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CASE REPORT

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Recurrent strokes after transcatheter aortic valve replacement in an elderly patient with severe bicuspid aortic valve stenosis: a case report

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Abstract

Background Transcatheter aortic valve replacement (TAVR) has evolved from a novel technology to an established therapy for high-risk patients with symptomatic severe aortic valve stenosis (AS). Recently, its use has also been extended to low-risk patients, resulting in its increasing utilization in patients with bicuspid aortic valve (BAV). But as a serious post-TAVR complication, ischemic stroke was associated with a nearly 6-fold increased 30-day mortality. BAV presents unique challenges for post-TAVR antithrombotic therapy due to its distinct valvular anatomy.

Case presentation We present a case of a 72-year-old female who presented with angina pectoris symptoms and was found to have severe BAV stenosis (Type 0). According to the patient's age, obvious symptom and willingness herself, TAVR was successful performed with deployment of a 23 mm Venus-A Plus valve (Venus Medtech, Hangzhou, China). A post-procedure echocardiogram confirmed the appropriate placement of the bioprosthetic valve with minor paravalvular regurgitation. Six months after TAVR, this patient experienced multiple strokes, presenting a significant challenge for clinicians.

Conclusions This case underscores the serious complications that can occur post-TAVR and highlights the need for improved strategies to prevent early strokes.

Keywords Transcatheter aortic valve replacement (TAVR), Bicuspid aortic valve disease, Stroke, Antithrombotic treatment, Small aortic annulus

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Introduction

Transcatheter aortic valve replacement (TAVR) has become the established treatment for aortic stenosis (AS) in patients at increased risk of surgery based on multiple randomized clinical trials and registries [1–4]. Recent advancements have extended the use of TAVR for treating AS to low-risk patients [4], resulting in its increasing utilization in patients with bicuspid aortic valve (BAV). BAV is the most frequent congenital heart disease, occurring in 1–2% of the population, and approximately 10% of patients currently undergoing TAVR have a BAV [5]. Therefore, the TAVR procedure and prognosis in patients with BAV have attracted increasing attention from clinicians.

Post-TAVR stroke is always a serious complication associated with increased mortality [6, 7]. A stenotic BAV has distinctive annular dimensions, bulky leaflets, severe calcification and a high association with aortopathy [5]. The complexity of the procedure due to the specific anatomy of BAV may be responsible for the increased stroke complication [8–10]. However, the current classification of post-TAVR antithrombotic regimens is relatively straightforward, and the optimal therapy for different patient types remains uncertain [11]. Here, we present a case of a 72-year-old female with BAV undergoing TAVR, who suffered from an ischemic stroke at 6 months after procedure while taking aspirin and clopidogrel, even followed by recurrent strokes while adjusting anticoagulants.

Case presentation

A 72-year-old female was hospitalized due to deteriorative angina pectoris symptoms of 11-days duration. The patient exhibited normal liver and kidney function test results, with no evidence of comorbidities such as peripheral arterial disease or tumors. She underwent Transthoracic Echocardiography (TTE) that revealed severe BAV stenosis with a peak velocity of 5.1 m/s, a mean gradient of 56 mmHg and aortic valve area of 0.4–0.6 cm^2 with mild aortic valve regurgitation. She had a normal left ventricular size with mild ventricular septum hypertrophy, normal left ventricular ejection fraction with an estimated ejection fraction of 60%, grade 2 diastolic dysfunction, normal right ventricular size, and systolic function.

The patient underwent cardiac computed tomography (CCT), which confirmed the presence of a BAV with oval annulus. Measurements were taken, including the heights of the left coronary artery (13.0 mm), right coronary artery (15.5 mm), and the aortic annulus (Figs. 1A and 14.6×23.3 mm, avg: 19.0 mm, area: 272.3 mm^2, perimeter: 60.9 mm), left ventricular outflow tract (LVOT, Figs. 1B and 13.0×24.5 mm, avg: 18.7 mm, area: 251.2 mm^2, perimeter: 62.9 mm), the sinus of Valsalva (Figs. 1C and 24.4×33.8 mm, avg: 29.1 mm), sinotubular junction diameter (Figs. 1D and 28.2×29.8 mm, avg: 29.0 mm), 4 mm above the valve (Figs. 1E and 17.8×22.6 mm, avg: 20.2 mm, area: 313.9 mm^2, perimeter: 63.6 mm), proximal ascending aorta (Fig. 1F, 40 mm above the valve,

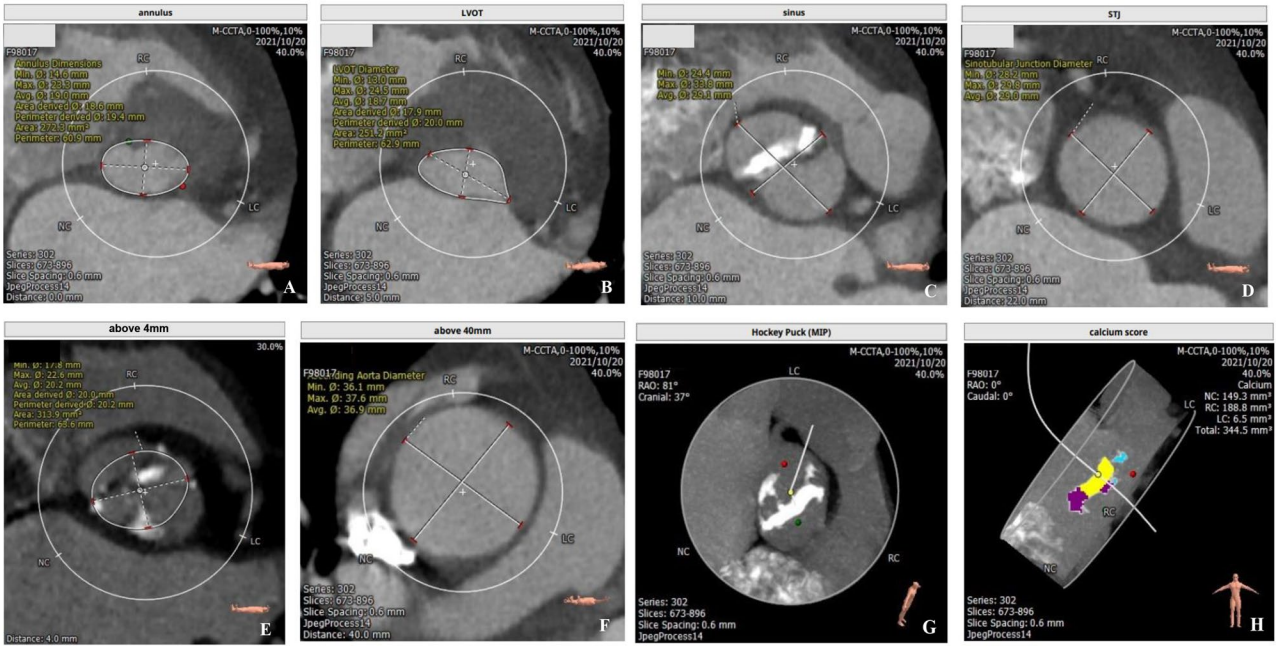

Fig. 1 Pre-procedural TAVR CTA measurements. **A** - Aortic annulus measurements, **B** - Left ventricular outflow tract measurements, **C** - Sinus of Valsalva measurements, **D** - Sinotubular junction measurements, **E** – 4 mm above the valve measurements, **F** - Ascending Aorta measurements, **G** - Hockey Puck (MIP), **H** - Calcium score

36.1×37.6 mm, avg: 36.9 mm). The valve shows mild calcification with unilateral distribution, with a calcification score of 344.5 mm^3 (Fig. 1G and H). Meanwhile, CCT did not reveal stenosis greater than 50% in any coronary artery branch.

A multidisciplinary heart valve team evaluated the patient's case carefully. Severe aortic stenosis was diagnosed by TEE, and since it was associated with significant cardiac symptoms, the patient was indicated for valve intervention. Although the patient was <75 years at low-risk for SAVR (EuroScore II 1.32% and STS 2.273%), CCT showed its valvular and peri-valvular anatomical structure suitable for TAVR, coupled with the patient herself strongly rejected SAVR, it was decided to proceed with the TAVR procedure finally. Intraprocedural valvuloplasty was conducted using a Numed Z-Med-II 18.0–40 mm balloon (Venus Medtech, Hangzhou, China) through transfemoral access. Following this step, a 23 mm Venus-A Plus valve (Venus Medtech, Hangzhou, China) was meticulously positioned and deployed under rapid ventricular pacing. Angiography of ascending aorta and aortic root confirmed the appropriate placement of the prosthesis and minor paravalvular regurgitation. The patient was discharged on the fourth day of TAVR without any complications, and her blood pressure was monitored within the range of 107–138/46–57 mmHg.

The initial antithrombotic regimen of post-TAVR was aspirin (100 mg daily) and dual antiplatelet therapy with clopidogrel (75 mg daily). One month after TAVR, TTE and CCT (Fig. 2) both reported that the structure and function of prosthesis was in good condition, no valvular microthrombus and neoplasm were found. Within 6 months after TAVR, there was no major adverse cardiac events occurred on this patient.

However, six months after the TAVR, the patient had a sudden ischemic stroke, manifested as slurred speech and right limbs weakness. On physical examination, strength was 5-/5 in right limbs. A branch occlusion of the left middle cerebral artery was diagnosis by cerebral CTA examination (Fig. 3). Emergency cerebral arteriography and thrombus aspiration were performed by neurosurgeons, then the antithrombotic treatment changed to rivaroxaban (15 mg daily). When this stroke event occurred, all coagulation indicators such as PT, APTT were in the normal range, CT found no thrombus attachment to valve stents. The carotid artery CT revealed a 2 mm aneurysm in the C6 segment of the right internal carotid artery, with no evidence of unstable plaque, ulceration, or significant luminal stenosis that could predispose to thrombus formation. Two months later, she was diagnosed with acute lacunar cerebral infarction by cerebral MRI (Fig. 4) due to dizziness and left limbs weakness. The patient exhibited decreased strength in the left lower limb and diminished sensation in the left limbs, with positive Babinski signs bilaterally. Rivaroxaban was replaced with warfarin (3.75 mg daily) during hospitalization. Unfortunately, the patient suffered left frontal lobe hemorrhage (Fig. 5) with INR 4.24 one month after taking warfarin, therefore the antithrombotic treatment was stopped. Patient experienced sudden dizziness and right limbs weakness with grade 4-/5 muscle strength. During rehabilitation, the patient underwent several

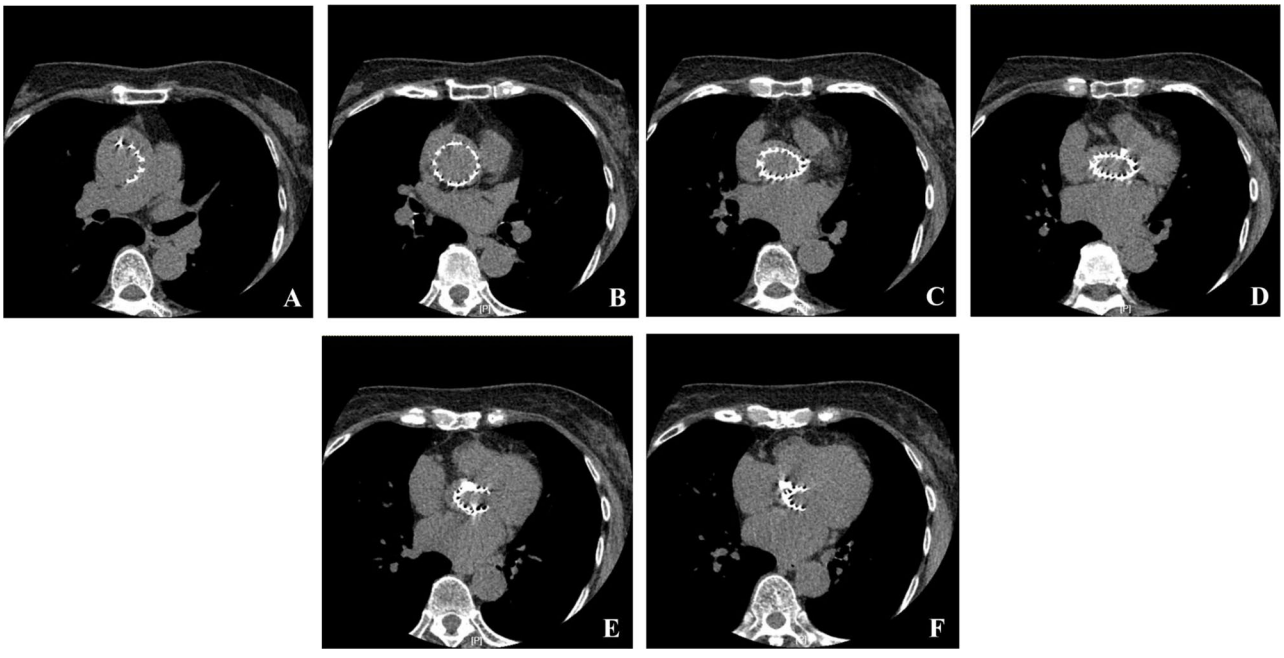

Fig. 2 CTA measurements at 1 month after TAVR. **A** to **D** show the condition of the prosthesis

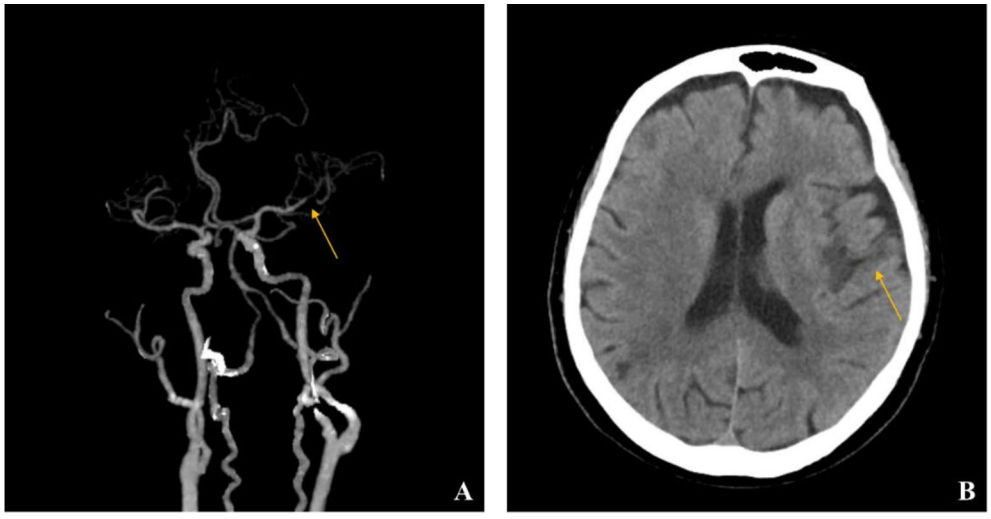

Fig. 3 Cerebral CTA examination at 6 months after TAVR. **A** - Cerebral arteriography; Arrow indicates the blocked cerebral artery, **B** - Cerebral CT; Arrow indicates ischemic brain tissue

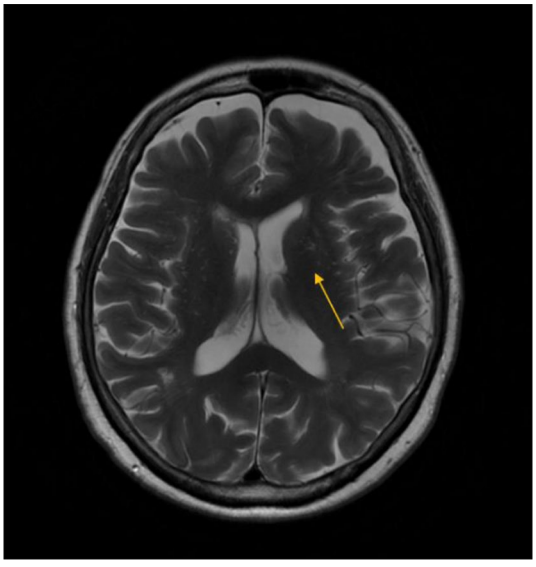

Fig. 4 Cerebral MRI examination at 8 months after TAVR. T2 image of cerebral MRI; Arrow indicates the cerebral lacunar infarction in left corona radiata

examinations. TTE demonstrated an aortic valve forward flow velocity of 2.44 m/s, with a small amount of regurgitation observed in the artificial valve at the short-axis view from the 12 o'clock to the 1 o'clock position, and the transesophageal echocardiography (TEE) excluded valve thrombus and patent foramen ovale (Fig. 6). The 24-hour Holter did not detect atrial fibrillation. The 24-hour ambulatory blood pressure monitoring results after discharge indicated a daytime average of 115/62 mmHg and a nighttime average of 99/56 mmHg, with a systolic blood pressure variability of 0.16 and a diastolic blood pressure variability of 0.19.

The drug withdrawal lasted for 40 days, the patient was hospitalized due to recurrent ischemia stroke, which presented as speech inability and left limbs hemiplegia. On physical examination, strength was 3/5 in right limbs and Babinski sign was positive on the left side. It was revealed that embolism at the end of the right carotid artery by emergency cerebral angiography, the neurosurgeons immediately performed thrombus aspiration. Warfarin was given alternately 3 mg/1.5 mg daily ever since. The changes of antithrombotic regimen are shown in Table 1.

Discussion

TAVR has become an established and widely adopted approach to treat aortic stenosis in the past decade [11]. Following the approval of TAVR for low-risk patients by the US Food and Drug Administration (FDA) in 2019, an increasing proportion of younger people are undergoing TAVR surgery [12]. It was accounted for up to 50% of patients requiring surgery in the younger population due to the early degeneration proneness of BAV [13]. Distinct anatomy and complication make TAVR for BAV disease much more challenging [13], which leads to BAV as an exclusion criterion in the large pivotal trials. To date, there is still a lack of extensive experience in the application of TAVR in patients with BAV [1–4, 14].

This case report of a 72-year-old female patient who underwent early recurrent strokes after successful TAVR. According to the Valve Academic Research Consortium 3 (VARC-3) definition of ischemic stroke, those that occur between 30 days and 1 year after index procedure are referred to as early ischemic strokes [15]. Although no direct evidence of valve thrombosis was found, after exclusion of atrial fibrillation, patent foramen ovale, or abnormal coagulation function, the implanted valve was considered to be the cause of thrombosis. Makkar RR et

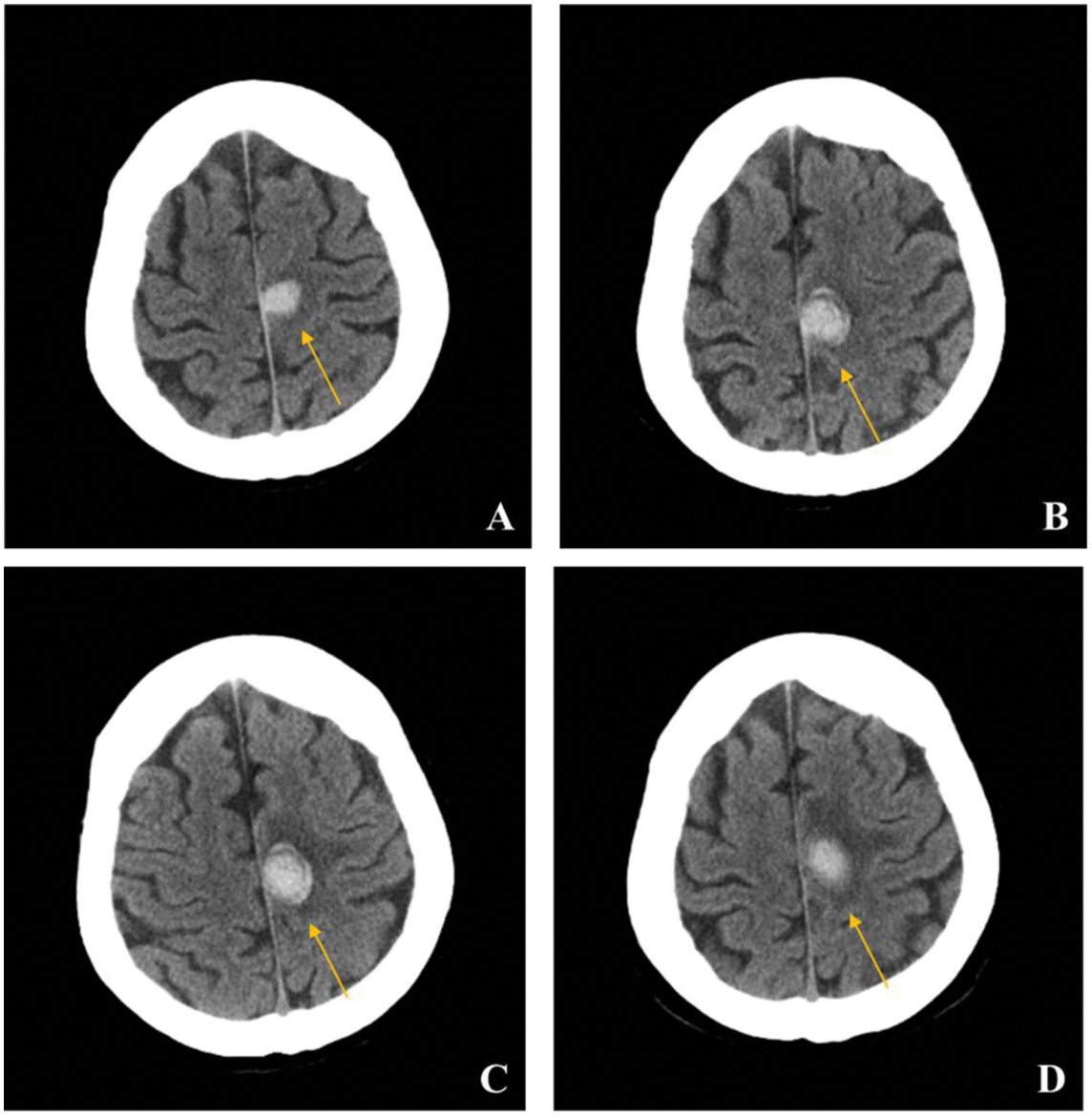

Fig. 5 Cerebral CT examination at 9 months after TAVR. From **A** to **D**, the arrows indicate the change of hemorrhagic foci in left frontal lobe

al. [10] showed that BAV patients undergoing TAVR had higher rate of in-hospital and 30-day stroke compared to tricuspid aortic valve patients. The unique anatomy of BAV not only poses challenges to operation, but also puts forward high requirements for the prevention of complications. Our case report adds to valuable evidence regarding the antithrombotic regimen after TAVR in BAV.

Small aortic annulus (SAA) is defined by an international multicenter registry as annular area < 400 mm^2 and/or annular perimeter < 72 mm based on CT measurements [16]. SAA predisposes to patient-prosthesis mismatch, which is known to be associated with decreased coronary flow reserve, reduced exercise tolerance, and earlier structural valve degeneration, in addition to higher all-cause mortality and cardiac mortality after AVR [17]. The PARTNER trial [18] showed that in patients with SAA, the TAVR cohort was associated with higher rates of stroke (6.3% vs. 0%, $p=0.02$) and major vascular complications (18.4% vs. 7.2%, $p=0.03$). In addition, the type of transcatheter heart valve (THV) was also related to stroke. The valves implanted during TAVR are categorized into self-expanding valve (SEV) and balloon-expandable valve (BEV). It is commonly accepted that SEV has better systolic hemodynamic performance compared with BEV because of the supra-annular position of the leaflets. A recent study of SAA patients receiving TAVR by Taishi Okuno et al. [19] confirmed this, however, it also found an increased risk of disabling stroke in patients with SEV at 5 years. The patient in this

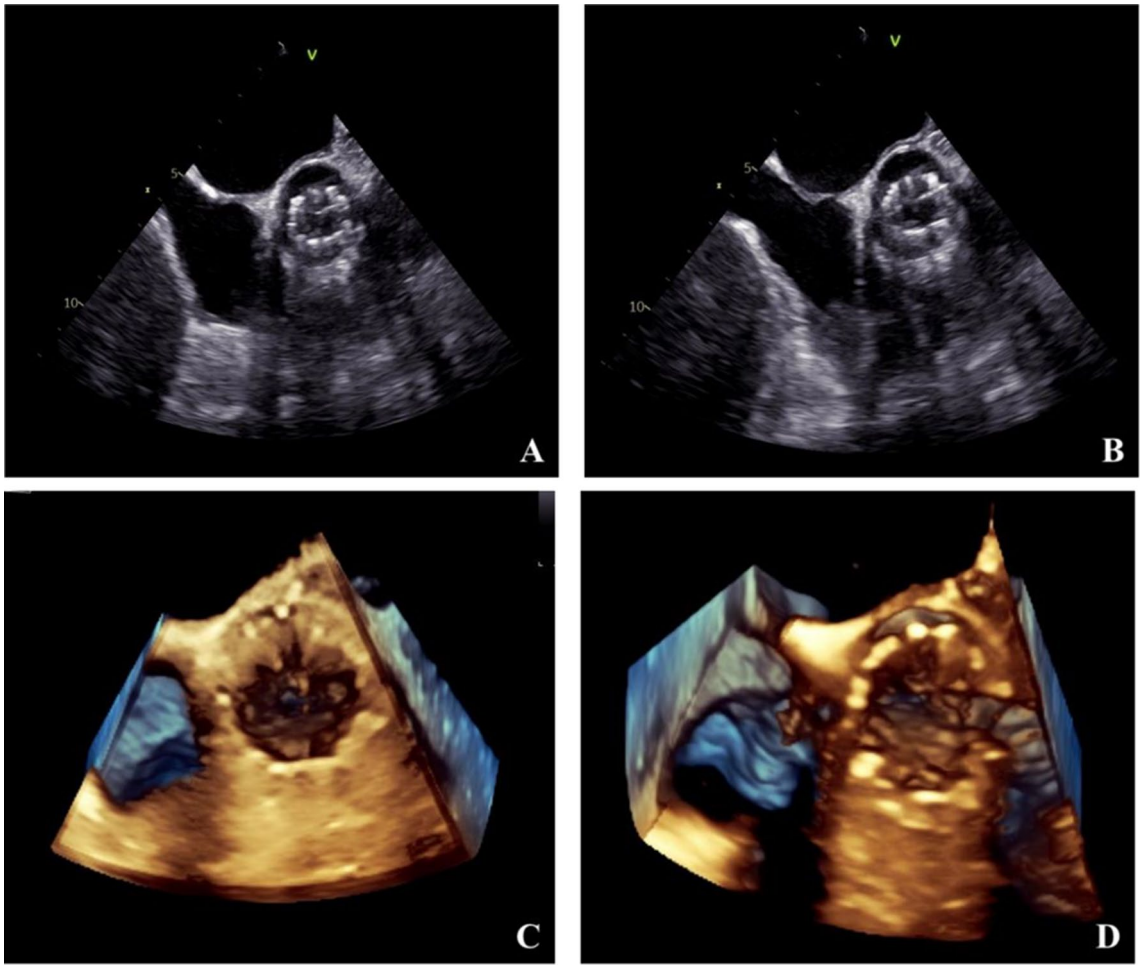

Fig. 6 TEE examination at 17 days after cerebral hemorrhage. **A**, **B** – 2D images of aortic valve, **C**, **D** – 4D images of aortic valve

Table 1 Antithrombotic regimen after TAVR

	Time (from TAVR), month	Antithrombotic treatment	Dose
post-TAVR	immediately	Aspirin Clopidogrel	100 mg daily 75 mg daily
Ischemia stroke	6	Rivaroxaban	15 mg daily
Ischemia stroke	8	Warfarin	3.75 mg daily
Cerebral hemorrhage	9	-	-
Ischemia stroke	10	Warfarin	3 mg/1.5 mg Qod

case had a relatively small aortic annulus with a perimeter of only 60.9 mm, therefore we chose a 23-mm prosthesis to matched it and the ratio of effective orifice area (EOA) to body surface area was 0.87 cm^2/m^2 at 1 month after TAVR. The presence of SEV might be one of the factors leading to thrombus formation in patients. Therefore, in BAV stenosis patients with SAA, clinicians need to evaluate the aortic valve and perivalvular structure more carefully. The choice of surgical protocol and types of implanted valves should aim to maximize benefits and improve the quality of life for patients.

In ESC guidelines 2021, lifelong single-antiplatelet therapy (SAPT) was recommended after TAVR in patients with no baseline indication for oral anticoagulation (OAC) (I, A), routine use OAC was not recommended (III, B) [20]. Because it was initially believed that transcatheter aortic valves would behave similarly to coronary stents in term of rheology. Recently, Yusuke Kobari et al. [21] compared the clinical outcomes of nonantithrombotic therapy, SAPT and dual-antiplatelet therapy (DAPT) after TAVR, and indicated that not receiving antithrombotic therapy was not associated with an increased risk of net adverse clinical events (NACEs), which challenged the necessity of SAPT. However, many studies now reported that a large number of patients had subclinical leaflet thrombosis (SLT) with transcatheter and surgical bioprosthetic aortic valves, whose presence has been associated with the occurrence of cerebrovascular events, but antiplatelet therapy does not seem efficient enough to prevent SLT [22]. On the other hand,

some studies suggested that NOACs and warfarin were effective in the prevention and treatment of SLT, but these findings did not correlate with clinical improvement and were associated with an increased risk of mortality and major bleeding events in TAVR patients with no underlying indication for OAC [22–24]. Antithrombotic treatment for lacunar stroke, in particular, should be approached with greater caution to avoid increasing the risk of hemorrhagic stroke. These discrepancies in opinions of studies suggest that the current simple classification of anticoagulation regimen after TAVR might be not feasible. Particularly, there are no reliable results on antithrombotic scheme for patients with BAV stenosis post-TAVR. We highly recommend that an individualized scoring system should be established for the post-TAVR antithrombotic strategy.

Conclusion

Our case report describes a single patient experience and cannot definitively address the surgical protocol and antithrombotic scheme of TAVR in BAV patients with similar characteristics. Large RCTs are necessary to further explore appropriate surgical method and antithrombotic treatment in order to optimize post-procedural management. Despite these limitations, this case emphasizes the prudent option of surgical treatment in SAA patients and highlights the potential of different types of antithrombotic drugs for early stroke prevention after TAVR in BAV patients, offering avenues for a broader range of treatment strategies for these patients in the future.

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Author contributions
X.M. wrote the main manuscript text. X.W., C.Y. and H.Z. prepared Figs. 1, 2, 3, 4, 5 and 6. All authors reviewed the manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available due to the project which is still in the follow-up, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures in this study were approved by Beijing Hospital Ethics Committee on July 5, 2021 (2021BJYYEC-034-04). The informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
The informed consent from participant for publication of identifying information/images has been obtained from patient herself.

Competing interests
The authors declare no competing interests.

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