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Review article

Current recommendations in the treatment of aortic stenosis: (T)AVR in focus

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Summary According to US data, one-third of all patients with aortic stenosis have severe aortic stenosis, as well as numerous comorbidities and comedication, and transcatheter intervention is the recommended treatment modality in cases where there is a primary indication for aortic valve replacement, as an equally effective and much safer technique compared to standard surgery.

Key words aortic stenosis, heart failure, transcatheter aortic valve replacement

Aortic stenosis (AS) and modalities of treatment

The prevalence of significant aortic stenosis (moderate or severe) is known to increase with age. Two large epidemiological studies involving nearly 29,000 participants point out that the prevalence of AS ranges from a negligible 0.02% to 0.1% in persons between 18 and 44 years of age to a significant 4.6% in patients older than 75 years[1-2].

The only effective treatment modality for severe AS is valve replacement (AVR)[3]. Although they alleviate symptoms in the short term, optimal drug therapy and balloon valvuloplasty alone do not affect the prognosis and further evolution of AS[3]. According to data from the USA, one third of all patients with aortic stenosis have severe aortic stenosis, as well as numerous comorbidities and comedication[1]. Current AHA / ACC recommendations emphasize the place of TAVR as the primary modality of definitive treatment of AS or as an alternative technique to SAVR in patients in whom classical surgery is contraindicated, or operative risk is elevated (high or intermediate)[3-5]. In some developed countries, TAVR is becoming the standard (USA) and dominant (Germany) modality of definitive aortic valve management[6-7]. In high-risk patients with severe aortic stenosis and left ventricular dysfunction, comparable mortality and recovery of LV function have been reported between the two techniques, with TAVR proving to be a practical alternative for patients with severe AS and LV dysfunction who are at increased operative risk for classical surgery[5].

The most significant predictors of unfavorable TAVR outcome are poor functional capacity (estimated by a 6-minute walk test) and low mean transaortic systolic pressure gradient. The remaining significant negative predictors include lung diseases that require oxygen therapy, kidney damage, as well as ischemic brain disease with pre-existing cognitive dysfunction[8].

Assessment of the severity of aortic stenosis and recommended diagnostic-therapeutic modalities

The assessment of the severity of aortic stenosis includes the following parameters: aortic valve morphology (calcified / non calcified), mean transaortic systolic pressure gradient (low / high gradient AS), aortic valve area (AVA; severe / moderate), flow (flow; low / normal SVI). AVA is a sensitive but insufficiently specific parameter that is under subjective influences, so, according to the current recommendations, in assessing the severity of AS, besides anatomy, valvular hemodynamics (systolic pressure gradient over the aortic orifice (ΔP), maximum velocity of the jet passing through the stenotic orifice) and hemodynamic consequences (left ventricular ejection fraction, indexed systolic volume) are included (Table 1)[4]. Based on all previous said, aortic stenosis staging has been proposed (Table 1)[3,9-10].

There are four stages of AS: risk of AS, progressive AS (mild and moderate), asymptomatic and symptomatic AS[3-4,9-10]. Surgical (SAVR) or transcatheter aortic valve replacement (TAVR) is indicated primarily for stage D AS with some exceptions for stage C[4,9-10].

Aortic valve replacement (AVR) for moderate AS should be considered at the same time with cardiac surgery due to other indications (class IIA). There is no current indication for primary intervention in the treatment of moderate AS[4-5,10-12]. A study (TAVR UNLOAD) testing the premise that transcatheter aortic valve replacement (TAVR) and

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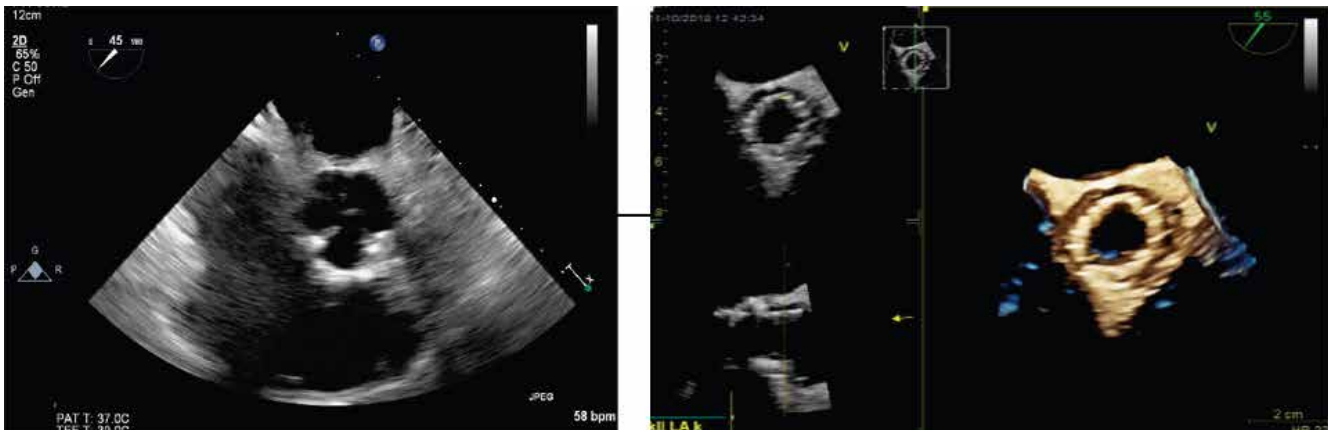
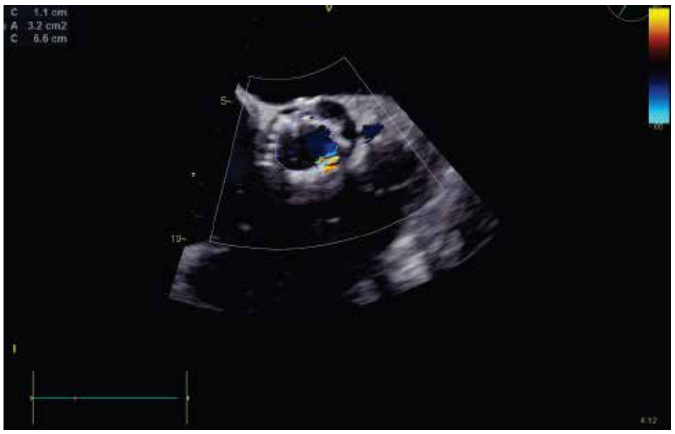
Table 1 Aortic stenosis staging (adopted from *Kanwar A, Thaden JJ, Nkomo VT. Management of Patients with Aortic Valve Stenosis. Mayo Clin Proc. 2018;93(4):488-508.*)

Stage	Definition and symptoms	Valve anatomy, valve hemodynamic and hemodynamic consequences	AVR
A	At risk of AS None symptoms	Bicuspid AV, another congenital valve anomaly, aortic valve sclerosis, aortic Vmax < 2m/s	Not recommended
B	Progessive AS None symptoms	Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or rheumatic valve changes wuth commissural fusion; **- mild** aortic Vmax 2-2,9 m/s or mean ΔP< 20 mmHg **- moderate** aortic Vmax 3-3,9 m/s or mean ΔP 20-39 mmHg LV diastolic dysfunction Normal LVEF	B2 stage (TAVR UNLOAD)
C1	Asymptomatic severe AS None symptoms	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening aortic Vmax ≥4m/s or mean ΔP≥40 mmHg AVA typically ≤ 1 cm² (AVAi ≤ 0.6 cm²/m²) **Very severe** aortic Vmax ≥5 m/s or mean ΔP≥60 mmHg LV diastolic dysfunction Mild LV hypertrophy Normal LVEF -Exertional testing for confirming symptom status	AVR should be considered in symptomatic very severe aortic stenosis
C2	Asymptomatic severe AS with left ventricular dysfunction None symptoms	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening aortic Vmax ≥4m/s or mean ΔP≥40 mmHg AVA typically ≤ 1 cm² (AVAi ≤ 0.6 cm²/m²) LVEF <50%	AVR is recommended for LVEF preservation
D1	Symptomatic severe high-gradient AS Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional presyncope or syncope	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening aortic Vmax ≥4m/s or mean ΔP≥40 mmHg AVA typically ≤ 1 cm² (AVAi ≤ 0.6 cm²/m²) but may be larger with mixed AS/AR LV diastolic dysfunction Mild LV hypertrophy Pulmonary hypertension may be present	Recommended
D2	Symptomatic severe AS(*low- flow/low- gradient*) with reduced LVEF Heart failure, angina, presyncope and syncope	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening AVA ≤ 1 cm² with resting aortic v max <4m/s or mean ΔP<40 mmHg Dobutamine stress echocardiography: AVA ≤ 1 cm² with v max ≥4m/s with any flow rate LV diastolic dysfunction Mild LV hypertrophy LVEF <50%	AVR should be considered in severe aortic stenosis (LVEF recovery even in patients with no coronary flow reserve)
D3	Symptomatic severe *low-gradient* AS with normal LVEF or paradoxical *low-flow* severe AS Heart failure, angina, presyncope and syncope	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening AVA ≤ 1 cm² with resting aortic v max <4m/s or mean ΔP<40 mmHg AVAi ≤0.6 cm²/m² SVi <35ml/m² Measured when patient is normotensive (systolic BP < 140mmHg) Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling , LVEF ≥50%	AVR should be considered in symptomatic patients with severe AS and no other reasons for symptoms

AS- aortic stenosis, AR-aortic regurgitation, AVA -aortic valve area, AVAi - aortic valve area indexed to body surface area, BP -blood pressure, HF- heart failure, LV – left ventricular, LVEF – left ventricular ejection fraction, mean ΔP- mean systolic pressure gradient over the aortic orifice
aortic v max -maximum velocity of the jet passing through the stenotic orifice





Figures 1a, 1b, 1c. Valve implantation during TAVI: positioning, partial opening and complete expansion of the valve (Nemanja Djenić, Zorica Mladenović)

optimization of heart failure therapy improves clinical outcomes compared to optimal heart failure therapy per se in patients with heart failure with reduced EF (HFrEF) and proven moderate AS is underway[12]. The previously cited study is based on the fact that the afterload reduction is the basis for the modern treatment of heart failure. Moderate AS increases afterload, and can be effectively treated by TAVR, and if study results support the implementation of TAVR in the treatment of this category of patients with AS, it may significantly facilitate the therapeutic decision considering optimal valve replacement time in patients with moderate AS.

Stage C1 implies asymptomatic severe aortic stenosis with preserved EF, and an exercise stress test is indicated in these patients as a part of the evaluation of physical exertion tolerance (Table 1). AVR is recommended in patients who have developed symptoms or blood pressure decline during a stress test (Table 1)[4-5,10-12]. Having in mind all previous said facts, the design of the EARLY TAVR study (Evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis) seems to be promised, expecting to define the role of TAVR in the treatment of patients with asymptomatic severe aortic stenosis[13]. A mechanism that explains the improvement of coronary flow reserve in patients immediately after TAVR procedures include a prompt decline in microvascular resistance and a concomitant increase in microvascular flow, leading to an increase in coronary vasodilator reserve and from the standpoint of cardiac function physiology justifying the implementation of the technique in standard treatment[14].

Stage C2 includes asymptomatic AS with LK dysfunction (Table 1). Due to LV dysfunction, the exertional testing is contraindicated[4]. AVR is recommended (class I)[4]. The HAVEC group points out asymptomatic patients with "paradoxical" LF-LG AS (stage C3?) in whom AVR should be considered if high risk of progression to symptomatic AS has been assessed based on complementary imaging methods (class IIa)[6]. Here, the importance of strain analysis as an additional diagnostic tool in the assessment of subclinical LV dysfunction should be especially emphasized[16]. Namely, deformation indices such as myocardial strains (global, longitudinal, circumferential, radial) of the left ventricle are considered to be more sensitive markers of myocardial dysfunction than the ejection fraction. This stems from the fact that the myocardial strain is a measure of the deformation of primarily subendocardial myocardial fibers, which are the first to react to ischemia and other adverse stimuli, with preserved EF.

Using strain echocardiography, LV systolic dysfunction can be early detected in patients with AS who have normal EF. In this way, reliable data for the clinical early diagnosis and treatment of LV dysfunction, as well as for monitoring the therapeutic effect of therapy are obtained[16]. Taking into account that preserved global longitudinal strain (GLS) is indicative of myocardial reserve and preserved myocardial tissue plasticity, it is not surprising that there is a clear link between increased basal strain values and increased risk of progression to symptomatic AS that implies AVR. Besides strains, the risk assessment includes the calcium score on cardiac MSCT and assessment of myocardial fibrosis extensiveness by CMR[15].

Stage D1 is a morpho-functionally symptomatic severe AS with high mean transaortic systolic pressure gradient

(ΔP) and preserved systolic LV function (Table 1). AVR is recommended (class I recommendation)[4]. Stage D2 occurs in patients with AS, often associated with coronary artery disease. Ischemic cardiomyopathy is the cause of decreased LVEF in these patients[4]. AVR should be considered in severe aortic stenosis because LVEF recovery has been observed even in patients without coronary flow reserve (IIa)[18].

In stage D1, a low-dose dobutamine stress echocardiography is recommended to assess AS severity and coronary reserve[4,17,18]. If the coronary reserve is reduced (during a low-dose dobutamine test an increase in LVEF less than 5% or an increase in SVi less than 20%), TAVR has an advantage over standard intervention, with the proviso that, according to the guidelines of European associations of cardiologists and cardiac surgeons, LVEF <20% is relative contraindication for TAVI (Figures 1a, b, c)[4,7,17,18].

Stage D3 is a symptomatic *low flow-low gradient* severe AS. The most common cause is hypertrophic LV, where indexed stroke volume is reduced despite preserved EF. At this stage, aortic valve replacement should be considered (IIa)[4]. Stage D4 includes patients with symptomatic severe AS with normal flow and low mean transaortic systolic pressure gradient. As part of the morphological evaluation of the degree of stenosis, it is indicated to complete the examination with a calcium score[4,15,18]. If severe AS is very likely (calcium score in men ≥3000 and in women ≥1600), AVR should be considered (IIa)[18].

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Sažetak

Najnovije preoporuke u lečenju aortne stenoze: (T)AVR u fokusu

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Prema podacima iz SAD, trećina svih pacijenata sa aortnom stenozom imaju tesnu aortnu stenozu, kao i brojne komorbiditete i komedikaciju, te se kao preporučen modalitet lečenja u slučajevima kada postoji primarna indikacija za zamenu aortnog zalistka nameće transkateterska intervencija, kao jednako efikasna i znatno bezbednija tehnika u poredjenju sa standardnom hirurgijom.

Ključne reči: *aortna stenoza, srčana slabost, transkateterska zamena aortnog zalistka*