Clinical case

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Cardiovascular Conundrum: Discovering Bioprosthetic Valve Stenosis in a 67-Year-Old Woman with Acute Coronary Syndrome Presentation

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Abstract. Bioprosthetic valve stenosis is characterized by an increase in transvalvular velocity and pressure gradient alongside thickened or calcified leaflets. It is a condition typically observed after bioprosthetic heart valve implantation because of structural valve degeneration, a process that typically begins around 7–8 years post-implantation and can culminate in valve stenosis or regurgitation due to calcification, leaflet tear, or pannus formation. Uncommonly, bioprosthetic aortic valve (BAV) stenosis may provoke acute coronary syndrome (ACS)-like symptoms in patients, unrelated to coronary artery obstruction, possibly due to a supply-demand mismatch impacting coronary vasculature, particularly under conditions of tachycardia and myocardial hypertrophy. A case illustration featuring a 67-year-old woman with BAV stenosis experiencing ACS-like symptoms 9 years post-surgical aortic valve replacement highlights the diagnostic challenges. Unstable angina and cardiac biomarker results were suggestive of ACS, but transthoracic echocardiogram (TTE) revealed a moderately stenotic BAV in the patient. A significant decrease in left ventricular ejection fraction and left ventricular stroke volume over time, compared with prior TTE assessments across the years, signifies the hemodynamic compromise linked to BAV stenosis. Adhering rigorously to American College of Cardiology/American Heart Association guidelines mandating routine TTE evaluations at 5-and 10-year intervals post-implantation and yearly thereafter for all BAV recipients, regardless of clinical status, is imperative to avert potential complications. Thus, prioritizing early detection of valve dysfunction via TTE in suspected ACS patients with prior BAV placement is crucial in devising optimal treatment strategies and enhancing patient care.

Keywords: bioprosthetic heart valves, aortic stenosis, acute coronary syndrome, ACS, structural valve degeneration, echocardiography

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Клинический случай

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Сердечно-сосудистая загадка: обнаружение стеноза биопротеза клапана у 67-летней женщины с проявлением острого коронарного синдрома

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Аннотация. Стеноз биопротезного клапана характеризуется увеличением трансклапанной скорости и градиента давления наряду с утолщением или кальцификацией створок. Это состояние обычно наблюдается после имплантации биопротеза клапана сердца из-за структурной дегенерации клапана — процесса, который обычно начинается примерно через 7–8 лет после имплантации и может завершиться стенозом клапана или регургитацией из-за кальцификации, разрыва створки или образования паннуса. В редких случаях стеноз биопротезированного аортального клапана может провоцировать симптомы подобные острому коронарному синдрому (ОКС), у пациентов без обструкции коронарных артерий. Это возможно из-за несоответствия между потребностью и обеспечением коронарного кровоснабжения, особенно в условиях тахикардии и гипертрофии миокарда. На примере 67-летней женщины со стенозом биопротезированного аортального клапана, у которой через 9 лет с момента хирургической замены аортального клапана появляются симптомы, сходные с проявлениями ОКС, видны диагностические сложности. Нестабильная стенокардия и наличие кардиоспецифических биомаркеров свидетельствовали об ОКС, но трансторакальная эхокардиография (ЭхоКГ) выявила умеренный стеноз биопротеза у пациента. Значительное снижение фракции выброса левого желудочка и ударного объема с течением времени по сравнению с предыдущими оценками ЭхоКГ за последние годы указывает на нарушение гемодинамики, связанное со стенозом биопротеза. Строгое соблюдение рекомендаций Американского коллед-

жа кардиологии и Американской кардиологической ассоциации, предписывающих проводить регулярные обследования с интервалом в 5 и 10 лет после имплантации и ежегодно в дальнейшем для всех реципиентов биопротеза, независимо от клинического статуса является обязательным условием предотвращения потенциальных осложнений. Таким образом, приоритетное внимание к раннему выявлению дисфункции клапанов с помощью ЭхоКГ у пациентов с подозрением на ОКС и предварительной установкой биопротеза имеет решающее значение для разработки оптимальных стратегий лечения и улучшения ухода за пациентами.

Ключевые слова: биопротезы клапанов сердца, аортальный стеноз, острый коронарный синдром, структурная дегенерация клапана, эхокардиография

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Abbreviations: ACS — acute coronary syndrome; **ARB** — angiotensin II receptor blockers; **BAV** — bioprosthetic aortic valve; **BHV** — bioprosthetic heart valve; **CPK** — creatine phosphokinase; **FIO_2** — fraction of inspired oxygen; **Glut** — glutaraldehyde; **LA** — left atrium; **LDH** — lactate dehydrogenase; **LV** — left ventricular; **LVEF** — left ventricular ejection fraction; **pCO_2** — partial pressure of carbon dioxide; **PG** — pressure gradient; **pH** — potential of hydrogen (*lat*. pondus Hydrogenii); **pO_2** — partial pressure of oxygen; **RFA** — radio frequency ablation; **SAVR** — surgical aortic valve replacement; **SpO_2** — oxygen saturation; **SVD** — structural valve degeneration; **tCO_2** — total carbon dioxide; **TTE** — transthoracic echocardiogram; **ViV** — Valve-in-Valve.

Introduction

Historically, bioprosthetic heart valves (BHVs) are valves constructed from porcine or bovine tissues fixed with glutaraldehyde (Glut). In Paris 1965, French Surgeon Alain Carpentier, along with his team pioneered the first successful xenograft replacement of the aortic valve in a human with a porcine valve. Over the years, BHVs have undergone significant advancements to enhance their longevity and robustness, enabling them to operate effectively in an unpredictable chemical, mechanical, and immune-responsive setting. By 2050, the number of aortic valve replacements (AVR) per year is projected to reach a staggering 850,000 [1]. They are however still prone to structural valve degeneration (SVD), irreversible changes that usually begin 7–8 years after valve implantation which involves calcification, leaflet tear, or pannus formation eventually manifesting as valve stenosis or regurgitation [2–4]. Bioprosthetic valve stenosis is defined by a gradual rise in transvalvular velocity and pressure gradient together with abnormally thickened or calcified leaflets [5].

Acute coronary syndrome (ACS) categorizes a spectrum of cardiovascular conditions encompassing ST-elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina, often caused by sudden, reduced blood flow to the heart [6]. In some cases, individuals with AV stenosis can show ACS-like symptoms without obstructed coronary arteries, as reported in medical literature [7, 8]. In this case report, we present the clinical manifestations of a bioprosthetic aortic valve (BAV) stenosis that is not often reported, in a 67-year-old woman initially presenting with ACS 9 years post-surgical aortic valve replacement (SAVR). We will also briefly discuss the diagnostic approach and treatment strategies based on existing guidelines and literature for such conditions and the pathophysiological mechanisms of SVD.

Case summary

Presenting complaint. Our patient was a 67-year-old woman who presented to the cardiology intensive care unit due to a first episode of chest pain at rest and shortness of breath during light exercises.

History of presenting illness. The patient reported experiencing chest pain with shortness of breath during light exercises about two weeks ago. She also complains of heart palpitations and occasionally almost losing consciousness. She was regularly taking angiotensin II receptor blockers (ARB), betablockers, anticoagulants and calcium channel blockers.

Past medical history. Our patient presented with a complex medical background (Fig. 1).

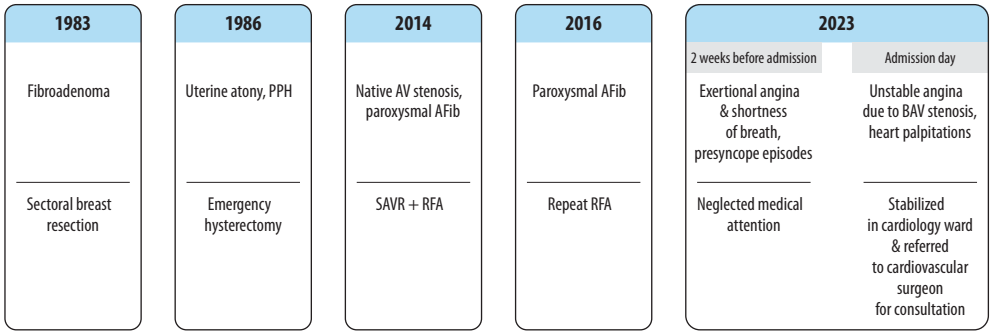

Fig. 1. Medical background of the patient. The figure outlines the chronological sequence of events and the associated clinical interventions in the patient's medical history

In 1983, the patient underwent a sectoral resection of the right breast for fibroadenoma and in 1986, a hysterectomy for postpartum hemorrhage due to uterine atony. In 2014, she had been diagnosed with mild aortic stenosis along with paroxysmal atrial fibrillation. SAVR was performed and a bovine pericardial valve (Uniline-A-21) was opted. Left atrial appendage ligation was carried out to reduce the risk of stroke along with bipolar radio frequency ablation (RFA) of the pulmonary vein orifices.

In 2016, underwent a repeat RFA of the right atrial appendage, venous collector, right superior and right inferior pulmonary veins orifices due to persistent arrythmia despite her being on anti-arrhythmic medication. The patient also had a history of hypertension, with a peak of 200/100 mmHg on some occasions.

Physical examination. Physical examination results showed no signs of cyanosis and edema, body mass index was 25.9, blood pressure was 115/72 mmHg. Heart rate was 70 bpm, rhythm was regular, a systolic ejection murmur was heard at the right upper sternal border. Lung auscultation revealed normal vesicular sounds without any abnormal sounds. Physical examination of other body systems showed no abnormalities.

Investigations. Tests for cardiac biomarkers revealed elevated troponin levels on repeated testing 12 hours apart and elevated total creatine phosphokinase (CPK), CPK-MB and lactate dehydrogenase (LDH) levels. Glucose and lactate levels were also elevated. Other laboratory parameter findings were insignificant (Table 1). Echocardiogram showed a sinus rhythm of 68 bpm. ST depression of 1 mm was present at the II, III, V4, V5 and V6 leads. A single supraventricular extrasystole wave was noted. Fraction of inspired oxygen (FIO_2) — 21 %; oxygen saturation (SpO_2) — 97 %.

Table 1

Laboratory analysis results

Parameters	Normal range	Result
Glucose, mmol/L	3,89–5,90	7,25
Lactate, mmol/L	0,3–1,5	2,3
Urea, mmol/L	2,5–8,3	5,8
Creatinine, μmol/L	58,0–96,0	82,4
Glomerular filtration rate, ml/min/1,73 m^2	68–123	67
Troponin I, ng/ml	0,00–0,04	0,22 (0,27)*
Total CPK, IU/L	0–145	174
CPK-MB, IU/L	0,25	24,6
LDH, IU/L	0–248	466,2
Aspartate aminotransferase, IU/L	11–36	23,0
Alanine aminotransferase, IU/L	10–37	14,9
Total bilirubin, μmol/L	5–21	10,0
Direct bilirubin, μmol/L	0,0–3,4	2,2
Indirect bilirubin, μmol/L	75 % of total	7,8
Total protein, g/L	65–83	63,1
Triglyceride, mmol/L	0,0–1,7	0,91
Cholesterol, mmol/L	0,0–5,2	5,07
Low-density lipoprotein, mmol/L	1,0–4,1	3,15
High-density lipoprotein, mmol/L	1,03–1,75	1,77

End of table 1

Parameters	Normal range	Result
Ionized Ca^{2+}, mmol/L	1,13–1,32	1,14
Potassium, mmol/L	3,5–5,1	3,5
Sodium, mmol/L	135–145	136
pO_2, mmHg	24–40	30
pCO_2, mmHg	41–51	48
tCO_2A, mmol/L	27–33	30,6
Blood pH	7,35–7,45	7,39
Hemoglobin, g/L	135–180	139
Hematocrit, %	41–53	42
International normalized ratio	0,87–1,15	1,18
Activated partial thromboplastin clotting time, sec	25–36	29,7
Prothrombin time, sec	9,4–12,5	12,9

Notes: laboratory tests showed elevated troponin, total CPK, CPK-MB, and LDH levels; glucose and lactate levels were also elevated; pO_2 — partial pressure of oxygen; pCO_2 — partial pressure of carbon dioxide; tCO_2 — total carbon dioxide; pH — potential of hydrogen (*lat*. pondus Hydrogenii); * repeat troponin test.

Transthoracic echocardiogram (TTE) results revealed normal local myocardium contractions. The bioprosthetic aortic valve implanted 9 years ago was heavily calcified and stenotic, aortic cusps mobility was limited, PG_{max} — 75 mmHg, PG_{mean} — 32 mmHg*, a dilated ascending aorta was also noted. Aortic wall thickening and mitral valve cusps thickening was also observed. The left atrium was enlarged, asymmetrical hypertrophy of the left ventricular (LV) wall was present along with a mild pulmonary hypertension (Table 2). Diagnostic coronary angiography was put on hold due to absence of absolute indication for it and the relative stability of the patient's condition. Chest computer tomography was unremarkable.

Table 2

Dynamics of patient's TTE parameters from 2014 to 2023

Parameters	2014			2016 (repeat RFA)	2023
	Pre-SAVR & RFA	Post-SAVR & RFA	13 days post-SAVR & RFA		
LV:					
LVEF, %	75	64	62	65	58
internal dimension at end-diastole, cm	5,2	5,3	4,8	4,4	4,5

* PG — pressure gradient.

End of table 2

Parameters	2014			2016 (repeat RFA)	2023
	Pre-SAVR & RFA	Post-SAVR & RFA	13 days post-SAVR & RFA		
internal dimension at end-systole, cm	2,9	3,3	3,2	2,8	2,7
end-diastole volume, ml	130	135	108	110	78
end-systole volume, ml	32	44	41	45	33
posterior wall thickness, cm	1,3	—	1,2	—	1,1
systolic discharge, ml	98	91	67	75	45
mass, g	278	—	219	—	—
LA:					
dimension, cm	3,8	—	3,4	3,2	4,3
volume, ml	—	—	55	—	64
volume, ml/m^2	—	—	—	70,0	41,0
Right ventricle dimension, cm	1,7	—	2,0	—	3,0
Right atrium dimension, cm	4,1×4,6	5,4×4,3	4,4×5,1	—	—
Interventricular septum diameter, cm	1,3	—	1,2	—	1,2–1,5
Ascending aorta diameter, cm	3,9	—	3,5	2,7	3,5
Pulmonary artery systolic pressure, mmHg	10	28	10	—	34

Notes: TTE results pre- and post-surgical procedures over the years; BAV performance from 2014 to 2016 was unremarkable; routine TTE screenings could have benefited the patient during the period from 2016 to 2023 by early detection of valve dysfunction as BAV stenosis advanced; LVEF — left ventricular ejection fraction; LA — left atrium.

Diagnosis. Provisional diagnosis upon admission was ACS due to unstable angina and elevated cardiac biomarkers. After considering for TTE findings, a final diagnosis of bioprosthetic aortic valve stenosis causing symptomatic chronic heart failure with preserved ejection fraction was made. The patient was subsequently placed in a cardiology ward for further observation. Patient was discharged after 4 days from the hospital in a stable condition and was given a diet recommendation and a medical prescription of ARB, betablockers, statins, anticoagulants and proton pump inhibitors. She was referred to a cardiovascular surgeon for further consultation.

Discussion

Chest pain with shortness of breath during light exercises and several episodes of near syncope in the patient occurred likely due to supply-demand shortage to the coronary and cranial vasculature because of BAV stenosis. Her first episode of angina at rest could have been provoked by supraventricular tachycardia, as she made mention of heart palpitations. Echocardiogram also revealed a single supraventricular extrasystole wave. Heart palpitations are likely a result of electrophysiological remodeling due to LA dilation. Myocardial hypertrophy is also a factor than can exacerbate the supply-demand disproportion, leading to possible subendocardial ischemia of the inferior and lateral wall. In comparison with the patient's past TTE results, a significant decrease was also noted in LVEF and LV stroke volume across the years, reflecting the hemodynamic compromise associated with the BAV stenosis.

Patients suffering from aortic stenosis are known to usually remain asymptomatic for many years [9]. The onset of heart failure is preceded by structural and functional alterations in the heart muscle with left ventricular hypertrophy followed by degeneration and death of cardiac myocytes [10]. Left ventricular hypertrophy is known to also reduces coronary flow reserve in aortic stenosis, a functional index of the severity of coronary artery insufficiency. Low coronary perfusion pressure, decreased capillary density, increased intramyocardial systolic pressure, delayed myocardial relaxation, and decreased diastolic perfusion time are the main causes of this reduction in coronary flow reserve. Increased LV diastolic filling pressure also results in decreased perfusion, especially in the subendocardial layer [7]. Previous studies in native stenotic aortic valve revealed elevated troponin levels [7, 8]. In our patient with BAV stenosis, this discovery reveals a consistent pattern indicating the progression from cardiomyocyte ischemia to myocardial cell death, accompanied by the release of cardiac troponins.

In accordance with American College of Cardiology/American Heart Association guidelines for the management of patients with valvular heart disease, patients with bioprosthetic valve replacements should undergo TTE at 5- and 10-years post-implantation and annually thereafter, regardless of their clinical condition, to monitor for valve dysfunction (increase in mean gradient of $\geqslant$10 mmHg or worsening of valve regurgitation). Early and more frequent TTE screening may be necessary for high-risk patients. Risk factors for accelerated valve deterioration include age at implantation <60, smoking, diabetes, chronic kidney disease, initial mean gradient $\geqslant$15 mmHg, and valve type. 3D transesophageal echocardiography or 4D computer tomography imaging can also be useful to rule out leaflet thrombosis. Repeat SAVR is recommended for low-surgical-risk patients with symptomatic severe bioprosthetic valve stenosis, while high-risk patients may undergo transcatheter Valve-in-Valve (ViV) procedures [5].

A 2018 review utilizing the Valve-in-Valve International Data framework introduced a methodology for standardizing the definition of SVD and establishing guidelines for the precise timing of clinical and TTE imaging follow-up evaluations

based on valve condition rather than patient clinical status (Fig. 2) [4]. This stringent criterion for managing SVD has the potential to elevate the quality of clinical care and improve the interpretation of durability analyses in upcoming research endeavors.

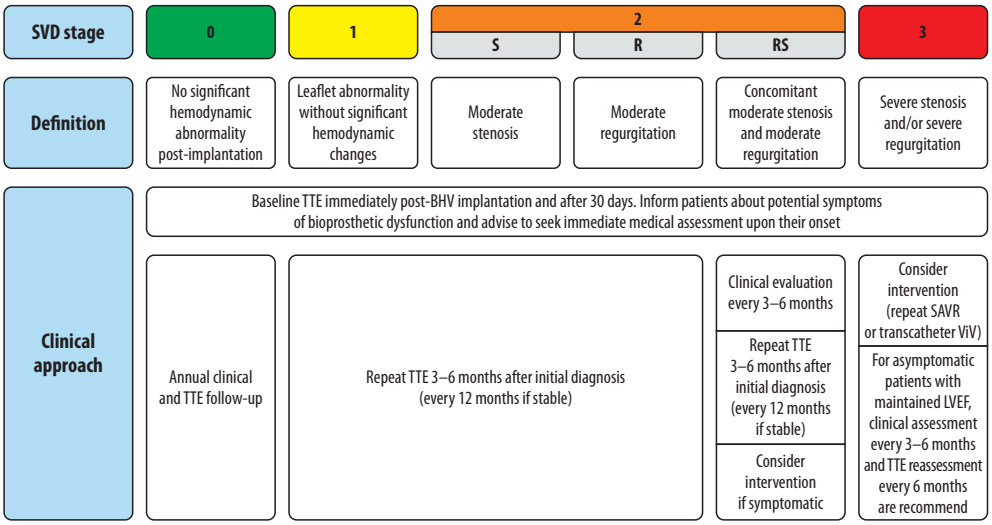

Fig. 2. Clinical approach to various stages of SVD. Staging of SVD based on mean pressure gradient (PG_{mean}) and peak velocity (Stage 0 & Stage 1 — PG_{mean} < 20 mmHg, peak velocity <3 m/s; Stage 2 — PG_{mean} = 20–40 mmHg, peak velocity 3–4 m/s; Stage 3 — PG_{mean} > 40 mmHg, peak velocity >4 m/s). Adapted from [4]

Mechanisms and etiology of SVD. A leading manifestation of SVDs is the presence of calcification, which was observed in our patient in the form of a calcified stenotic BAV. This process consists of 2 stages. The initiation stage starts with the influx of Ca^{2+} due to an increase in cell permeability. The propagation stage is influenced by changes in calcium and phosphorus metabolism and involves the growth of calcium enriched crystals in nucleation sites formed in the initiation stage [11]. BHV dysfunction due to calcification is a multifactorial process that can be classified into chemical, mechanical and immunological factors [11].

Chemical. The process of Glut fixation, a critical preparatory step before BHV implantation, has been demonstrated to increase the susceptibility of xenografts to calcification. While this fixation method diminishes tissue immunogenicity and enhances graft tissue durability through collagen cross-linking (primarily Type I collagen in xenografts) via Schiff base formation, any remaining aldehydes on the graft surface may serve as nucleation sites for calcification [11].

Calcium phosphate crystals tend to precipitate in the interstitial spaces between collagen fibers, which are normally protected from calcification by proteoglycans. Proteoglycans within BHV tissues itself could not be cross-linked by Glut, caus-

ing it to eventually degrade over time and hence unmasking calcification-prone areas that facilitate mineralization (D. T. Simionescu (2004) and J. J. Lovekamp et al. (2006), as cited in [2]). Glut also induces cell death, which causes cessation of ionic pumps leading to influx of Ca^{2+} ions into the cells [12]. These calcium ions can accumulate on sites rich in organic phosphates (cell membranes and organelles) and bind to acidic phospholipids, calcium-binding proteins, and inorganic phosphates intracellularly, creating a favorable environment for the nucleation of calcium phosphate crystals [2].

Mechanical. Pericardial BHV's are more prone to mechanical degradation due to their lack of structures present in native heart leaflets (fibrosa, spongiosa, and ventricularis) which allow for load damping, high elasticity, and a nonlinear response to stress [13]. Their decreased ability to absorb strain energy means that mechanical pressure on them is increased which speeds up the delamination and destruction of fibrous components. Damaged collagen and elastin fibers could then serve as sites for Ca^{2+} deposition [2]. This results in a vicious cycle, since leaflet or valve calcification and BHV stenosis affect hemodynamic flow, resulting in further aggravation of mechanical stresses followed by calcification [2, 11]. It was further verified by computer simulation that calcification began near the BHV leaflet margins where mechanical stress was at its highest [14].

Inflammatory. The relationship between patient age and immune response intensity is well-established. Consequently, elevated valve calcification and a stronger immune response in younger patients can hinder BHV from achieving their average typical lifespan of 15 years [15]. The European Society of Cardiology and American Heart Association guidelines hence recommends mechanical valves for aortic valve replacements in patients under 60 years old and 50 years old, respectively [16].

Alpha-gal carbohydrates unique to animal tissues, are present as epitopes on decellularized xenograft tissues. These epitopes can stimulate the production of anti-gal antibodies post-xenotransplantation [17]. Decellularized bovine pericardium treated with alpha-galactosidase showed lower levels of calcification due to the removal of alpha-gal epitopes, compared to normal Glut-fixed pericardium which showed higher levels of calcium [18].

Red blood cells were found in cavities of explanted BHVs in areas of tissue loosening and delamination due to the influence of blood pressure and constant mechanical stresses [2]. After the degradation of red blood cells, its fragments along with oxidized extracellular matrixes can serve as nucleation sites for calcification [2].

This case study would have been enhanced by the inclusion of a coronary angiography study to definitively eliminate the possibility of significant atherosclerotic plaques as the primary underlying cause of ACS. Moreover, additional details regarding the patient's clinical status and hemodynamic data on valve performance following a repeated SAVR or transcatheter ViV procedure, if chosen, would have improved the report. Examination of the explanted valve from the patient would have provided valuable insights into the degree of valve stenosis.

Further research is imperative in large-scale cohort studies to meticulously monitor SVD across various bioprosthetic valve types within diverse risk and age group cohorts. The advancement and deployment of a universally endorsed SVD stage classification system will significantly enhance the diagnostic and treatment paradigms for SVD management on a global scale.

Conclusion

This case report underscores the critical significance of meticulous valve type selection tailored to distinct risk and age categories in the context of aortic valve replacements surgery. In addition, adhering to recommended guidelines for routine TTE post-valve implantation serves as a vital cornerstone in proactively surveilling for potential valve dysfunction, irrespective of the patient's clinical status. Furthermore, the early detection capabilities of TTE in patients presenting with ACS and a prior history of BAV implantation are instrumental in shaping appropriate treatment strategies and avoiding inaccurate medical care.

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