Almanah 2014.: bolesti aortnog zalistka

Almanac 2014: Aortic Valve Disease

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SAŽETAK: Tijekom zadnjih nekoliko godina došlo je do značajnog napretka u dijagnosticiranju bolesti aortnog zalistka i u našem razumijevanju patofiziologije te bolesti, a transkateterska implantacija aortnog zalistka preobrazila je njezino kliničko liječenje. Ovaj članak sažeto prikazuje nova istraživanja o bolestima aortnog zalistka objavljena u časopisu *Heart* u 2013. i 2014. godini u kontekstu drugih velikih istraživanja objavljenih u općim medicinskim časopisima, uz raspravu o mogućem utjecaju tih, novih otkrića na klinički pristup liječenju odraslih pacijenata s bolesti aortnog zalistka.

SUMMARY: The past few years have seen major advances in the diagnosis of aortic valve disease and in our understanding of the pathophysiology of disease. In addition, transcatheter aortic valve implantation has transformed our clinical management options. This article summarises new aortic valve disease research published in Heart in 2013 and 2014, within the context of other major studies published in general medical journals, including a discussion of the potential impact of these new research findings on the clinical approach to management of adults with aortic valve disease.

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Nove smjernice o bolestima zalistaka iz 2014. koje su objavili *American Heart Association i American College of Cardiology* u skladu su s osnovnim principima izloženima u smjernicama Europskog kardiološkog društva iz 2012. godine, no uvode nekoliko novih pojmova.[1,2] Nove smjernice ističu važnost centara izvrsnosti za liječenje bolesti srčanih zalistaka s multidisciplinarnim ordinacijama za liječenje bolesti zalistaka[3] kako bi se integrirale klinička, slikovna, intervencijska i kirurška stručnost koje su potrebne za optimalnu njegu ovakvih pacijenata. Usto, pojam stupnja bolesti zalistka sada ima središnju ulogu u dijagnozi i liječenju. Svaki stupanj bolesti zalistka određen je simptomima, anatomijom i hemodinamskim promjenama na zalistku te promjenama u lijevoj klijetki (LV). Postoje četiri stupnja:

- **stupanj A:** postoji rizik za bolesti zalistka, primjerice pacijenti s aortnom sklerozom ili bikuspidnim aortnim zalistkom

The new 2014 American Heart Association/American College of Cardiology valve guidelines remain congruent with the basic principles put forth in the 2012 European Society of Cardiology document and go on to introduce several new concepts.[1,2] These guidelines emphasise the importance of centres of excellence in valvular heartdisease with multidisciplinary Heart Valve Clinics[3] to integrate the clinical, imaging, interventional and surgical expertise needed for optimal care of these patients. In addition, the concept of valve disease stages now is central to diagnosis and management. Each valve stage is defined by patient symptoms, valve anatomy, valve haemodynamics and LV changes. The four stages are:

- **Stage A:** At risk for valve disease, for example, patients with aortic sclerosis or a bicuspid aortic valve.
- **Stage B:** Progressive valve disease, equivalent to mild-to-moderate aortic stenosis (AS).

- **stupanj B:** progresivna bolest zalistka ekvivalentna aortnoj stenozi (AS) blagog do umjerenog stupnja
- **stupanj C:** teška asimptomatska bolest zalistka definirana anatomskim i hemodinamskim promjenama zalistka, s podvrstama za normalnu ili abnormalnu funkciju LV
- **stupanj D:** teška simptomatska AS, uključujući i podvrste za tešku aortnu stenozu niskog gradijenta i niskog protoka s niskom ili normalnom ejekcijskom frakcijom LV.

Važne promjene u ovim smjernicama jesu i:

1. integrirani pristup procjeni rizika prije kirurškog ili transkateterskog zahvata;
2. mogućnost ranije intervencije u odraslih s asimptomatskom vrlo teškom AS, definirano kao brzina protoka nad aortnim zalistkom od 5 m/s ili više.[4]

BIKUSPIDNA BOLEST AORTNOG ZALISTKA

Kongenitalni bikuspidni aortni zalisak pojavljuje se u oko 1% populacije, a gotovo svi ti pacijenti trebaju kirurški zahvat na srcu, bilo zbog aortne regurgitacije u mladosti bilo kasnije tijekom života zbog AS-a. Većina pacijenata s bikuspidnim aortnim zaliskom također imaju veće dimenzije sinusa aorte i uzlazne aorte nego ostali. Također ova skupina pacijenata ima rizik od progresivne dilatacije aorte i povećani rizik za disekciju aorte. No još uvijek ne znamo kako odrediti koji pacijenti imaju najveći rizik za progresivnu aortnu bolest te stoga trebaju češće ponavljanje slikovne dijagnostike. U studiji slučajeva i kontrola s 43 pacijenta sukladnih po dobi i spolu, u pacijenata s bikuspidnom bolesti aortnog zalistka nađeni su dokazi disfunkcije endotela i pojave upalnih biomarkera, pri čemu je razmjer tih abnormalnosti bio sukladan s disfunkcijom zalistka, no ne i s progresivnom dilatacijom aorte.[5] Retrospektivna multicentrična studija potvrdila je da je dilatacija aorte prisutna u 87% pacijenata s bikuspidnim aortnim zaliskom (n = 353), pri čemu je dilatacija sinusa bila češća u slučajevima stapanja desnog s lijevim koronarnim kuspisom, dok uzlazna dilatacija nije ovisila o morfologiji zalistka (**slika 1**). Brzina dilatacije nije ovisila o početnom promjeru aorte i morfologiji zalistka, a 43% pacijenata s bikuspidnom bolesti aortnog zalistka nije doživjelo znatnu promjenu veličine aorte tijekom prosječnoga vremena praćenja od 3,6 ± 1,2 godine.[6]

U kohortnoj studiji u jednoj ustanovi s pacijentima koji su imali disekciju aorte, oni s bikuspidnim zalistkom (47 pacijenata prema 53 s trolisnim zalistkom) bili su gotovo za desetljeće mlađi te su češće imali podatak o dilataciji aorte (49% prema 17%, p = 0,001) ili prethodno implantirani aortni zalistak (AVR; 23% prema 6%, p = 0,02).[7] Promjer aorte bio je veći u pacijenata s bikuspidnim aortnim zalistkom (66 ± 15 prema 56 ± 11 mm, p = 0,0004), no klinička je slika bila ista. Ove dvije studije upućuju na potrebu za pažljivom procjenom aorte i primjerenim redovitim procjenama u odraslih pacijenata s bikuspidnim aortnim zaliskom te na važnost obrazovanja pacijenata o znakovima disekcije aorte. Također treba razmotriti i probir bliske rodbine pacijenata s bikuspidnim aortnim zalistkom i dilacijom aorte, jer je u nekim obiteljima prisutan nasljedni oblik te bolesti.

- **Stage C:** Severe asymptomatic valve disease, defined by valve anatomy and haemodynamics, with subdivisions for normal or abnormal LV function.
- **Stage D:** Severe symptomatic AS, including subsets for low-gradient low-flow severe AS with a low or normal LVEF.

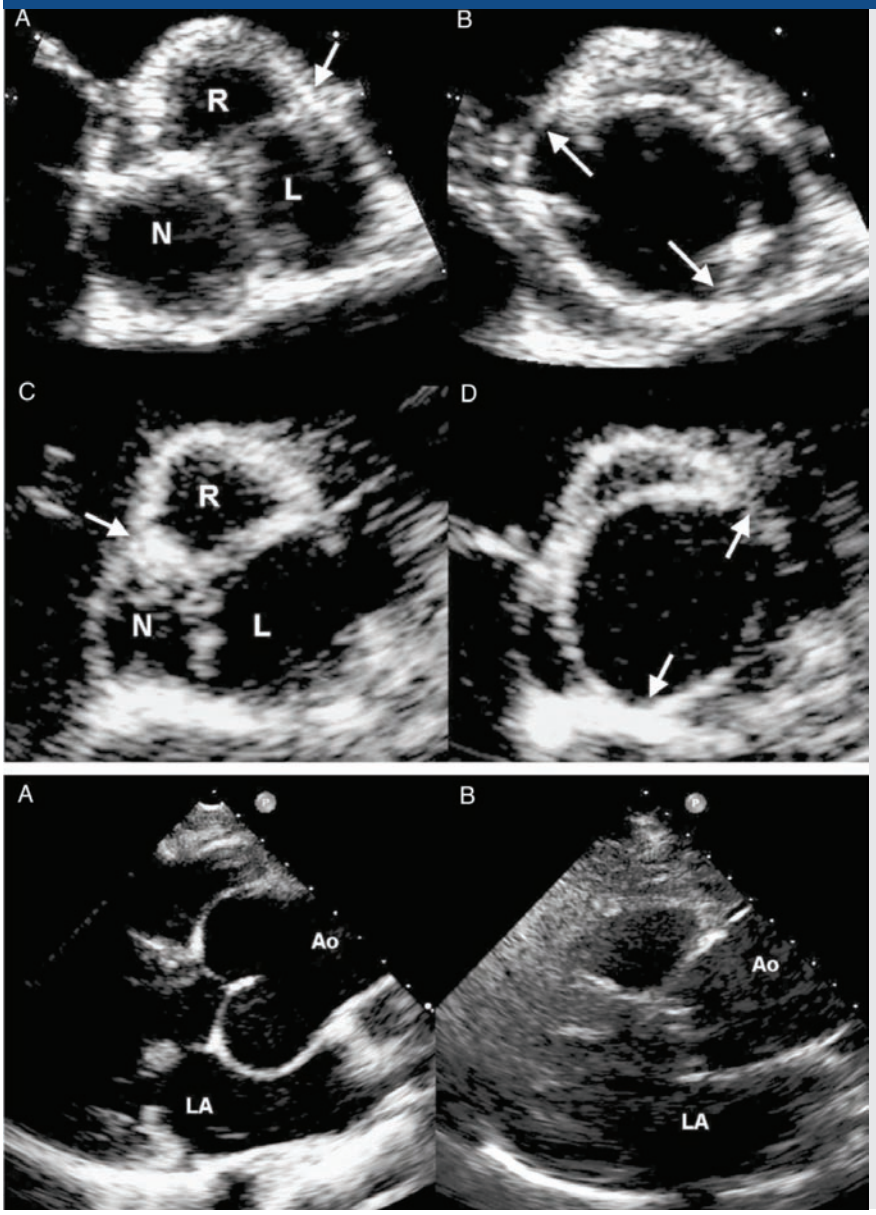
Other important changes in these guidelines are (**1**) an integrated approach to risk assessment before surgery or transcatheter interventions and (**2**) consideration of earlier intervention in adults with asymptomatic very severe AS, defined as an aortic velocity of 5 m/s or higher.[4]

BICUSPID AORTIC VALVE DISEASE

A congenitally bicuspid aortic valve is present in about 1% of the population with nearly all of these patients eventually requiring valve surgery either for aortic regurgitation as young adults or for AS later in life. Most patients with a bicuspid aortic valve also have aortic sinus and ascending aortic dimensions larger than the normal population. In addition, a subset of bicuspid aortic valve patients is at risk of progressive aortic dilation and has an increased risk of aortic dissection. However, we do not know how to identify which patients are at risk for progressive aortic disease and thus require more frequent imaging. In a case control study of 43 patients, matched for age and gender, bicuspid valve patients had evidence for endothelial dysfunction and inflammatory biomarkers with the severity of these abnormalities correlating with valve dysfunction but not with progressive aortic dilation.[5] A retrospective multicentre study confirmed that aortic dilation was present in 87% of bicuspid valve patients (n=353), with sinus dilation more typical with right–left coronary cusp fusion but ascending dilation independent of valve morphology (**Figure 1**). The rate of aortic dilation was not related to baseline aortic diameter or valve morphology and 43% of bicuspid valve patients had no significant change in aortic size over a mean follow-up of 3.6±1.2 years.[6]

In a single centre cohort of patients who present with an aortic dissection, those with a bicuspid valve (47 patients compared with 53 with a trileaflet valve) were almost a decade younger and more often had a history of aortic dilation (49% vs 17%, p=0.001) or previous aortic valve replacement (AVR; 23% vs 6%, p=0.02).[7] Aortic diameter was larger in bicuspid valve patients (66±15 vs 56±11 mm, p=0.0004) but the clinical presentation was otherwise similar.Taken together, these studies underline the need for careful evaluation of the aorta and appropriate periodic evaluation in adults with a bicuspid aortic valve, as well as the importance of educating patients about symptoms of aortic dissection. In addition, screening first degree relatives of patients with a bicuspid valve and dilated aorta should be considered because some families have an inherited form of this condition.

FIGURE 1.



(A) *Basic morphologies of bicuspid aortic valve (BAV).* Panel A shows a typical BAV in diastole with a small raphe (arrow) between the right (R) and left (L) coronary cusps. In systole (panel B), commissures are located at 10 and 4 oíclock (arrows). Panel C depicts an atypical BAV in diastole with a prominent raphe (arrow) between the right (R) and non-coronary (N) cusps. In systole (panel D), commissures are located at 1 and 7 o'clock (arrows).

(B) *Aortic dilatation phenotypes.* Panel A depicts a patient with Marfan syndrome and predominant dilatation of the sinuses of Valsalva. Panel B depicts a patient with BAV and predominant dilatation of the tubular ascending aorta. LA, left atrium; Ao, ascending aorta.[6]

KALCIFICIRAJUĆA BOLEST AORTNOG ZALISTKA

PREVALENCIJA

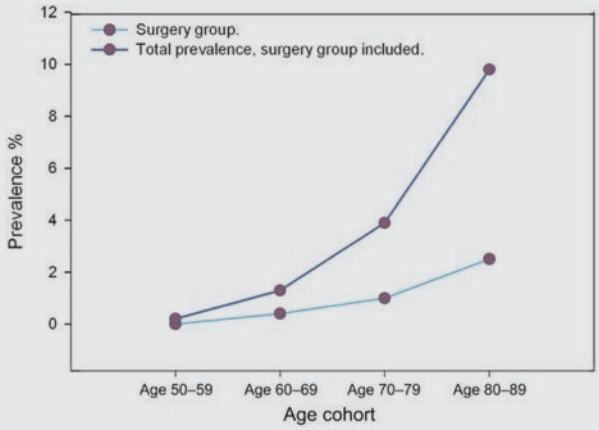
Prevalencija kalcificirajuće bolesti aortnog zaliska raste s pacijentovom životnom dobi. Blage promjene, odnosno aortoskleroza (stupanj A bolesti) prisutne su u oko 25% ljudi starijih od 65 godina te su biljeg neželjenih kardiovaskularnih zbivanja uz popratni, 50% viši rizik od smrti tijekom petogodišnjeg razdoblja, čak i u odsutnosti opstrukcije zalistka.[8] To je potvrđeno u Heinz Nixdorf studiji kod 3944 pacijenta. Prisutnost opsežnijih kalcifikacija (zbroj kalcifikacija aortnog zalistka u 3. tercili) povezan je s većom učestalosti koronarnih (HR 2,11, 95% CI 1,28 – 3,81) i kardiovaskularnih zbivanja (HR 1,67, 95% CI 1,08 – 2,58), čak i nakon što se uzmu u obzir drugi čimbenici rizika prema

CALCIFIC AORTIC VALVE DISEASE

PREVALENCE

The prevalence of calcific aortic valve disease increases with age. Mild changes, termed aortic sclerosis (Stage A disease) are present in about 25% of all adults over 65 years of age and are a marker for adverse cardiovascular events with about a 50% increased risk of mortality over 5 years even in the absence of valve obstruction.[8] These findings were confirmed in a study of 3944 subjects in the Heinz Nixdorf study. Aortic valve calcification scores in the third tertile were associated with a higher incidence of coronary (HR 2.11, 95% CI 1.28 to 3.81) and cardiovascular events (HR 1.67, 95% CI 1.08 to 2.58), even after adjustment for Framingham risk factors.[9] Although valve calcification did not provide additive predictive

FIGURE 2.



Prevalence of aortic stenosis. **The figure shows weighted mean values in the combined survey of Tromsø 4, 5 and 6, with hospital data included. The surgery group is included in the main group.[10]**

Framinghamskoj ljestvici rizika.[9] Iako kalcifikacije zalistka nisu imale dodatnu prediktivnu vrijednost nad zbrojem koronarnog kalcija u tom istraživanju, u kliničkoj praksi oslikavanje ehokardiografijom izbjegava ionizirajuće zračenje i dostupnije je od kompjutorizirane tomografije. Stoga ostaje nejasno bi li ehokardiografski nalaz aortoskleroze trebalo pribrojiti modelima za procjenu kardiovaskularnog rizika.

U populacijskoj Tromsø studiji s uključena 3273 ispitanika, teška kalcificirajuća bolest bila je prisutna u njih 164, uz jasno povećanje zastupljenosti opstrukcije zalistka sa životnom dobi (**slika 2**). U starijih od 50 godina godišnja incidencija AS-a bila je 4,9%, s prosječnim godišnjim porastom transvalvularnog aortnog gradijenta od 3,2 mm Hg.[10] U onih pacijenata koji su bili liječeni zamjenom zalistka zbog teške simptomatske bolesti ishodi su bili slični onima u pacijenata s AS-om i u općoj populaciji.

GENETIKA

Iako se fenotip kalcificirajuće bolesti aortnog zalistka obično pojavljuje kasno u životu, sve je više dokaza da postoji genska predispozicija za tu bolest. U studiji genomske analize povezanosti kod 6942 ispitanika pojedinačni je nukleotidni polimorfizam (SNP) u lokusu za lipoprotein (a) (Lp(a)) bio povezan s prisutnošću kalcifikacija aortnog zalistka utvrđenih kompjutoriziranom tomografijom.[11] Genski određena vrijednost serumskog Lp(a) također je bila povezana s većom učestalosti AS-a i s AVR-om.[11] U drugoj studiji, koja je u dizajnu primjenjivala mendelijansku randomizaciju, vrijednost LDL kolesterola u plazmi bila je povezana s povećanim rizikom od pojave AS-a (HR za mmol/L, 1,51; 95% CI 1,07 – 2,14; p = 0,02).[12] Zbroj čimbenika rizika temeljen na SNP uz predispoziciju povećanih lipida u plazmi također je bio povezan s kalcifikacijama aortnog zalistka i AS-om.[12] Spomenute su studije jasan dokaz da je genska predispozicija povišenoj razini lipida u serumu povezana s razvojem kalcificirajuće bolesti aortnog zalistka. U budućnosti bi to moglo omogućiti usredotočenje liječenja na pacijente s najvećim rizikom od te bolesti.

MJERENJE TEŽINE AORTNE STENOZE

Ehokardiografsko i hemodinamsko mjerenje težine AS-a može uzrokovati zbunjenost, zbog razmišljanja da se brzina

value over coronary calcium scores in this study, in clinical practice echocardiographical imaging avoids ionising radiation and is more widely available than CT imaging. Thus, it remains unclear if aortic sclerosis on echocardiography should be additive to risk models for cardiovascular risk.

In the Tromsø population-based study of 3273 participants, more severe calcific disease was present in 164 subjects with a marked increase in prevalence of significant valve obstruction with age (**Figure 2**). In adults over 50 years of age, the annual incidence rate of AS was 4.9% with an average annual increase in aortic transvalvular gradient of 3.2 mm Hg.[10] In these patients, who were treated with valve replacement as needed for severe symptomatic disease, outcomes were similar for patients with AS and the general population.

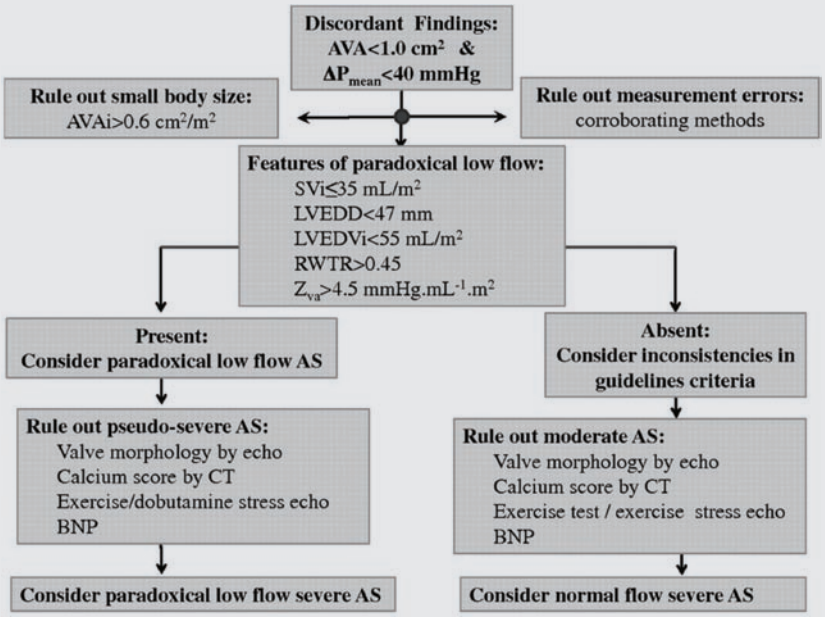
GENETICS

Although the phenotype of calcific aortic valve disease typically presents late in life, there is increasing evidence that there is an underlying genetic predisposition to this condition. In a genome-wide association study of 6942 participants, a single nucleotide polymorphism (SNP) in the locus for lipoprotein(a) (Lp(a)) was associated with the presence of aortic valve calcification as assessed by CT scanning.[11] In addition, genetically determined serum Lp(a) was associated with both incident AS and with AVR.[11] In a separate study using a Mendelian randomisation study design, plasma low-density lipoprotein cholesterol was associated with an increased risk of incident AS (HR per mmol/L, 1.51; 95% CI 1.07 to 2.14; p=0.02).[12] An SNP-based risk score for predisposition to elevated plasma lipids was also associated with aortic valve calcium and AS.[12] Taken together, these studies are strong evidence that an underlying genetic predisposition to elevated serum lipid levels is associated with the development of calcific valve disease. In the future, this might allow therapy to be targeted towards patients at highest risk of developing valve disease.

MEASURE OF AS SEVERITY

Echocardiographical and haemodynamical measures of AS severity have generated considerable confusion, in large part related to the naive notion that velocity, gradient and valve

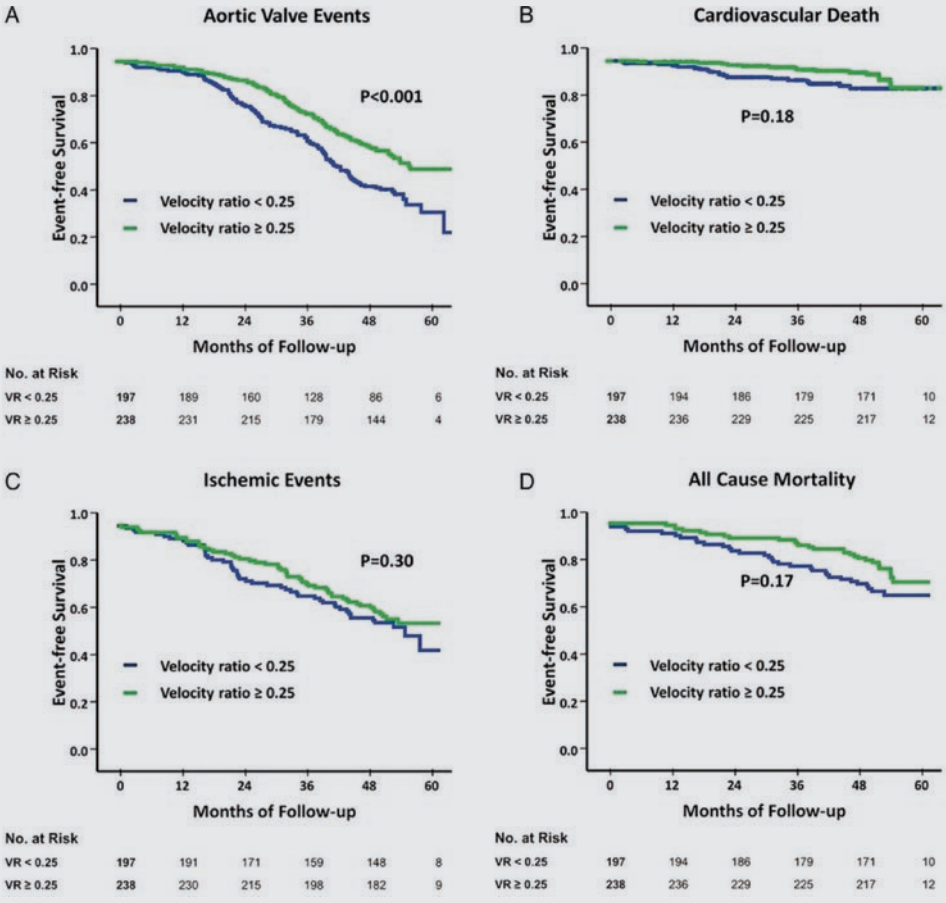
FIGURE 3.



Proposed algorithm for differential diagnosis in patients with aortic stenosis and preserved LVEF presenting with a small AVA (<1.0 cm²) but a low mean gradient (<40 mm Hg).

AS, aortic stenosis; AVA, aortic valve area; AVAi, indexed aortic valve area; ΔPmean, mean transvalvular gradient; BNP, B-type natriuretic peptide; CT, multislice CT; LVEDD, LV end-diastolic diameter; LVEDVi, indexed LV end-diastolic volume; RWTR, relative wall thickness ratio; SVi, stroke volume index; Zva, valvuloarterial impedance.[15]

FIGURE 4.



Kaplan-Meier curves demonstrating significantly more aortic valve events over 42±14 months in patients with a velocity ratio <0.25 (blue line) versus patients with a velocity ratio ≥0.25 (p<0.001 with log-rank test, **(A)** and a trend towards an increased rate of cardiovascular death **(B).** There was no statistically significant difference with respect to ischaemic events **(C)** or all-cause mortality **(D).**[13,16]

protoka, gradijent i veličina zalistka uvijek moraju „poklapati" i pripadati kategorijama blage, umjerene i teške bolesti. Idealno bi bilo kada bi se jednim jednostavnim mjerenjem mogla točno odrediti teška AS kod koje je nužna zamjena zalistka. Međutim, u kliničkoj praksi procjena treba uključivati mjerenje brzine aortnog protoka, srednjega transaortnog gradijenta i izračun areje zalistka. Iako u teoriji ima smisla prilagoditi područje zalistka veličini tijela, indeksiranje areje aortnog zalistka (AVA) prema veličini tijela povećava prevalencije naizgled „teške" AS jer se time u tu kategoriju uključuju pacijenti s blagim i umjerenim oblikom bolesti.[13] Nadalje, indeksiranje AVA ne povećava predikciju kliničkih zbivanja u pacijenata s blagom do umjerenom AS.[14] Pibarot i Dumesnil predlažu algoritam za rješavanje prividnih razlika između areje zalistka i srednjega gradijenta, što je prikazano na **slici 3**.[15]

Još jedna mjera težine AS-a koja uzima u obzir veličinu tijela jest omjer brzine protoka proksimalno i u samom stenoziranom zalistku, pri čemu je normalna vrijednost bliža 1,0, a niže vrijednosti označuju ozbiljnije slučajeve AS-a. Primjerice, omjer brzine protoka od 0,25 znači da je područje zalistka samo 25% od normalnog u te osobe. Omjer brzine protoka najkorisniji je pri razlikovanju teške AS sa slabim protokom od umjerene AS u pacijenata s malim područjem zalistka, ali samo blago povećanom brzinom protoka ili gradijentom. U 435 pacijenata uključenih u *Simvastatin and Ezetimibe in Aortic Stenosis* studiju s AVA < 1,0 cm^2, srednjim gradijentom ≤ 40 mm Hg i LVEF ≥ 55%, zbivanja vezana za aortni zalistak bila su češća u onih pacijenata s omjerom brzine protoka od < 0,25 u usporedbi s onima s većim omjerom (57% prema 41%; p < 0,001), ali nisu donijela dodatnu vrijednost srednjem gradijentu za predviđanje kliničkih zbivanja (**slika 4**).[16]

AORTNA STENOZA S NISKIM PROTOKOM I NISKIM GRADIJENTOM

Sve češće prepoznata simptomatska AS u pacijenata sa samo umjerenim povećanjem transvalvularne brzine protoka ili srednjim gradijentom dovele su do daljnjeg istraživanja teške AS s niskim protokom i niskim gradijentom. Otkrilo se da je to stanje moguće čak i uz normalnu vrijednost LVEF-a. Nove smjernice za bolesti zalistaka[4] objašnjavaju to pitanje novim definicijama teške AS:

- **stupanj D1 ili teška simptomatska AS s visokim gradijentom:** ključne su varijable kalcificirani ili zadebljani aortni zalistak koji je smanjene pokretljivosti te brzina protoka nad aortom viša od 4 m/s. AVA je najčešće 1,0 cm^2 ili manje, no ta vrijednost nije nužna za dijagnozu;
- **stupanj D2 ili teška simptomatska AS s niskim gradijentom uz sniženu vrijednost LVEF-a:** ključne su varijable kalcificirani nepomični zalistci s vrijednosti AVA ≤ 1,0 cm^2 u mirovanju, brzina protoka nad aortom < 4 m/s ili srednjim gradijentom < 40 mm Hg i vrijednost LVEF-a < 50%. Pri opterećenju niskom dozom dobutamina brzina je protoka ≥ 4 m/s, pri čemu AVA ostaje ≤ 1,0 cm^2.
- **stupanj D3 ili teška simptomatska AS s niskim gradijentom i normalnom vrijednosti LVEF-a:** dijagnoza se temelji na kalcificiranom nepomičnom zalistku s vrijednosti AVA ≤ 1,0 cm^2, brzini protoka nad aortom < 4 m/s ili srednjim gradijentom < 40 mm Hg, indeksiranim vrijednostima AVA

area should always ëmatchí and fall into clear categories of mild, moderate or severe. Ideally, a simple single measure would allow accurate diagnosis of AS severe enough to require valve replacement. Unfortunately, it is not that easy. In clinical practice, evaluation should include measurement of aortic velocity, mean transaortic gradient and calculation of valve area by the continuity equation. Although adjusting valve area for body size makes sense conceptually, indexing aortic valve area (AVA) for body size significantly increased the prevalence of apparently ësevereí AS by including larger patients with only mild-to-moderate disease.[13] In addition, indexing AVA did not improve the predictive accuracy for clinical events in patients with mild-to-moderate AS.[14] In an editorial, Professors Pibarot and Dumesnil suggest a practical approach to resolving apparent discrepancies between valve area and mean gradient as shown in **Figure 3**.[15]

Another measure of AS severity that accounts for body size is the ratio of the velocity proximal to and in the stenotic valveó the velocity ratioówith normal being close to 1.0 and with smaller numbers indicating more severe valve disease. For example, a velocity ratio of 0.25 indicates a valve area 25% of normal for that individual. The velocity ratio is most useful to help distinguish low-flow severe AS from moderate AS in patients with a small valve area but only a moderately increased velocity or gradient. In 435 patients in the Simvastatin and Ezetimibe in Aortic Stenosis study with an AVA<1.0 cm^2, mean gradient ≤40 mm Hg and LVEF≥55%, aortic valve events occurred more often in patients with a velocity ratio <0.25 compared with those with a higher velocity ratio (57% vs 41%; p<0.001) but did not provide additive value to mean gradient for prediction of clinical events (**Figure 4**).[16]

LOW-OUTPUT LOW-GRADIENT AS

Increased recognition of symptomatic AS in patients with only a moderate increase in transvalvular velocity or mean gradient has led to further studies on low-output low-gradient severe AS and the realisation that this condition can occur even with a normal LVEF. The new valve guidelines[4] provide clarity to this discussion with new definitions of severe AS:

- **Stage D1 or high-gradient severe symptomatic AS.** Key parameters are a calcified or thickened aortic valve with reduced mobility and an aortic velocity over 4 m/s. AVA is typically 1.0 cm^2 or less but this number is not required for diagnosis.
- **Stage D2 or low-gradient severe symptomatic AS with a low LVEF.** Key measures are a calcified immobile valve with a resting AVA ≤1.0 cm^2, aortic velocity <4 m/s or mean gradient <40 mm Hg and an LVEF<50%. With low-dose dobutamine stress, velocity is ≥4 m/s with AVA remaining ≤1.0 cm^2.
- **Stage D3 or low-gradient severe symptomatic AS with a normal LVEF.** Diagnosis is based on a calcified immobile valve with an AVA ≤1.0 cm^2, aortic velocity <4 m/s or mean gradient <40 mm Hg, indexed AVA ≤0.6 cm^2/m^2 and an indexed stroke volume <35 mL/m^2 measured with the patient is normotensive.

SYMPTOMS IN AS

When symptom status is unclear in adults with AS, previous studies have suggested that measurement of serum B-natri-

≤ 0,6 cm^2/m^2 i udarnim volumenom < 35 mL/m^2 mjerenim u normotenzivnog pacijenta.

SIMPTOMI KOD AORTNE STENOZE

Rezultati prethodnih studija pokazali su da razina moždanog natrijuretskog peptida (BNP) u serumu donosi dodatnu prognostičku vrijednost u odraslih pacijenata s AS i nejasnim simptomima. No, u novoj studiji koja je provedena u jednom centru kod 361 pacijenta starijeg od 70 godina s barem blagim stupnjem AS, razina NT-proBNP samo je slabo korelirala s ishodima pri univarijatnoj analizi, no ne i u multivarijatnoj analizi prilagođenoj prema dobi, spolu i ozbiljnosti AS-a te se čini se da ova pretraga treba pažljivo primjenjivati u starijih pacijenata s AS-om.[17]

TRANSKATETERSKA IMPLANTACIJA AORTNOG ZALISTKA

Transkateterska implantacija aortnog zalistka (TAVI) široko je prihvaćena kao najprimjereni pristup u pacijenata sa simptomatskom teškom AS koji imaju previsok rizik za kirurško liječenje.[18] Randomizirana klinička studija sa samoširećom bioprotezom aortalnog zalistka u 795 pacijenata u 45 američkih centara potvrdila je uspješnost ovog postupka u visokorizičnih pacijenata za kiruršku intervenciju.[19] Ukupna smrtnost nakon godina dana bila je niža kod TAVI u usporedbi s kirurškom AVR (14,2% prema 19,1%).[19] Izbor između širenja s pomoću balona i samoširеće TAVI ovisi u određenoj mjeri o osobinama pacijenta, no mala randomizirana studija pokazuje da je uspješni postupak vjerojatniji s uporabom zalistka koji se proširuje balonom.[20]

STRATIFIKACIJA RIZIKA

Evaluacija rizika kod pacijenata u kojih se primjenjuje kirurška ili transkateterska zamjena zalistka dosad se većinom temeljila na bodovanju rizika kirurškim ljestvicama, koje možda nisu u potpunosti primjenjive na transkateterske postupke. Smjernice za bolesti zalistaka iz 2014. godine preporučuju da, uz bodovanje rizika kirurškim ljestvicama, treba također uzeti u obzir čimbenike kao što su krhkost, bolesti drugih organa i specifične proceduralne čimbenike. Istraživači studije FRANCE-2 predložili su jednostavno bodovanje rizika za ranu smrtnost nakon TAVI na temelju prediktora smrtnosti nakon 30 dana analizom rezultata 3833 uzastopna pacijenta podvrgnuta balonskom širenju (67%) ili samoširećem (33%) TAVI (**slika 5**).[21,22]

Početna težina mitralne regurgitacije (MR) nezavisni je prediktor smrtnosti nakon TAVI.[23] No, stupanj MR-a poboljšava se nakon zbrinjavanja AS-a u oko polovice pacijenata, a smanjenje MR-a povezano je i s boljim ishodima. Vrijednost širine distribucije volumena eritrocita (RDW) još je jedna moguća varijabla za stratifikaciju rizika pri provođenju TAVI, pri čemu su početna vrijednost RDW ≥ 15,5% i znatniji porast RDW tijekom vremena nezavisni prediktori smrtnosti nakon transkateterske zamjene aortnog zalistka (TAVR).[24] Vrijednost RDW vjerojatno je biljeg komorbiditeta, uključujući uremiju, neishranjenost, nedostatak željeza i upalu. Rizik pri TAVI postupku može se također smanjiti izbjegavanjem opće anestezije

uretic peptide (BNP) levels provides additional prognostic value. However, in a single centre study of 361 patients older than 70 years with at least mild AS, Nt-proBNP levels correlated only modestly with outcome on univariate analysis, but not on multivariate analysis when adjusted for age, sex and AS severity suggesting this parameter be used with caution in elderly patients with AS.[17]

TRANSCATHETER AORTIC VALVE IMPLANTATION

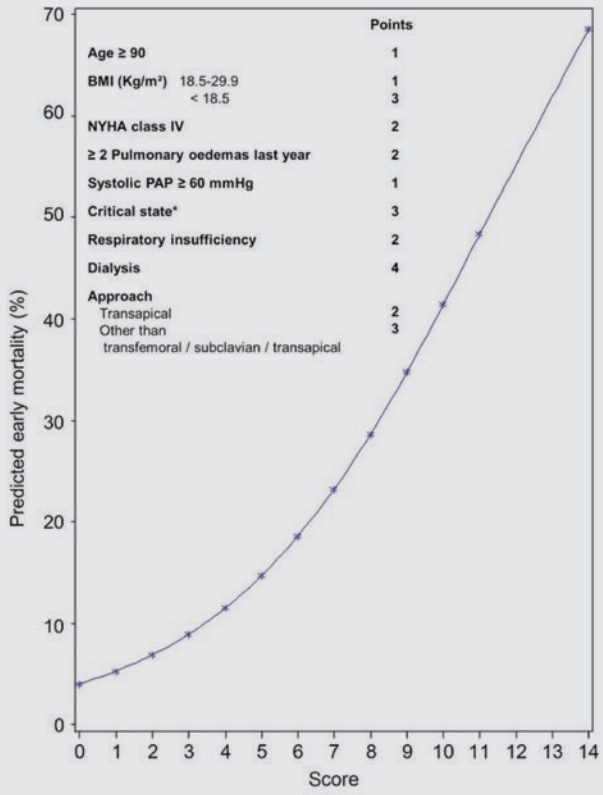
Transcatheter aortic valve implantation (TAVI) is widely accepted as the most appropriate approach for patients with symptomatic severe AS who have a prohibitive risk for surgical intervention.[18] The randomised clinical trial of a transcatheter selfexpanding aortic valve bioprosthesis in 795 patients at 45 centres in the USA confirmed the benefit of this procedure in patients at high risk for surgical intervention.[19] All-cause mortality at 1 year was lower with TAVI compared with surgical AVR (14.2% vs 19.1%).[19] The choice of balloon-expandable versus self-expanding TAVI depends to some extent on patient characteristics, but a small, randomised study suggests that a successful procedure is more likely with a balloon-expandable valve.[20]

RISK STRATIFICATION

Evaluation of risk in patients being considered for surgical or transcatheter valve replacement has largely been based on surgical risk scores, which may be not fully applicable to transcatheter procedures. The 2014 Valve Guidelines recommend that, in addition to surgical risk scores, factors such as frailty, other organ system involvement and procedural specific factors also be considered. A simple risk score for prediction of early mortality after TAVI has been proposed by the FRANCE-2 Investigators based on predictors of 30-day mortality in 3833 consecutive patients undergoing balloon-expandable (67%) or self-expanding (33%) TAVI (**Figure 5**).[21,22]

The baseline severity of mitral regurgitation is an independent predictor of mortality after TAVI.[23] However, mitral regurgitation does improve after relief of AS in about half of the patients, and a decrease in MR severity is associated with better outcomes. Another potential variable for risk stratification of patients being considered for TAVI is the red cell distribution width (RDW) with a baseline RDW ≥15.5% and a greater increase in RDWover time both found to be independently predictive of mortality after transcatheter aortic valve replacement (TAVR).[24] It is likely that RDW serves as a marker of various comorbidities, including uraemia, malnutrition, iron deficiency and inflammation. The risk of TAVI might be further decreased by avoiding general anaesthesia for this procedure as has been piloted by a group in Germany.[25,26] A series of 461 patients underwent TAVI with local anaesthesia only, with valve placement guided by fluoroscopy, rather than transoesophageal echocardiography (TOE), with a total combined safety end point, as defined by the Valve Academic Research Consortium consensus statement, of only 12.6%. Rates for specific complications were: death (5%), cerebral complications (2.1%), vascular complications (7.1%), life-threatening

FIGURE 5.



FRANCE-2 risk score or prediction of early mortality after transcatheter aortic valve implantation.[21] The relationship between the score value and predicted early mortality after transcatheter aortic valve implantation is shown.

*The definition of critical state corresponds to the definition of the Euroscore as follows: any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intra-aortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria <10 mL/h).[21]

BMI, body mass index; NYHA, New York Heart Association; PAP, pulmonary artery pressure.

zije pri tom postupku, kao što su to pokazali rezultati njemačkog pilot- istraživanja.[25,26] Serija od 461 pacijenta podvrgnuta je postupku TAVI samo u lokalnoj anesteziji i vođenjem zamjene zalistka fluoroskopijom umjesto transezofagijskom ehokardiografijom, što je rezultiralo ukupnim kombiniranim završnim ishodom sigurnosti, prema definiciji skupine *Valve Academic Research Consortium*, od samo 12,6%. Učestalost pojedinih komplikacija bila je ovakva: smrtni ishod (5%), cerebralne komplikacije (2,1%), vaskularne komplikacije (7,1%), krvarenje opasno za život (4,8%), akutna ozljeda bubrega (1,1%) i implantacija elektrostimulatora (12,8%).

KOMPLIKACIJE

Paravalvularna aortna regurgitacija nakon TAVR postupka i dalje je klinički problem s obzirom na povezanost s lošim kliničkim ishodima.[23] Kod 1432 uzastopna pacijenta u njemačkom TAVI registru od kojih 201 (15,2%) s višim stupnjem od blage paravalvularne AR, njih 61 (31%) umrlo je unutar jedne godine.[20] Nezavisni su prediktori smrtnosti u pacijenata s paravalvularnom AR bili početno viši stupanj od blage AR, viši sistolički plućni arterijski tlak te muški spol.

Krvarenje i dalje komplicira TAVI postupke, a krvarenje opasno za život pojavljuje se u 13%, ozbiljno krvarenje u 9%, a blago krvarenje u 5% od 250 pacijenata podvrgnutih postupku TAVI u nedavnom istraživanju.[27] Jedini nezavisni prediktor krvarenja opasnog za život bio je transapikalni pristup.

Transkateterski zalistci često imaju niži transvalvularni gradijent tlaka i velik prostor ušća u usporedbi s kirurškim

bleeding (4.8%), acute kidney injury (1.1%) and pacemaker implantation (12.8%).

COMPLICATIONS

Paravalvular aortic regurgitation after TAVR continues to be a clinical concern, given the association with poor clinical outcomes.[23] In 1432 consecutive patients in the German TAVI registry, in the 201 (15.2%) with more than mild paravalvular AR, 61 (31%) died within 1 year.[20] Independent predictors of mortality in those with paravalvular AR were more than mild baseline mitral regurgitation, a higher systolic pulmonary artery pressure and male sex.

Bleeding continues to complicate TAVI procedures, with lifethreatening bleeding occurring in 13%, major bleeding in 9% and minor bleeding in 5% of the 250 patients undergoing TAVI in a recent series.[27] The only independent predictor of lifethreatening bleeding was a transapical access approach.

Transcatheter valves often have a lower transvalvular pressure gradient and large orifice area than a comparable sized surgical bioprosthetic valve. Whether these favourable haemodynamics translate into improved reverse LV remodelling after TAVI has not been established. In a study comparing 25 TAVI and 25 surgical AVR patients matched for gender and AS severity, the 6-month postprocedure decrease in LV volumes and mass, as measured by cardiovascular magnetic resonance, were similar in both groups with baseline myocardial scar and LV volumes being the strongest predictors of reverse remodelling.[28]

bioprostetskim zalistkom podjednake veličine. Nije još utvrđeno dovode li te pozitivne hemodinamiske osobine do poboljšanog remodeliranja lijeve klijetke nakon postupka TAVI. U studiji koja je usporedila 25 pacijenata s TAVI u odnosu na 25 pacijenata usklađenih po spolu i ozbiljnosti AS s kirurškom zamjenom valvule, šestomjesečno smanjenje u volumenu i masi lijeve klijetke mjereno magnetnom rezonancijom nakon zahvata bilo je slično u objema grupama, a početni ožiljak miokarda i volumen lijeve klijetke bili su najjači prediktori reverznog remodeliranja.[28]

TROŠKOVNA UČINKOVITOST

Kao i kod svake novije tehnologije, dosta je zabrinutosti oko financijskog opterećenja postupaka TAVI na zdravstveni sustav. Koristeći se Markovljevim modelom s desetogodišnjim obzorom, kohortno istraživanje s visokorizičnim pacijentima pokazalo je da je postupak TAVI isplativ u usporedbi s kirurškom zamjenom zalistka usprkos višoj cijeni postupka, zbog skraćenja duljine i cijene bolničkog liječenja.[29] Ove se procjene mogu mijenjati ovisno o dugoročnim ishodima, pa stoga to pitanje treba nastaviti istraživati.

UMJETNI AORTNI ZALISTCI

U presječnoj studiji kod više od 82 milijuna pacijenata sa zdravstvenim osiguranjem Medicare, u dobi od 65 ili više godina koji su bili liječeni kirurškom zamjenom aortne valvule u SAD-u između 1999. i 2011. godine, učestalost primjene AVR rasla je 1,6% godišnje, uz snizivanje stope smrtnosti unutar 30 dana prilagođeno dobi, spolu i rasi od 4,1% godišnje.[30] Iako se povećao broj ugrađenih zalistaka od prirodnih materijala, oko 24% pacijenata starijih od 85 godina u 2011. godini dobili su mehanički zalistak, što upućuje na potrebu za poboljšanjem edukacije o primjerenom izboru umjetnog zalistka kod kirurga i kardiologa.

BIRANJE VRSTE ZALISTKA

U pacijenata koji se liječe kirurškom zamjenom, postojeće smjernice preporučuju ugradnju zalistka od prirodnih materijala u pacijenata starijih od 70 godina, jer je ta vrsta zalistka trajnija u starijih ljudi, a izbjegnuti su rizici od dugoročnog antikoagulantnog liječenja antagonistima vitamina K.[1,2] Nadalo se da će noviji oralni antikoagulansi učiniti mehaničke zalistke boljim izborom. No, randomizirana studija koja je usporedila dabigatran s varfarinom nakon implantacije mehaničkoga mitralnog zalistka morala je biti prekinuta zbog previsoke učestalosti troboembolije i krvarenja u pacijenata koji su bili randomizirani na dabigatran.[31] Iako pacijenti s mehaničkim aortnim zalistcima nisu bili uključeni u tu studiju, treba pažljivo razmisliti o tome jesu li druge kliničke studije primjerene za tu skupinu pacijenata. Iz kliničke perspektive, varfarin je trenutačno jedina prihvatljiva antikoagulacijska terapija u pacijenata s mehaničkim zalistkom srca.

Rana smrtnost nakon AVR-a u pacijenata s mehaničkim zalistkom veća je nego u onih sa zalistkom od prirodnih materijala (neprilagođena kirurška stopa smrtnosti od 1,04% prema 0,57%), prema retrospektivnoj analizi više od 66 000 pacijenata starijih od 65 godina.[32] Ova je razlika potvrđena primjenom modela miješanih učinaka za smrtnost unutar 30 dana (prila-

COST EFFECTIVENESS

As with any newer technology, there is concern about the costs of TAVI for the healthcare system. Using a Markov model with a 10-year horizon, TAVI was cost-effective compared with surgical AVR despite higher procedural costs due to a reduced length and cost of hospital stay in this high-risk cohort.[29] However, these estimates could vary depending on long-term outcomes so that continued attention to this issue is needed.

PROSTHETIC AORTIC VALVES

In a cross-sectional study of over 82 million Medicare beneficiaries, aged 65 years or older, undergoing AVR in the USA from 1999 to 2011, the rate of AVR increased by 1.6% per year, when adjusted for age, sex and race with an adjusted annual decrease in 30-day mortality of 4.1%.[30] Although the number of bioprosthetic valves implanted increased, about 24% of patients aged 85 years and older still received a mechanical valve in 2011, suggesting that improved education about appropriate valve choice is needed among surgeons and cardiologists.

CHOICE OF VALVE TYPE

In patients undergoing surgical AVR, current guidelines recommend a bioprosthetic valve in patients over 70 years because this valve type is durable in older adults and the risks of long-term anticoagulation with a vitamin-K antagonist are avoided.[1,2] There was hope that the newer oral anticoagulants might make mechanical valves a more attractive option. Disappointingly, a randomised trial of dabigatran versus warfarin after mechanical mitral valve replacement had to be terminated prematurely due to an excess rate of thromboembolic and bleeding events in patients randomised to dabigatran.[31] Although patients with mechanical aortic valves were not included in this study, it now will require careful consideration whether other clinical trials are appropriate in this population. From a clinical point of view, warfarin currently remains the only accepted antithrombotic therapy for patients with a mechanical heart valve.

Early mortality after AVR in patients receiving a mechanical valve was higher than in those receiving a bioprosthetic valve (unadjusted surgical mortality rates of 1.04% vs 0.57%) in a retrospective analysis of over 66 000 adults over 65 years of age.[32] This difference was confirmed using a mixed effects model for 30-day mortality (adjusted OR, 1.18 (95% CI 1.09 to 1.28; p<0.001); relative risk, 1.16; Number needed to treat (NNT), 121).32 However, longer-term outcomes were not different either in this study or in a younger population in another retrospective study. In a retrospective cohort analysis of 4259 patients aged 50–69 years who received either a bioprosthetic or mechanical AVR, there was no significant difference in 15-year survival or stroke.[33] As expected, patients with a mechanical valve had a lower likelihood of reoperation but a greater likelihood of major bleeding.[33]

PATIENT–PROSTHESIS MISMATCH

Some patients, particularly elderly women, have a small aortic annulus with suboptimal haemodynamics after valve replacementó a condition called patient–prosthesis mismatch (PPM). Previous studies have suggested that PPM is associated with increased mortality, less regression of LV hypertro-

gođeni OR, 1,18 /95% CI 1,09 – 1,28; p < 0,001/; relativni rizik 1,16; broj potreban za liječenje 121).[32] Ipak, dugoročni ishodi nisu se razlikovali ni u ovoj studiji ni u mlađoj populaciji u drugoj retrospektivnoj studiji. U retrospektivnoj kohortnoj analizi kod 4259 pacijenata između 50 i 69 godina koji su dobili mehanički zalistak ili zalistak od prirodnih materijala nije bilo značajne razlike u petnaestogodišnjem preživljenju ni u učestalosti moždanog udara.[33] Prema očekivanjima, pacijenti s mehaničkim zalistkom imali su manju vjerojatnost ponovne operacije, no veću vjerojatnost ozbiljnoga krvarenja.[33]

NEPODUDARNOST PACIJENTA I PROTEZE

Neki pacijenti, pogotovo starije žene, imaju mali aortni prsten sa suboptimalnim hemodinamskim promjenama nakon zamjene zalistka – stanje koje se naziva nepodudarnošću pacijenta i proteze (PPM). Prema prijašnjim je studijama PPM bio povezan s povišenom smrtnosti, smanjenom regresijom hipertrofije lijeve klijetke i povećanom incidencijom postoperativnog zatajivanja srca, pogotovo u pacijenata koji su početno imali nisku vrijednost EF. S druge strane, moguće je da utjecaj PPM-a ovisi o dobi u trenutku zamjene zalistka.[34] U seriji slučajeva od 707 odraslih pacijenata podvrgnutih zamjeni zalistka zbog teške AS, PPM je bio prisutan u njih 42%, definiran kao indeksirana efektivna površina ušća ≤ 0,85 cm^2/m^2. PPM je bio prisutan u 26% pacijenata mlađih od 70 godina te je bio povezan sa smanjenim preživljenjem i učestalijim zatajivanjem srca u pacijenata sa sistoličkom disfunkcijom lijeve klijetke tijekom medijana godina praćenja od 7,3 godine. S druge strane, iako je PPM češći u pacijenata starijih od 70 godina (68%), PPM je povezan samo sa smanjenom regresijom mase lijeve klijetke, ali ne sa smrtnosti ili zatajivanjem srca u toj dobnoj skupini (**slika 6**).

POSTUPCI UGRADNJE ZALISTKA U ZALISTAK

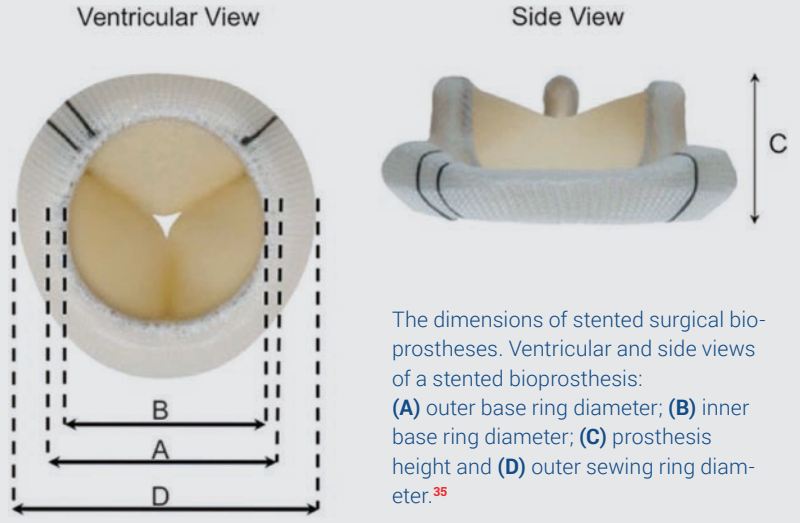
Obećavajući rezultati primjene transkateterske implantacije zalistka unutar propadajućeg zalistka od prirodnih materijala – ugradnja zalistka u zalitsak – znatno mijenjaju kliničko liječenje toga izazovnog kliničkog problema.[35,36] Prvi je korak u kliničkoj procjeni razlučivanje između stenoze zalistka od prirodnih materijala i PPM, jer hemodinamske vrijednosti mogu biti slične u obama slučajevima, no stenoza će dobro reagirati na postupak ugradnje zalistka u zalistak primjenom TAVI, dok će se PPM pogoršati dodatnim smanjenjem efektivne površine ušća. Korisno je proučiti vremenski tijek promjena u hemodinamskim vrijednostima zaliska jer će PPM biti primjetan na početnim vrijednostima postoperativne ehokardiografije. Stenoza umjetnog zalistka očitovat će se pak postupnim povećanjem transvalvularne brzine protoka i gradijenta. Izravna vizualizacija listića zalistka s pomoću transezofagijske ehokardiografije ili slikovnoga prikaza kompjutoriziranom tomografijom također može olakšati dijagnozu. Važno je

phy and a higher incidence of heart failure postoperatively, especially in patients with a low EF at baseline. However, the impact of PPM may depend on age at time of valve replacement.[34] In a series of 707 adults undergoing valve replacement for severe AS, PPM was present in 42%, defined as an indexed effective orifice area ≤0.85 cm^2/m^2. PPM was present in 26% of patients <70 years of age and was associated with decreased survival and increased heart failure in those with LV systolic dysfunction over a median follow-up of 7.3 years. Conversely, although PPM was more common in those over 70 years of age (68%), PPM was only associated with reduced LV mass regression but not with mortality or heart failure in this older age group (**Figure 6**).

VALVE-IN-VALVE PROCEDURES

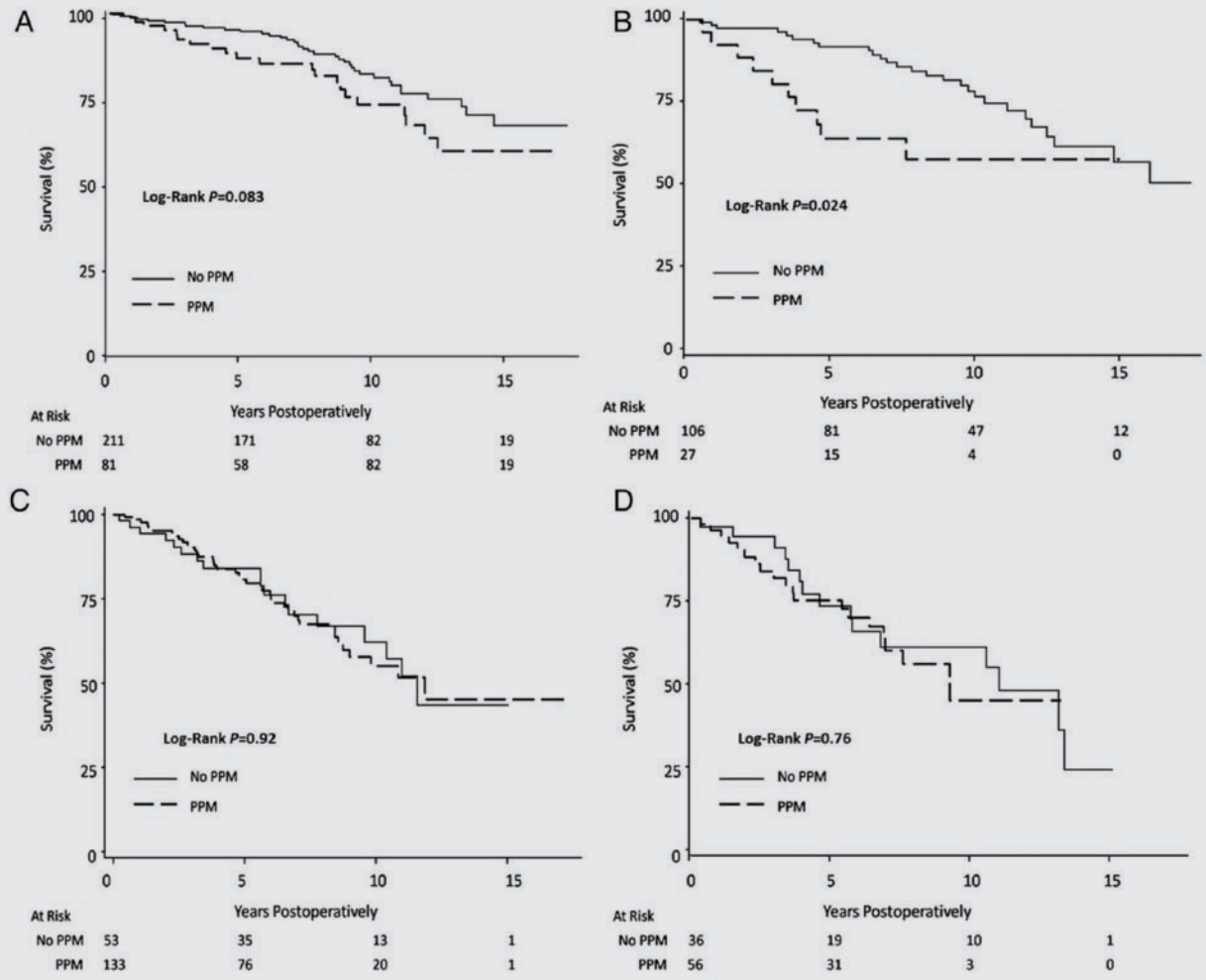
The promising results with the use of transcatheter valve implantation within a failing bioprosthetic valveóvalve-in-valve procedureóare changing the clinical management of this challenging clinical situation.[35,36] The first step in clinical evaluation is to distinguish bioprosthetic valve stenosis from PPM, as haemodynamics may be similar, yet stenosis will be improved by valve-in-valve TAVI, whereas PPM will be worsened with further reduction in the effective orifice area by the transcatheter valve. Looking at the time course of changes in valve haemodynamics is helpful because PPM will be evident on the baseline postoperative echocardiography. In contrast, prosthetic valve stenosis will show an increased transvalvular velocity and gradient over time. Direct visualisation of the valve leaflets on TOE or CT imaging also may clarify the diagnosis. In addition, an understanding of the dimensions and design of surgical bioprosthetic valves is needed for proper placement of a valve-in-valve TAVI (**Figure 7**). The Valve-in-Valve International Data Registry reported a 1-year survival of 83.2% in 459 patients undergoing this procedure.[36] The mean patient age was 77.6 years, 56% were men and all were high risk for repeat surgical AVR. Bioprosthetic valve dysfunction was predominantly stenosis in about 39%,

FIGURE 6.



The dimensions of stented surgical bioprostheses. Ventricular and side views of a stented bioprosthesis: **(A)** outer base ring diameter; **(B)** inner base ring diameter; **(C)** prosthesis height and **(D)** outer sewing ring diameter.[35]

FIGURE 7.



Effect of prosthesis—patient mismatch (PPM) on freedom from death and congestive heart failure (CHF). The effect of PPM on freedom from death and CHF after aortic valve replacement in patients **(A)** under 70 years of age with normal LV function, **(B)** under 70 years of age with LV dysfunction, **(C)** 70 years and older with normal LV function and **(D)** 70 years and older with LV dysfunction.[34]

razumjeti dimenzije i dizajn kirurških zalistaka od prirodnih materijala da bi se ispravno postavio TAVI zalistak u zalistku (**slika 7**). Prema podatcima *Valve-in-Valve International Data Registry*, jednogodišnje preživljenje iznosilo je u 83,2% od 459 pacijenata koji su prošli taj postupak.[36] Prosječna dob pacijenata bila je 77,6 godina, 56% bili su muškarci, a svi su bili pod visokim rizikom za ponovnu kirurško zamjenu valvule. Disfunkcija zalistka od prirodnih materijala očitovala se kao stenoza u 39% slučajeva, regurgitacija u 30%, a kombinirana disfunkcija zalistka u ostalim slučajevima. Nakon jednomjesečnoga praćenja 7,6% pacijenata doživjelo je smrtni ishod, 1,7% je doživjelo teži moždani udar, no 92% preživjelih pacijenata imalo je dobar funkcionalni status.

regurgitation in 30% and combined valve dysfunction in the remainder. At 1-month follow-up, 7.6% had died and 1.7% suffered a major stroke, but 92.6% of the surviving patients had a good functional status.

Competing interests: None.

Provenance and peer review: Commissioned; internally peer reviewed.

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