key events from diagnosis through treatment and follow-up. Key events include pre-procedural treatment with intravenous immunoglobulin before valve implantation, and follow-up showing no thrombotic or bleeding complications.

Case presentation

An 81-year-old male presented to the emergency department for progressively worsening dyspnoea. Past medical history was relevant for hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and acquired Von Willebrand syndrome (AvWS) associated with IgG kappa light chains monoclonal gammopathy.

At admission, the patient was hemodynamically stable with a peripheral oxygen saturation of 94% in room air. Physical examination unveiled mild pulmonary congestion, a systolic murmur of 3/6 on the Levine scale, and no signs of peripheral oedema. Laboratory exams showed high-sensitive troponin I of 50 ng/L, natriuretic peptide type-B of 630 pg/mL, and creatinine of 0.9 mg/dL. Initial work-up included an electrocardiogram (EKG) showing sinus rhythm with left anterior hemiblock. The echocardiogram revealed a hypertrophic, diffusely hypokinetic left ventricle and an ejection fraction (EF) of 40%. Classical type low-flow low-gradient severe AS was diagnosed with a mean gradient of 30 mmHg, maximal gradient 49 of mmHg, maximal velocity of 3.51 m/s, stroke volume 27 mL, doppler velocity index (DVI) 0.21, and continuity equation valve area of 0.8 cm^2.

(*Figure 1*). The patient was admitted to the cardiology ward and was started on intravenous furosemide. After congestive symptoms resolved, heart failure therapy with angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, and sodium-glucose cotransporter 2 inhibitors was started.

Pre-procedural coronary angiography did not show relevant coronary stenosis. At thoracic computed tomography, Agatston's score was 2700. At transthoracic echocardiogram, the flow rate[8] was 271 mL/s, and the mean gradient-effective orifice area ratio of 37.5[9]. Given the patient's clinical presentation, along with echocardiographic findings and a computed tomography (CT) calcium score suggesting severe stenosis, the Heart Team determined that this was sufficient for decision-making, recommending TAVI as the preferred interventional approach. Laboratory tests revealed FVIII coagulant activity (FVIII:C) of 23% (n.v. 50–150%), vWF antigen (vWF:Ag) 24% (n.v. 50–120%), ristocetin co-factor activity (vWF:RCo) 6% (n.v 50–150%), confirming the previous diagnosis of von Willebrand's disease (*Table 1*).

Although no previous major bleeding events were reported, the patient was considered at increased bleeding risk due to AvWS. Intravenous immunoglobulins (IVIG) 2 g/kg were administered over two days[10], leading to values normalization (FVIII:C 88%, vWF:RCo

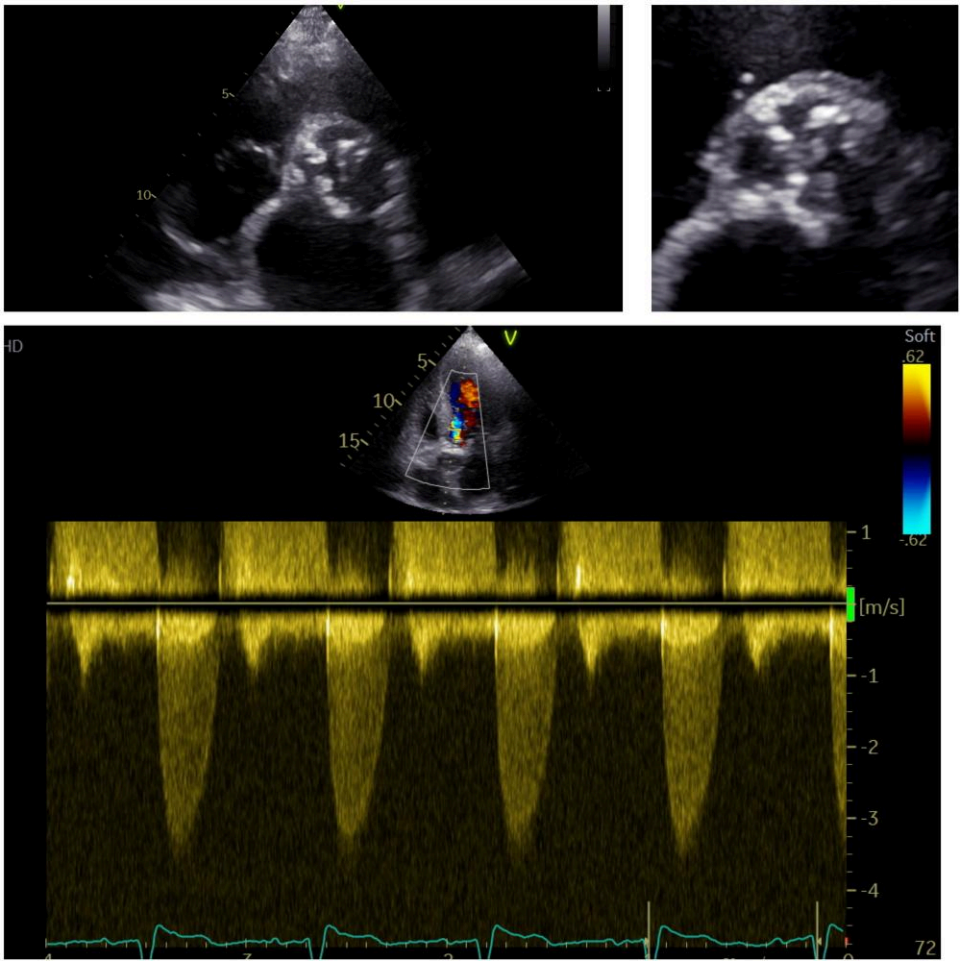


Figure 1 Echocardiogram upon admission revealed classical low-flow low-gradient severe aortic stenosis. Ejection fraction = 40%, stroke volume = 27 mL, mean gradient = 30 mmHg, maximal gradient = 49 of mmHg, maximal velocity rate = 3.51 m/s, continuity equation valve area = 0.8 cm^2, and index area 0.45 cm^2, DVI 0.21. In the parasternal short axis, the aortic valve appears extremely calcified, with a fibrocalcific replacement of the cusps.

Table 1 Reference values for first-line test in von Willebrand's disease diagnostic algorithm

Bleeding-assessment tools	**Normal values**
Factor VIII coagulant activity (FVIII:C)	50–150%
Von Willebrand Factor antigen (vWF:Ag)	50–120%
Ristocetin co-factor activity (vWF:RCo)	50–150%

vW disease is ruled out if all test results are normal. If any of these tests show abnormalities, a diagnosis of vW disease is likely to be done.

84%, and vWF:Ag 91%). Given values normalization, TAVI was performed without specific haemostatic measures beyond vascular closure devices. Unfractionated heparin was administered to achieve an activated clotting time target > 200 s. A 7-Fr left and 14-Fr right femoral artery accesses were utilized for Acurate Neo 2L™ valve implantation (*Figure 2*). Haemostasis was achieved with two Perclose and one AngioSeal™. No peri-procedural bleeding complications occurred.

Post-procedural tests showed FVIII:C 128%, vWF:Ag 127%, vWF:RCo 121%. Post-operative echocardiogram showed the correct positioning of the prosthesis, a mean aortic gradient of 6 mmHg, a maximal aortic gradient of 10 mmHg, and no significant paravalvular leak (*Figure 3*).

Remaining hospitalization was uneventful; the patient was discharged without antithrombotic therapy and with furosemide 25 mg die, without any re-hospitalization for heart failure in the following year. He subsequently underwent further investigations to rule out cardiac amyloidosis, which was excluded. Six-month follow-up echocardiography showed a progressive improvement in cardiac function (EF 52%). At one-year, the patient remained free from ischaemic or haemorrhagic events.

Discussion

The present report describes a novel approach to the peri-operative management of patients with AvWS and aortic stenosis undergoing TAVI. Pre-treatment with IVIG effectively improved the coagulation profile allowing safe valvular prosthesis implantation without additional safety measures.

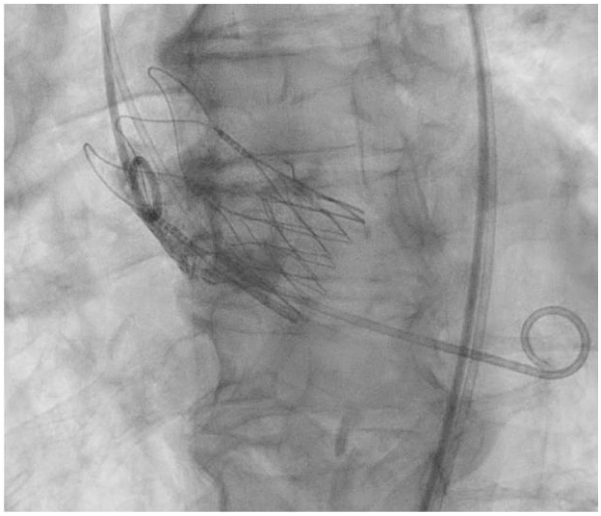


Figure 2 Prosthetic valve implantation (Acurate Neo 2L ™). Intraprocedural echocardiographic monitoring confirmed the correct positioning of the valve with no bleeding complications.

The most common pathophysiologic mechanism of AvWS in patients with aortic stenosis is believed to be related to shear stress[2]. As blood passes through the stenotic valve, proteolysis of large vWF multimers occurs, reducing coagulation cascade activity and increasing bleeding risk. Unlike most cases described in literature, this report involves two coexisting pathophysiological mechanisms in the same patient. In addition to the shearing forces from valvular stenosis, immune complexes associated with MGUS form with vWF, leading to increased degradation by the reticuloendothelial system[1]. This dual mechanism is highlighted by the improvement in vWF:RCo, FVIII:C, and vWF:Ag levels after IVIG infusion, with further enhancement observed following TAVI, where levels peaked at 128%, 121%, and 127%, respectively. The concurrent addressing of both mechanisms likely contributed to the significant improvement in vWF levels (*Figure 4*).

Peri-operative management of AvWS is poorly documented, with traditional approaches typically involving the administration of vWF prior to the intervention. While this method has proven effective in patients with AS, its efficacy in those with concurrent MGUS-related AvWS remains unclear[11].

IVIG was selected as the preferred approach in this case as previous use in interventional procedures has demonstrated promising outcomes[12]. Additionally, direct action on the IgG K chains temporarily reduced vWF degradation, facilitating haemostasis also in the

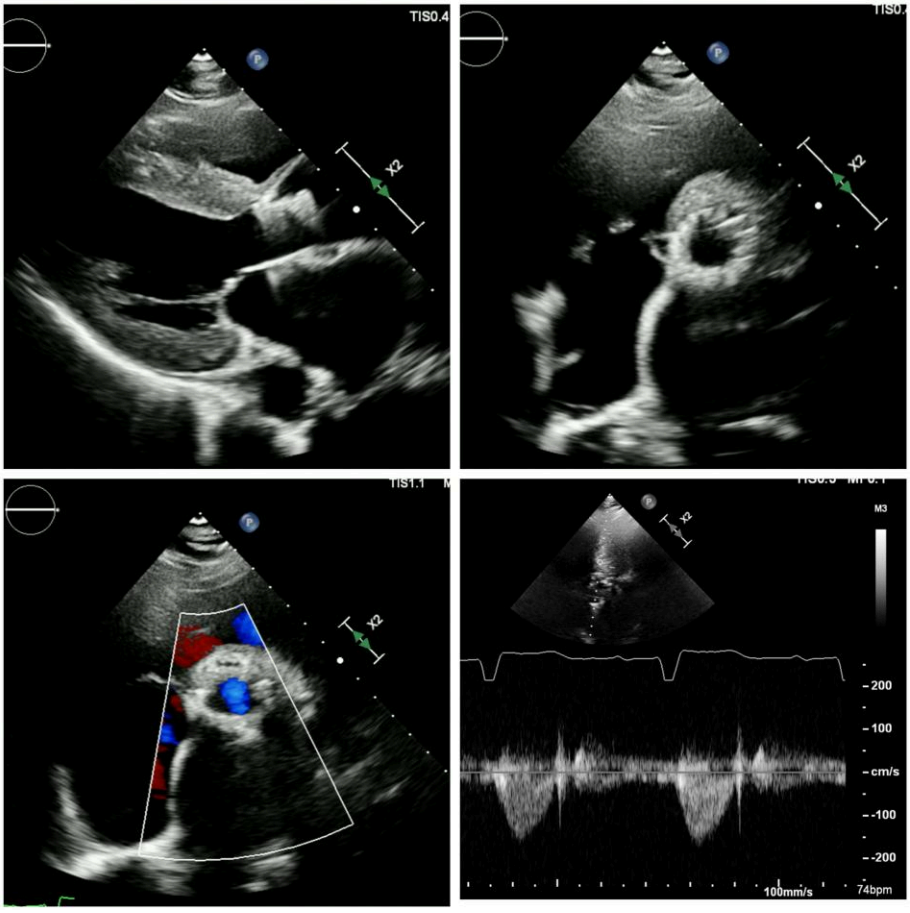


Figure 3 (*A*, *B*) Post-procedural echocardiography in parasternal long axis, (*C*) short axis, and (*D*) five-chamber views. No significant paravalvular leaks were observed. (*D*) Mean aortic gradient was 5 mmHg.

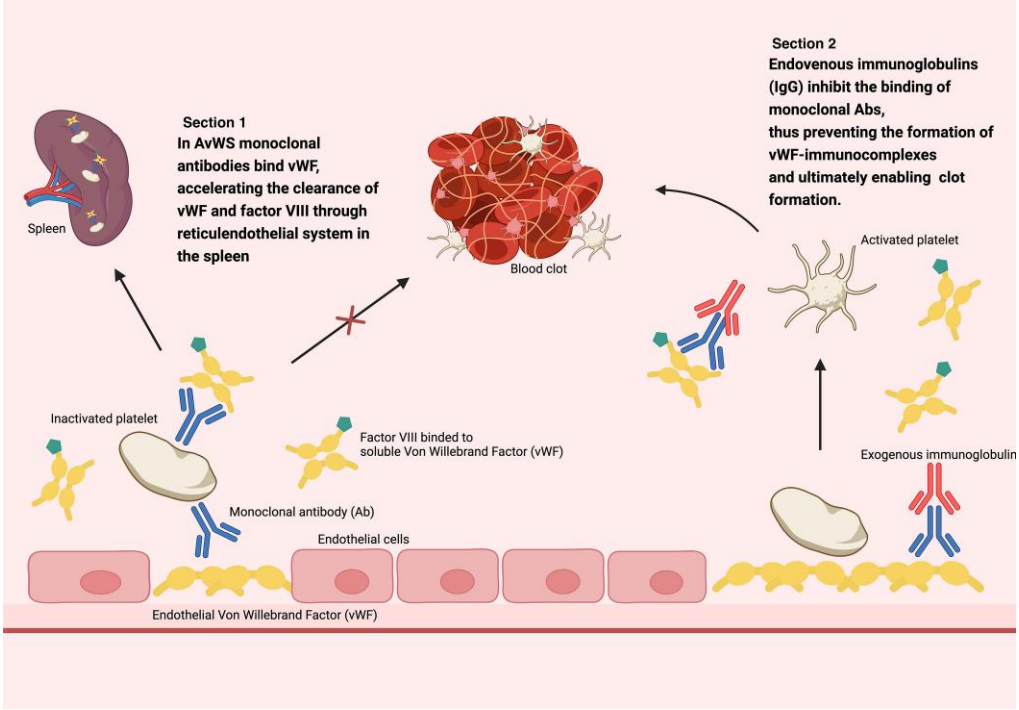


Figure 4 Section 1 (left) illustrates the pathophysiology of AvWS secondary to monoclonal gammopathy. IgM antibodies bind to both endothelial von Willebrand factor (vWF) and the soluble vWF carried by factor VIII. This interaction results in the formation of an immunocomplex, which hinders platelet activation, thereby elevating the risk of bleeding. In addition, immunocomplexes are rapidly degraded by the reticulendothelial system, causing a decrease in vWF and factor VIII. Section 2 (right) represents the mechanism of action of intravenous immunoglobulins in the treatment of AvWS. Immunoglobulins inhibit the binding of IgM antibodies, thus preventing the formation of immunocomplexes with vWF. The inhibition of immunocomplex formation prevents rapid clearance, thereby facilitating the normalization of factor VIII and von Willebrand factor (vWF) levels and ultimately enabling proper clot formation.

post-operative period. This was evidenced by the normalization of FVIII, vWF antigen, and vWF activity levels before the intervention[13].

Finally, the choice of antithrombotic treatment upon discharge is an area of controversy. The patient was deemed to be at high bleeding risk due to the persistence of AvWS, which was attributed to both the increased clearance of vWF multimers caused by MGUS-related monoclonal antibodies and the potential risk of developing paravalvular leaks that could increase shear stress, perpetuating the pathogenic mechanism[14]. Current guidelines recommend lifelong single antiplatelet therapy (SAPT) for patients undergoing TAVI without a concomitant indication for dual antiplatelet or anticoagulant therapy[3]. However, studies on antithrombotic therapy after TAVI usually presented key exclusion criteria contraindications to anticoagulant or antiaggregant therapy, thereby excluding patients with AvWS[15,16]. While avoiding antiplatelet therapy could increase the risk of thrombotic events, such as stroke or leaflet thrombosis, studies have shown that von Willebrand factor (vWF) activity prior to TAVI is lower in patients without as compared with those presenting leaflet thrombosis[17]. Furthermore, recent data from the OCEAN-TAVI registry have shown that in patients at high bleeding risk, the avoidance of any antithrombotic drug did not increase the risk of stroke, cardiovascular death, or myocardial infarction and reduced the risk of life-threatening bleeds[18]. New trials are currently investigating the non-inferiority of no antithrombotic regimen with respect to single antiplatelet therapy[19]. Therefore, no antiplatelet therapy can be a valuable option in patients at high bleeding risk, as further suggested by the absence of bleeding or ischaemic events at 1-year follow-up in our patient.

Conclusions

AvWS secondary to MGUS is a rare bleeding disorder that can cause severe bleeding events. This case highlights the feasibility of performing TAVI in AvWS secondary to MGUS. Pre-operative IVIG effectively reduced the bleeding risk and allowed appropriate haemostasis with vascular closure devices. No antiplatelet therapy after TAVI could be considered in patients with high bleeding risk.

Lead author biography

I am a cardiology resident focused on acute advanced cardiovascular care and structural heart interventions, driven by curiosity and a commitment to develop precise and effective approaches in cardiovascular care.

Acknowledgements

We thank the patient for consenting to share the case.

Statement of consent: The authors confirm that a written consent for submission and publication of this case report including images and text was obtained from the patient in line with COPE guidance.

Conflict of interest. None to declare.

Funding: No funding was provided for the preparation of this manuscript.

Data availability

Non-identifiable data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Gan TE, Sawers RJ, Koutts J. Pathogenesis of antibody-induced acquired von Willebrand Syndrome. *Am J Hematol* 1980;**9**:363–371.
2. Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von willebrand syndrome in aortic stenosis. *N Engl J Med* 2003;**349**:343–349.
3. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2022;**43**:561–632.
4. Généreux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012;**59**:2317–2326.
5. Généreux P, Cohen DJ, Mack M, Rodes-Cabau J, Yadav M, Xu K, et al. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2014;**64**:2605–2615.
6. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol* 2021;**77**:2717–2746.
7. Avvedimento M, Nuche J, Farjat-Pasos JI, Rodés-Cabau J. Bleeding events after transcatheter aortic valve replacement. *JACC State-of-the-Art Review. J Am Coll Cardiol* 2023;**81**:684–702.
8. Namasivayam M, He W, Churchill TW, Capoulade R, Liu S, Lee H, et al. Transvalvular flow rate determines prognostic value of aortic valve area in aortic stenosis. *J Am Coll Cardiol* 2020;**75**:1758–1769.
9. Hecht S, Annabi M-S, Stanová V, Dahou A, Burwash IG, Koschutnik M, et al. A novel echocardiographic parameter to confirm low-gradient aortic stenosis severity. *JACC Adv* 2024;**3**:101245.
10. Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. *Blood* 1998;**92**:2707–2711.
11. Mondal S, Hollander KN, Ibekwe SO, Williams B, Tanaka K. Heyde syndrome–pathophysiology and perioperative implications. *J Cardiothorac Vasc Anesth* 2021;**35**:3331–3339.
12. Dognin N, Salaun E, Champagne C, Domain G, O'Hara G, Philippon F, et al. Percutaneous left atrial appendage closure in patients with primary hemostasis disorders and atrial fibrillation. *J Interv Card Electrophysiol* 2022;**64**:497–509.
13. Abou-Ismail MY, Rodgers GM, Bray PF, Lim MY. Acquired von Willebrand syndrome in monoclonal gammopathy—a scoping review on hemostatic management. *Res Pract Thromb Haemost* 2021;**5**:356–365.
14. Van Belle E, Rauch A, Vincent F, Robin E, Kibler M, Labreuche J, et al. Von willebrand factor multimers during transcatheter aortic-valve replacement. *N Engl J Med* 2016;**375**:335–344.
15. Maes F, Stabile E, Ussia GP, Tamburino C, Pucciarelli A, Masson J-B, et al. Meta-analysis comparing single versus dual antiplatelet therapy following transcatheter aortic valve implantation. *Am J Cardiol* 2018;**122**:310–315.
16. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;**382**:1696–1707.
17. Steiner-Gager GM, Rogozarski J, Kronberger C, Dizdarevic AM, Quehenberger P, Schernthaner R, et al. Prediction model for leaflet thrombosis in patients undergoing transcatheter aortic valve implantation: the EFFORT study. *Clin Res Cardiol* 2024; Online ahead of print.
18. Kobari Y, Inohara T, Tsuruta H, Yashima F, Shimizu H, Fukuda K, et al. No antithrombotic therapy after transcatheter aortic valve replacement: insight from the OCEAN-TAVI registry. *JACC Cardiovasc Interv* 2023;**16**:79–91.
19. Inohara T, Otsuka T, Watanabe Y, Shirai S, Tada N, Yamanaka F, et al. Rationale and design of non-antithrombotic therapy after transcatheter aortic valve implantation (NAPT). *Trial. Contemp Clin Trials* 2023;**134**:107358.