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Review article

TAVI in the lights of new ESC guidelines and randomized clinical trials

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Abstract Aortic stenosis (AS) is the most common valvular disease requiring surgical (SAVR) or transcatheter intervention (TAVI) in Europe and North America. The first TAVI was performed in 2002 in order to find clinical application in a short period of time, and the initial ESC guidelines recommended this procedure in patients with a high risk of SAVR. ESC guidelines for the treatment of valvular diseases from 2021, the decision on the treatment modality of AS is defined by the Heart team, and SAVR is recommended in younger patients with a low risk of surgery (<75 years STS-PROM/EuroScore II<4%), and TAVI is recommended in elderly patients ≥75 years or in patients with high operative risk (STS-PROM/EuroScore II>8%) or in patients not suitable for surgery. On the other hand, large randomized clinical studies (The PARTNER 3, Evolut Low Risk and NOTION studies) showed that TAVI is safe even for patients with a low operative risk (STS-PROM/EuroScore II<4%) and that it is not inferior to SAVR (UK TAVI trial).

Kew words aortic stenosis, surgical aortic valve replacement (SAVR), transcatheter aortic valve intervention (TAVI)

Introduction

Aortic stenosis (AS) is the most common primary valve lesion requiring surgery (SAVR) or transcatheter intervention (TAVI) in Europe and North America[1,2]. AS prevalence rising rapidly as a consequence of the ageing population[3,4]. In patients with symptomatic severe AS there is unfavorable prognosis with survival rates of only 15–50% in 5 years[5,6]. Surgical valve replacement was the therapy of choice in patients with symptomatic AS, but the mortality after isolated surgical procedures is 1–3% in patients under 70 years, and 4–8% above 70 years[6]. In clinical practice at least 30% of patients with severe symptomatic AS was not undergo surgery for replacement of the aortic valve, due to advanced age, frequent comorbidities and frailty[7]. As an alternative of SAVR transcatheter aortic valve implantation (TAVI) was proposed and initiated in 2002[8], and achieved in short period clinical acceptance and initially ESC guidelines for valve disease recommended TAVI in high-risk surgical patients[6-8].

History facts

The first patient for TAVI (2002) was a dying patient who had all the contraindications for TAVI: he was only 57 years old; the contraction of the heart was poor with 10% ejection fraction, there was a thrombus inside in the left ventricle, and we did not have any femoral access because the arteries were occluded. We had to improvise, with a transseptal approach, coming from the femoral veins, to implant the valve. The TAVI procedure was finished successfully but four months later patient leg developed gangrene, we had to amputate it and it did not heal. So it was an extra cardiac cause of death

Evaluation of aortic stenosis

Echocardiography is key to confirming the diagnosis and severity of AS, assessing valve calcification, left ventricle (LV) function and wall thickness, detecting other valve disease or aortic pathology and providing prognostic information[9-11]. Current recommendations for evaluation of AS depend upon measurement of mean pressure gradient, peak transvalvular velocity (V_{max}) and valve area[12]. Clinical decision should take account of additional parameters: functional status, stroke volume, LV hypertrophy, LV function, ect. Low flow is arbitrary defined as stroke volume index (SVi)≤35ml/m^2

According to these four broad categories can be defined:

1. High-gradient aortic stenosis [mean gradient >_40 mmHg, peak velocity ≥4.0 m/s, valve area ≤1 cm2 (or ≤0.6 cm^2/m^2)]
2. Low-flow, low-gradient aortic stenosis with reduced ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm^2, LVEF<50%, SVi ≤35 mL/m^2).
3. Low-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg, valve area ≤1 cm^2, LVEF≥50%, SVi ≤35 mL/m^2).
4. Normal-flow, low-gradient aortic stenosis with preserved ejection fraction (mean gradient <40 mmHg,

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valve area ≤1 cm2, LVEF≥50%, SVi >35 mL/m^2). These patients usually have only moderate aortic stenosis.

Management of aortic stenosis according to the ESC guidelines 2021

Use of SAVR and TAVI as complementary treatment options have allowed a substantial increase in the overall number of patients with aortic stenosis undergoing surgical or transcatheter intervention in the past decade[13]. ESC guidelines suggested that RCTs have assessed the two modes of intervention across the spectrum of surgical risk in predominantly elderly patients and a detailed appraisal of the evidence base and it is written that these trials used surgical risk scores to govern patient selection and demonstrate that TAVI is superior to medical therapy in extreme-risk patients (197) and non-inferior to SAVR in high[15-18] and intermediate-risk patients at follow-up extending to 5 years[16-22]. The PARTNER 3 and Evolut Low Risk trials demonstrate that TAVI is non-inferior SAVR in low-risk patients at 2-year follow-up[23-27]. Rates of vascular complications, pacemaker implantation, and paravalvular regurgitation are consistently higher after TAVI, where a severe bleeding, acute kidney injury, and new-onset AF are more frequent after SAVR. Although the likelihood of paravalvular regurgitation has been reduced with newer transcatheter heart valve designs, pacemaker implantation (and new-onset left bundle branch block) may have long-term consequences[28-30] and further refinements are required. Most patients undergoing TAVI have a swift recovery, short hospital stay, and rapidly return to normal activities[30,31]. Despite these benefits, there is wide variation in worldwide access to the procedure as a result of high device costs and differing levels of health care resources[32-34].
In the summary the latest ESC guidelines form 2021. recommend that aortic valve intervention should be performed in Heart valve Centers (IC). The choice between SAVR and TAVI must be based upon careful evaluation of Heart team (IC). SAVR is recommended in younger patients with low risk for surgery (<75 years STS-PROME/EuroScore II<4%) (IB), on the other hand TAVI is recommended in older patients ≥75 years or in patients with high surgery risk (STS-PROME/EuroScore II>8%) or in patients unsuitable for surgery (IA)[1].

TAVI in clinical randomized trials

In the last fourteen yours there is 14 RCT for TAVI which include more than 9000 patients. Initially TAVI was recommended for high risk patients. From 2019 there are RCT for TAVI in low and intermediate risk patient.
The PARTNER 3[26] and Evolut Low Risk trials[27] demonstrate that TAVI is non-inferior SAVR in low-risk patients at 2-year follow-up. In the Partner 3 trial which include 71 centers, 1000 patients underwent randomization. The mean age of the patients was 73 years, and the mean Society of Thoracic Surgeons risk score was 1.9% (with scores ranging from 0 to 100% and higher scores indicating a greater risk of death within 30 days after the procedure). The Kaplan-Meier estimate of the rate of the primary composite end point at 1 year was significantly lower in the TAVI group than in the surgery group (8.5% vs. 15.1%; absolute difference, -6.6 percentage points; 95% confidence interval [CI], -10.8 to -2.5; P<0.001 for noninferiority; hazard ratio, 0.54; 95% CI, 0.37 to 0.79; P = 0.001 for superiority). At 30 days, TAVI resulted in a lower rate of stroke than surgery (P = 0.02) and in lower rates of death or stroke (P = 0.01) and new-onset atrial fibrillation (P<0.001). TAVI also resulted in a shorter index hospitalization than surgery (P<0.001) and in a lower risk of a poor treatment outcome (death or a low Kansas City Cardiomyopathy Questionnaire score) at 30 days (P<0.001). There were no significant between-group differences in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation. Among patients with severe aortic stenosis who were at low surgical risk, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than with surgery. Importantly, patients in the low-risk trials were predominantly male and relatively elderly (e.g. PARTNER 3: mean age 73.4 years, <70 years 24%, 7075 years 36%, >75 years 40%, >80 years 13%) whilst those with low-flow aortic stenosis or adverse anatomical characteristics for either procedure (including bicuspid aortic valves or complex coronary disease) were excluded.
In the Evolut Low Risk study which include 1468 patients who underwent randomization, an attempted TAVI or surgical procedure was performed in 1403. The patients' mean age was 74 years. The 24-month estimated incidence of the primary end point (death or disabling stroke at 24 months) was 5.3% in the TAVI group and 6.7% in the surgery group (difference, -1.4 percentage points; 95% Bayesian credible interval for difference, -4.9 to 2.1; posterior probability of noninferiority >0.999). At 30 days, patients who had undergone TAVI, as compared with surgery, had a lower incidence of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs 35.4%) and a higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%). At 12 months, patients in the TAVI group had lower aortic-valve gradients than those in the surgery group (8.6 mm Hg vs. 11.2 mm Hg) and larger effective orifice areas (2.3 cm2 vs. 2.0 cm2). Results of this trial suggested that patients with severe aortic stenosis who were at low surgical risk, TAVI with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the composite end point of death or disabling stroke at 24 months.
The Nordic Aortic Valve Intervention (NOTION trial)[19,24] was designed to compare transcatheter aortic valve replacement (TAVI) to surgical aortic valve replacement (SAVR) in patients 70 years or older with isolated severe aortic valve stenosis. The mean age of patients was 79.1±4.8 years and mean STS-PROM score was 3.0%±1.7%. After 5 years, there were no differences between TAVI and SAVR in the composite outcome (rate of all-cause mortality, stroke, or myocardial infarction at 1 year, p=0.86) or any of its components. TAVI patients

had larger prosthetic valve area (1.7 cm^2 vs. 1.2 cm^2, p<0.001) with a lower mean transprosthetic gradient (8.2 mm Hg vs. 13.7 mm Hg, p<0.001), both unchanged over time. More TAVI patients had moderate/severe total aortic regurgitation (8.2% vs. 0.0%, p<0.001) and a new pacemaker (43.7% vs. 8.7%, p<0.001). Four patients had prosthetic re-intervention and no difference was found for functional outcomes. NOTION trial demonstrated that ther was no statistical difference for major clinical outcomes 5 years after TAVI with a self-expanding prosthesis compared to SAVR. Higher rates of prosthetic regurgitation and pacemaker implantation were seen after TAVI.

The latest published study for TAVI in low risk patients was UK TAVI trial[35]. In this randomized clinical trial conducted at 34 UK centers, 913 patients aged 70 years or older with severe, symptomatic aortic stenosis and moderately increased operative risk due to age or comorbidity were enrolled. The primary outcome was all-cause mortality at 1 year. The primary hypothesis was that TAVI was noninferior to surgery. 913 patients randomized (median age, 81 years [IQR, 78 to 84 years]; 424 [46%] were female; median Society of Thoracic Surgeons mortality risk score, 2.6% [IQR, 2.0% to 3.4%]), 912 (99.9%) completed follow-up and were included in the noninferiority analysis. At 1 year, there were 21 deaths (4.6%) in the TAVI group and 30 deaths (6.6%) in the surgery group, with an adjusted absolute risk difference of -2.0% (1-sided 97.5% CI, -∞ to 1.2%; P < .001 for noninferiority). Of 30 prespecified secondary outcomes reported herein, 24 showed no significant difference at 1 year. TAVI was associated with significantly shorter postprocedural hospitalization (median of 3 days [IQR, 2 to 5 days] vs 8 days [IQR, 6 to 13 days] in the surgery group). At 1 year, there were significantly fewer major bleeding events after TAVI compared with surgery (7.2% vs 20.2%, respectively; adjusted hazard ratio [HR], 0.33 [95% CI, 0.24 to 0.45]) but significantly more vascular complications (10.3% vs 2.4%; adjusted HR, 4.42 [95% CI, 2.54 to 7.71]), conduction disturbances requiring pacemaker implantation (14.2% vs 7.3%; adjusted HR, 2.05 [95% CI, 1.43 to 2.94]), and mild (38.3% vs 11.7%) or moderate (2.3% vs 0.6%) aortic regurgitation (adjusted odds ratio for mild, moderate, or severe [no instance of severe reported] aortic regurgitation combined vs none, 4.89 [95% CI, 3.08 to 7.75]). This study proved that in patients aged 70 years or older with severe, symptomatic aortic stenosis and moderately increased operative risk, TAVI was noninferior to surgery with respect to all-cause mortality at 1 year.

There is some new potential indication fields for TAVI as it is asymptomatic severe aortic stenosis (RECOVERY, AVATAR, ENVOLVED and EARLY TAVR trials) and moderate AS "at risk" (UNLOAD, PROGRESS, EXPAND TAVR II trials).

TAVI in the Republic of Serbia

From 2014-2022 year in Republic of Serbia 245 TAVI procedures was performed. The first results of TAVI procedures in Serbia was published 2016[5] shown that all interventions were successfully performed without significant periprocedural complications. Immediate hemodynamic improvement was obtained in all the patients (peak gradient 94.2 ± 27.6 to 17.6 ± 5.2 mmHg, p < 0.001, mean pressure gradient 52.8 ± 14.5 to 8.0 ± 2.1 mmHg, p < 0.001). None of the patients developed heart block, stroke, vascular complication or significant aortic regurgitation. After 6months, the survival was 100% with New York Heart Association (NYHA) functional improvement in all the patients[5]. This resulta are encouraging, but new research is necessary considering that in 2022, 174 TAVIs were performed.

Conclusion

Aortic stenosis is a heterogeneous condition and selection of the most appropriate mode of intervention should be carefully considered by the HeartTeam for all patients, accounting for individual age and estimated life expectancy, comorbidities (including frailty and overall quality of life), anatomical and procedural characteristics, the relative risks of SAVR and TAVI and their long-term outcomes, prosthetic heart valve durability, feasibility of transfemoral TAVI, and local experience and outcome data.

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Sažetak

TAVI u svetlu novih ESC preporuka i randomizovanih kliničkih studija

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Aortna stenoza (AS) je najčešće valvularno oboljenja koje zahteva hirurško (SAVR) ili transkatetersku intervenciju (TAVI) u Evropi i Severnoj Americi. Prva TAVI urađena je 2002.godine da bi u kratkom vremenskom periodu našla kliničku primenu, a inicijalne ESC preporuke su ovu proceduru preporučivale kod pacijenata sa visokim rizikom za SAVR. ESC preporuke za lečenje valvularnih mana iz 2021.godine odluku o modalitetu lečenja AS definiše Heart team, a SAVR se preporučuje kod mlađih pacijenata sa niskim rizikom od operacije (<75 godina STS-PROM/EuroScore II<4%), a TAVI se preporučuje kod starijih pacijenata ≥75 godina ili kod pacijenata sa visokim operativnim rizikom (STS-PROM/EuroScore II>8%) ili kod pacijenata koji nisu pogodni za operaciju. Sa druge strane velike randomizovane kliničke studije (The PARTNER 3, Evolut Low Risk and NOTION studije) pokazale su da je TAVI bezbedna i za pacijente sa niskim operativnim rizikom (STS-PROM/EuroScore II<4%) i da je ne inferiona u odnosu na SAVR (UK TAVI trial).

Ključne reči: *aortna stenoza, hirurška zamena aortne valvule (SAVR), transkateterska zamena aortne valvule (TAVI)*