Godina 2017. u kardiologiji: bolesti srčanih zalistaka

The year in cardiology 2017: valvular heart disease

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Uvod

Europsko kardiološko društvo (ESC prema engl. *European Society of Cardiology*) i Europsko udruženje kardiotorakalnih kirurga (EACTS prema engl. *European Association of Cardiothoracic Surgeons*) objavili su 2017. godine smjernice za liječenje bolesti srčanih zalistaka.[1] Nove su smjernice sažetije i nadovezuju se na udžbenik Europskog kardiološkog društva koji je u izradi. Glavne se promjene odnose na transkatetersko liječenje bolesti srčanih zalistaka te na indikacije za kirurško i medikamentno liječenje. Smjernice predstavljaju novi koncept centara za srčane zalistke s preporukom kriterija koje takvi centri moraju zadovoljiti, a koji uključuju multidisciplinarne timove kompetentne u različitim intervencijama i tehnikama u dijagnostici i liječenju bolesti srčanih zalistaka, uz dostupnost važnih suradnih usluga, standardizirane procese i procjenu učinka.[2] Neke od promjena u posljednjim smjernicama istaknute su u ovome članku.

Preamble

A new joint European Society of Cardiology (ESC) and European Association of Cardiothoracic Surgeons (EACTS) guidelines on management of valvular heart disease (VHD) was published in 2017.[1] These guidelines are more focused, and are linked to the upcoming ESC textbook. The main changes concern the role of transcatheter valve treatment, indications for surgery as well as medical therapy. The guidelines present a new concept of Heart Valve Centres with recommended requirements, including multidisciplinary teams with competencies in various interventions and diagnostic techniques for VHD, the availability of important collaborative services, standardized processes and recording of performance data.[2] Some of changes in the latest guidelines are highlighted in this article.

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Epidemiologija bolesti srčanih zalistaka

Povezanost tradicionalnih čimbenika rizika kardiovaskularnih bolesti i teške aortne stenoze (AS) naglašena je u velikoj nasumično izabranoj populaciji starijih bolesnika.[3] Populacijski temeljena prospektivna kohorta 1297 slučajeva AS-a tijekom 15 godina praćenja utvrdila je pozitivnu povezanost debljine (na temelju vrijednosti indeksa tjelesne mase) i trbušne pretilosti (na temelju vrijednosti opsega struka) s incidencijom AS-a koja je bila podjednaka u obama spolovima.[4] Osobe s vrijednošću indeksa tjelesne mase ≥30 kg/m^2 imale su znatno povećani rizik od AS-a (omjer ugroženosti /HR/ 1,81, 95 % interval pouzdanosti /CI/ 1,47 – 2,23) u usporedbi s mršavijim osobama. Povećana prevalencija pretilosti ne samo da je odgovorna za povećanu učestalost AS nego je i promjenjivi čimbenik rizika za AS.

Prema nacionalnim statističkim podatcima, prevalencija bolesti srčanih zalistaka u zemljama članicama ESC-a iznosi otprilike 13,3 milijuna.[5] Dostupnost kirurških i transkateterskih metoda liječenja bolesti srčanih zalistaka veća je u zemljama članicama ESC-a s visokim prihodima nego u zemljama s umjerenim prihodima.

U svijetu je, općenito gledano, zdravstveni problem reumatske bolesti srčanih zalistaka u padu, no visoke stope i dalje perzistiraju u nekim zemljama u razvoju. Sustavan pregled fatalnih i nefatalnih slučajeva reumatske bolesti srca posljednjih 25 godina procjenjuje da se globalni dobno standardizirani mortalitet smanjio za 47,8 % od 1990. do 2015. godine.[6] Bez obzira na to, i dalje se očekuje otprilike 30 milijuna slučajeva reumatske bolesti i oko 300 000 smrti u 2015. godini, s najvišim mortalitetom u zemljama Oceanije, južne Azije, i centralne supsaharske Afrike.

Aortna stenoza

Ehokardiografija je slikovna dijagnostička metoda izbora u bolestima srčanih zalistaka. Ostale slikovne metode mogu se primjenjivati komplementarno kao dodatni izvor informacija i pridonose stratifikaciji rizika u pojedinih bolesnika.[7] Stupanj kalcifikacija aortnog zalistka utvrđen kompjutoriziranom tomografijom (CT) srca uključen je u smjernice kao kriterij razlikovanja teške „low-flow, low-gradient" AS od umjerene AS, posebno u slučaju bolesnika s očuvanom ejekcijskom frakcijom (EF). Osim toga, nove smjernice preporučuju uporabu CT angiografije umjesto invazivne konvencionalne koronarne angiografije u bolesnika s niskom vjerojatnošću koronarne bolesti srca unutar obrade za kardiokirurško liječenje bolesti zalistaka. CT angiografija još se može razmotriti u slučaju tehničke neizvedivosti ili povećanog rizika koji sa sobom nosi invazivna koronarna angiografija.

Liječenje bolesnika s asimptomatskom teškom AS i dalje je kontroverzno. Ipak, smjernice objavljene 2017. godine procjeni dodaju povišene vrijednosti plazmatskih natriuretskih peptida ili tešku plućnu hipertenziju (za koju nema drugog objašnjenja) kao rizične čimbenike koji pomažu u odluci za kirurško liječenje bolesnika s asimptomatskom teškom AS i očuvanom EF. Trenutačno, zamjena aortnog zalistka nije indicirana u takvih bolesnika, ali će se navedeno istražiti u randomiziranim kliničkim studijama EARLY TAVR (NCT03042104) i EVoLVeD (NCT03094143). Opservacijskom je studijom utvrđeno kako bolesnici s umjerenom AS i pridruženom disfunkcijom lijeve klijetke imaju visoki rizik od neželjenih događaja[8] te su upravo takvi bolesnici uključeni u kliničku studiju (TAVR)-UNLOAD (NCT02661451).

Epidemiology of valvular disease

The association between traditional cardiovascular risk factors and incident, severe aortic stenosis (AS) was highlighted in a large unselected elderly population.[3] Another study found that in a population-based prospective cohort with 1297 incident cases of AS during 15 years of follow-up both overall obesity reflected by body mass index (BMI) and abdominal adiposity based on waist circumference were positively associated with incidence of AS, with similar associations in men and women.[4] Individuals with BMI ≥30 kg/m^2 had a significantly [hazard ratio (HR) 1.81, 95% confidence interval (CI) 1.47–2.23] increased risk for incident AS compared with lean individuals. The increasing prevalence of obesity may both determine the increased prevalence of AS and be an important modifiable risk factor for AS.

Using data from national statistics, the prevalence of VHD in ESC member countries is approximately 13.3 million.[5] The access to both surgical and transcatheter heart valve treatment is better developed in high-income when compared with middle-income ESC member countries.

The health-related burden of rheumatic heart disease has declined worldwide, but high rates of disease persist in some of the developing countries. In a systematically review of fatal and non-fatal rheumatic heart disease over the last 25 years, it was estimated that global age-standardized mortality due to the disease fell by 47.8% from 1990 to 2015.[6] However, there were still more than 30 million cases of rheumatic heart disease and around 300 000 deaths in 2015; the highest mortality was observed in Oceania, South Asia, and central sub-Saharan Africa.

Aortic stenosis

Echocardiography is the first-line imaging technique for the evaluation of patients with VHD, but other imaging modalities can be used to obtain complementary information, and to aid risk stratification in individual patients.[7] Aortic valve calcification detected by cardiac computed tomography (CT) is listed in the guidelines among criteria for differentiating severe low-flow, low-gradient AS from moderate disease, particularly in the presence of preserved ejection fraction (EF). The 2017 VHD guidelines also contain a new recommendation that CT coronary angiography should be considered as an alternative to invasive angiography before valve surgery in patients with a low probability of coronary artery disease; it may also be considered when invasive coronary angiography is either technically not feasible or associated with increased risk.

The management of asymptomatic severe AS remains controversial. However, in the 2017 VHD guidelines, markedly elevated plasma natriuretic peptide levels or severe pulmonary hypertension without other explanation have been added as risk factors warranting consideration for surgery in asymptomatic severe AS with normal EF. Currently, aortic valve replacement (AVR) is not indicated in these patients, but it will be evaluated in the randomized EARLY TAVR trial (NCT03042104) and EVoLVeD trial (NCT03094143). An observational study demonstrated that patients with concomitant moderate AS and left ventricle systolic dysfunction are at high risk for clinical events,[8] which is the focus of the transcatheter aortic valve replacement (TAVR)-UNLOAD trial (NCT02661451).

Dvije su studije pokazale korisnost kliničkih bodovnih sustava u određivanju stupnja opće slabosti starijih bolesnika i u predikciji jednogodišnjeg mortaliteta nakon zamjene aortnog zalistka.[9,10] Prisutnost i opseg kalcifikacija mitralnog anulusa također se povezuju s ishodima nakon zamjene aortnog zalistka; sada postoje slični podatci i za bolesnike podvrgnute transkateterskoj implantaciji aortnog zalistka (TAVI).[11] Znatna kalcifikacija mitralnog anulusa susreće se u oko 10 % bolesnika; ona je neovisni prediktor cjelokupnog mortaliteta (HR 2,35, 95 % CI 1,19 – 4,66) i potrebe za trajnim elektrostimulatorom (omjer izgleda /OR/ 2,83, 95 % CI 1,08 – 7,47) nakon TAVI-ja.

Podatci dobiveni iz kirurških registara upućuju na porast broja implantiranih bioloških aortnih zalistaka čak i u dobnim skupinama u kojima su standardno preporučeni mehanički aortni zalistci (**slika 1**).[12,13] Optimalna dobna granica nakon koje se preporučuje biološki aortni zalistak i dalje ne postoji, odnosno nema dokaza koji bi je podržali. U bolesnika u dobi od 50 do 69 godina liječenih biološkim i mehaničkim aortnim zalistcima u sklopu kliničke studije analizirane s uparivanjem po vjerojatnosti sklonosti, preživljenje je bilo bolje u grupi liječenoj mehaničkim aortnim zalistcima (HR 1,34, 95 % CI 1,09 – 1,66) te je rizik pri reoperaciji bio niži.[13] Subanaliza te studije otkriva da se isto odnosi i na dobnu skupinu 50 – 59-godišnjaka, no ne i na 60 – 69-godišnjake. U meta-analizi, koja je uključila bolesnike u dobi od 18 do 55 godina liječene mehaničkim zalistcima, primjenom mikrosimulacije izračunani su očekivano trajanje života i cjeloživotni rizik od pojave neželjenih događaja.[14] Očekivano trajanje života kraće je u nositelja mehaničkih zalistaka, s rizikom od tromboembolijskih komplikacija od 18 % i od reintervencije od 10 %. Nedavna je studija stratificirala bolesnike u skupine prema dobi i poziciji umjetnog zalistka (aortni spram mitralnog) te rezultati upućuju na dugotrajno niži mortalitet u nositelja mehaničkih zalistaka implantiranih sve do 55. godine života u

Two studies demonstrated the utility of clinical scores for detecting frailty and predicting 1-year mortality after AVR in elderly patients.[9,10] The burden of mitral annular calcification is also associated with outcomes after AVR; there are now similar data in patients undergoing aortic valve implantation (TAVI).[11] Severe mitral annular calcification was encountered in 10% of patients; this was an independent predictor of both overall mortality (HR 2.35, 95% CI 1.19–4.66) and permanent pacemaker implantation [odds ratio (OR) 2.83, 95% CI 1.08–7.47] following TAVI.

Data from surgical registries describe an increase in the use of biological aortic valves even in the age groups were mechanical valves are usually recommended, **Figure 1**.[12, 13] There is still a gap in evidence regarding the optimal age cut-off at which a biological valve prosthesis should be preferred. In a propensity-matched study of patients aged 50–69 years treated with biological and mechanical aortic valve prostheses, survival was higher in the group with mechanical prostheses (HR 1.34, 95% CI 1.09–1.66), and the risk of reoperation was lower.[13] In a sub-analysis the benefit persisted in those aged 50–59 years, but not for those aged 60–69 years. In a meta-analysis of patients aged 18–55 years treated with mechanical valve prostheses, microsimulation was used to calculate life expectancy and lifetime event-risk.[14] Estimated life expectancy was shortened in patients with mechanical prostheses, and the risk of thromboembolism and re-intervention was 18% and 10%, respectively. A recent study stratified patients into different age groups on the basis of valve position [aortic vs. mitral valve (MV)], and found the long-term mortality benefit associated with a mechanical prosthesis, as compared with a biological prosthesis, persisted until 55 years of age among those undergoing aortic-valve replacement, and until 70 years of age among patients undergoing mitral-valve replacement.[15]

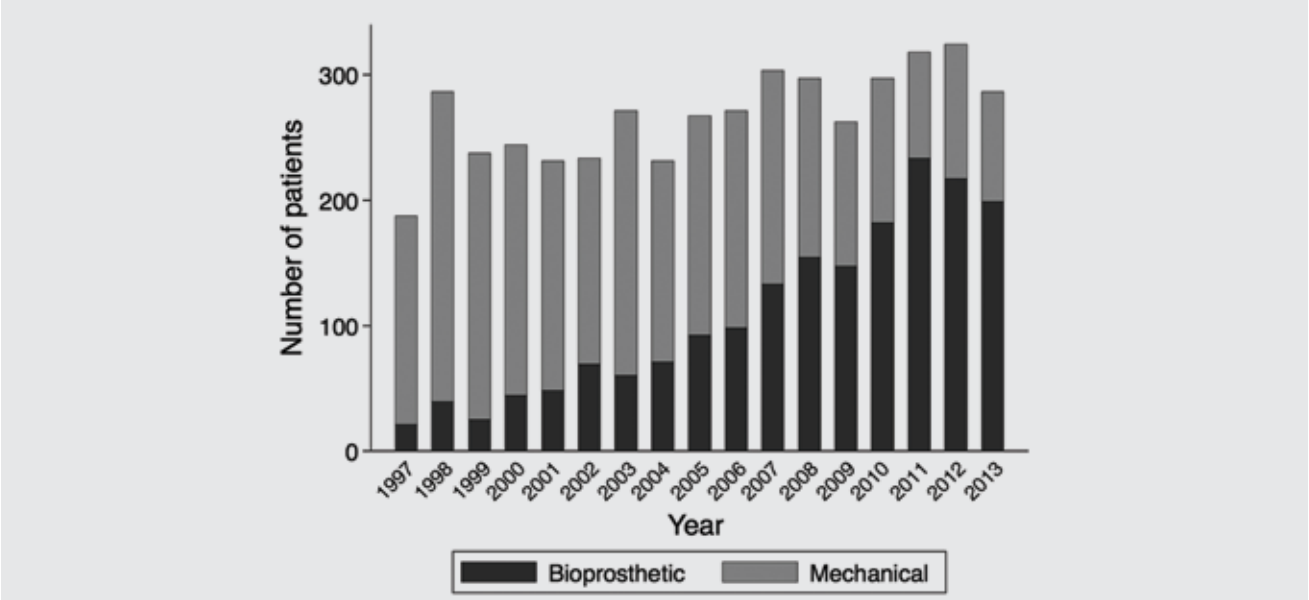

FIGURE 1. Number of aortic valve replacements per year. Number of patients aged 50–69 years who had undergone aortic valve replacements with mechanical or bioprosthetic valves in Sweden between 1997 and 2013. From Glaser *et al.*[13]

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slučaju aortne pozicije, odnosno do 70. godine života u slučaju mitralne pozicije.[15]

Izbor načina intervencije na zalistku, odnosno izbor između TAVI-ja i kirurške zamjene aortnog zalistka (SAVR prema engl. *surgical aortic valve replacement*) ovisi o pažljivoj individualnoj procjeni tima za srce, uzimajući u obzir rizike i koristi od pojedine intervencije (**tablica 1**). Iako je TAVI prihvatljiva alternativa kirurgiji u bolesnika s teškom AS i viso-

The choice of intervention with TAVI and surgical AVR (SAVR) depends on careful individual evaluation by the Heart Team, taking into consideration the risks and benefits of each approach (**Table 1**). Although, TAVI is an accepted alternative to surgery in patients with severe AS who are at high surgical risk, the SURTAVI trial provided additional data concerning intermediate risk patients.[16] The SURTAVI trial included 1746 patients and showed that TAVI with a self-expanding

TABLE 1. Aspects to be considered by the Heart Team for the decision between surgical aortic valve replacement and transcatheter aortic valve implantation in patients at increased surgical risk.

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE II <4% (logistic EuroSCORE I <10%)[a]		+
STS/EuroSCORE II ≥4% (logistic EuroSCORE I ≥10%)[a]	+	
Presence of severe comorbidity (not adequately reflected by scores)	+	
Age <75 years		+
Age ≥75 years	+	
Previous cardiac surgery	+	
Frailty	+	
Restricted mobility and conditions that may affect the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favourable access for transfemoral TAVI	+	
Unfavourable acess (any) for TAVI		+
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient–prosthesis mismatch	+	
Severe chest deformation or scoliosis	+	
Short distance between coronary ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavourable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern unfavourable for TAVI)		+
Presence of thrombi in aorta of LV		+
Cardiac conditions in addition to aortic stenosis that require consideration for concomitant intervention		
Severe CAD requiring revascularization by CABG		+
Severe primary mitral valve disease, which could be treated surgically		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy requiring myectomy		+

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CABG, coronary artery bypass grafting; CAD, coronary artery disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LV, left ventricle; STS, Society of Thoracic Surgeons.

[a]STS score (calculator: http://riskcalc.sts.org/stswebriskcalc/#/calculate); EuroSCORE II (calculator: http://www.euroscore.org/calc.html); logistic EuroSCORE I (calculator: http://www. euroscore.org/calcge.html). Scores have major limitations for practical use in this setting by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc. EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II with this regard; it is nevertheless provided here for comparison since it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality.

kim kirurškim rizikom, studija SURTAVI daje nove podatke o bolesnicima s umjerenim rizikom.[16] Klinička studija SURTAVI uključila je 1746 bolesnika i dokazala je kako TAVI sa samoproširujućim protezama nije inferioran SAVR-u u kontekstu procijenjene 24-mjesečne incidencije ukupnog mortaliteta i moždanog udara s invaliditetom (12,6 % prema 14,0 %). Kirurško je liječenje bilo povezano s višom stopom akutnoga bubrežnog oštećenja, fibrilacije atrija, potrebom za transfuzijskim liječenjem, dok je TAVI bio povezan s većom učestalosti rezidualne aortne regurgitacije (AR) i potrebom za implantacijom trajnog elektrostimulatora.

Iako randomizirane kliničke studije podupiru primjenu TAVI-ja u liječenju bolesnika s teškom AS i umjerenim ili znatnim kirurškim rizikom, primjena je tih rezultata u kliničkoj praksi izazovna. Ipak, analizom s uparivanjem po vjerojatnosti sklonosti 9464 bolesnika u Sjedinjenim Američkim Državama s umjerenim i visokim kirurškim rizikom koji su liječeni TAVI-jem ili SAVR-om zabilježena je slična učestalost smrtnosti, moždanog udara i vremena do ponovne hospitalizacije unutar prve godine, no bolesnici nakon TAVI-ja češće su bili otpušteni kući.[17]

Rastućim kliničkim iskustvom i novim generacijama uređaja[18-20] očekuje se širenje indikacije za TAVI na mlađe bolesnike, u kojih je češće prisutan bikuspisni aortni zalistak. Rana iskustva s TAVI-jem u bolesnika s bikuspisnim aortnim zalistcima upućivala su na probleme s optimalnim pozicioniranjem umjetnog zalistka i češćim paravalvularnim regurgitacijama. Petsto šezdeset jedan bolesnik s bikuspisnim aortnim zalistkom i 4546 bolesnika s trikupisnim aortnim zalistkom uspoređeni su analizom s uparivanjem po vjerojatnosti sklonosti u multicentričnom registru, dajući 546 parova bolesnika sa sličnim osnovnim karakteristikama.[21] TAVI u bolesnika s bikuspisnim aortnim zalistkom i AS-om, u usporedbi s bolesnicima čije valvula ima tri kuspisa, ima sličnu prognozu, no pokazuje manju stopu uspješnosti samog uređaja. Svakako, proširenje indikacije za TAVI na mlađe bolesnike može se poduprijeti tek nakon analize dugoročnih podataka, kojih još uvijek nema.

Trajnost bioloških srčanih zalistaka vrlo je važan problem. Usporedbe pojedinih proizvođača, kao i načina implantacije (transkateterski spram kirurškog) vrlo su teške zbog različitih kriterija izdržljivosti koji se primjenjuju. Zbog navedenoga Europsko udruženje za perkutane kardiovaskularne intervencije (EAPCI, prema engl. *European Association of Percutaneous Cardiovascular Interventions*) u suglasnosti s ESC-om i EACTS-om objavilo je standardiziranu definiciju disfunkcije bioloških zalistaka za buduće kliničke studije[22] (**slika 2**). Tim za srce pojedinih centara može razmotriti transkatetersku implantaciju zalistka u zalistak u liječenju degenerativno promijenjenoga kirurški implantiranoga biološkog aortnog zalistka, ovisno o riziku koji nosi reoperacija te o tipu i veličini samog umjetnog zalistka. TAVI u liječenju disfunkcije biološkog aortnog zalistka ima relativno malu učestalost komplikacija i smrtnosti, poboljšava hemodinamske parametre i ima odličan učinak na funkcijski kapacitet i kvalitetu života.[23,24] Nadalje, u klinički značajnih regurgitacija uz zalistak u bolesnika s visokim kirurškim rizikom može se razmotriti transkateterska intervencija, odnosno zatvaranje.[25]

Aortna regurgitacija

Smjernice za liječenje bolesti srčanih zalistaka iz 2017. godine preporučuju kako se u iskusnim centrima, prema odluci tima za srce, za liječenje pojedinih bolesnika s teškom aortnom re-

prosthesis was non-inferior to SAVR with regards to estimated incidence of all-cause mortality and disabling stroke at 24 months (12.6% vs. 14.0%). Surgery was associated with higher rates of acute kidney injury, atrial fibrillation, and transfusion requirements, whereas TAVI had higher rates of residual aortic regurgitation (AR) and need for pacemaker implantation.

Even though randomized trials support the use of TAVI for the treatment of AS in high- and intermediate-risk patients, the generalizability of these results to clinical practice may be challenged. However, in 9464 propensity-matched intermediate- and high-risk U.S. patients who underwent TAVI or SAVR, there were similar rates of death, stroke, and days alive and out-of-hospital to 1 year, but TAVI patients were more likely to be discharged home.[17]

With the increased clinical experience and newer generation devices,[18–20] TAVI is expected to expand to younger patients, where bicuspid aortic valves are more common. Early experience with TAVI in bicuspid aortic valves revealed difficulties with optimal valve positioning and more paravalvular leak. In a multi-centre registry, 561 patients with bicuspid AS and 4546 patients with tricuspid AS were compared after propensity score matching, assembling 546 pairs of patients with similar baseline characteristics.[21] Compared with TAVI for tricuspid AS, treatment in bicuspid AS was associated with a similar prognosis, but a lower device success rate. However, expansion of TAVI to younger patients can only be supported with the availability of long-term data, which are still lacking.

Longevity of bioprosthetic heart valves is an extremely important issue. However, comparisons of valve brands, as well as surgical and transcatheter implantation, have been difficult because different valve durability criteria have been used. The definitions of bioprosthetic valve dysfunction and failure have now been standardized for use in future studies in a consensus publication from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by ESC and EACTS,[22] **Figure 2**. Valve-in-valve TAVI should be considered as an option by the Heart Team for treating degenerated surgical bioprostheses depending on the risk of reoperation and the type and size of prosthesis. Thus, TAVI for bioprosthetic aortic valve failure has been associated with a relatively low complication rates and mortality, improved haemodynamics, and excellent functional and quality-of-life outcomes.[23,24] Furthermore, transcatheter closure may be considered for clinically significant paravalvular leaks in surgical high-risk patients.[25]

Aortic regurgitation

The 2017 VHD guidelines recommends that, in selected cases and in experienced centres, aortic valve repair, and valve-sparing aortic surgery, rather than AVR, should be considered by Heart Team for the treatment of severe AR. Consideration of valve sparing surgery, using re-implantation or remodelling with aortic annuloplasty techniques, is especially recommended in young patients with aortic root dilatation and tricuspid aortic valves, when performed by experienced surgeons. The timing of surgery in asymptomatic patients with severe AR and preserved EF remains controversial, although long-term (mean follow-up 6.6 years) survival after surgery is similar to an age- and sex-matched population.[26]

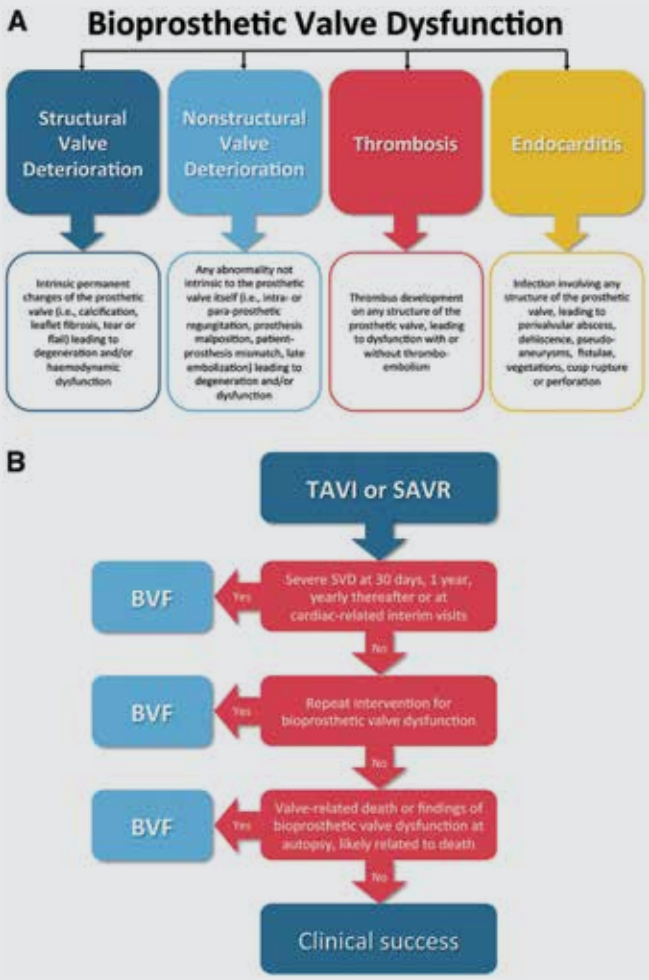

FIGURE 2. (A) Causes of bioprosthetic valve dysfunction. (B) Suggested assessment of bioprosthetic valve failure (BVF) in outcome studies of transcatheter aortic valve implantation or surgical aortic valve replacement (SAVR). SVD, structural valve deterioration. From Capodanno *et al*.[22]

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gurgitacijom treba razmotriti popravak aortnog zalistka, odnosno kirurško liječenje aorte s poštedom aortnog zalistka, umjesto konvencionalne zamjene aortnog zalistka. U mlađih bolesnika s dilatacijom korijena aorte i trikuspisnim aortnim zalistkom razmatranje kirurškog liječenja uz poštedu zalistka primjenom tehnike reimplantacije ili remodelacije s anuloplastikom posebno se preporučuje u iskusnih operatera. I dalje je kontroverzno optimalno vrijeme kirurškog liječenja u asimptomatskih bolesnika s očuvanom EF i teškom AR, iako je dugotrajno preživljenje nakon kirurgije slično onomu u općoj populaciji iste dobi i spola (prosječno praćenje nakon kirurškog zahvata 6,6 godina).[26]

TAVI u bolesnika s nekalcificiranim nativnim aortnim zalistkom i regurgitacijom inače je vrlo zahtjevan zahvat zbog rizika od embolizacije proteze i visoke stope regurgitacije uz zalistak. Ipak, nove generacije TAVI uređaja donose i bolje ishode s manje bolesnika kojima je potrebna implantacija dodatnog zalistka (10 %) te manje bolesnika sa značajnom rezidualnom AR (3 %).[27]

TAVI for non-calcified native aortic valve regurgitation has been challenging with prosthesis embolization and high rate of paravalvular leakage. However, newer generation TAVI systems has improved the outcome with fewer patients needing a second valve (10%) and having significant residual AR (3%).[27]

Mitral regurgitation

Echocardiography is essential to assess the aetiology of mitral regurgitation (MR), but quantitative grading remains challenging. The 2017 VHD guidelines state that the thresholds used to define severe secondary MR remain controversial and need to be evaluated with regards to their impact on prognosis after MV intervention. Integration of echocardiography-derived Doppler mitral flow and CT-derived cross-sectional mitral anatomical regurgitant orifice area to calculate mitral regurgitant volume has been evaluated.[28] In 73 patients undergoing TAVI, who also had either primary or secondary MR, this approach resulted in reclassification of MR from severe to non-severe in 10% and from non-severe to severe in

Mitralna regurgitacija

Ehokardiografija je esencijalna u procjeni etiologije mitralne regurgitacije (MR), no kvantitativna procjena i dalje je izazov. Prema smjernicama za liječenje bolesti srčanih zalistaka iz 2017. godine, dosadašnji su kriteriji za utvrđivanje teške sekundarne MR kontroverzni i zahtijevaju ponovnu procjenu s obzirom na prognostički utjecaj same intervencije na mitralnom zalistku. Ispitivana je važnost izračuna regurgitirajućeg volumena mitralnog protoka dobivena integracijom mjerenja mitralnoga protoka s pomoću doplerske ehokardiografije i površine poprečnoga presjeka anatomskoga mitralnoga regurgitirajućeg ušća dobivenog kompjutoriziranom tomografijom.[28] Ovaj integrirani pristup rezultirao je u reklasifikaciji MR iz teške u netešku u 10 % bolesnika, i neteške u tešku u 14 % bolesnika u studiji koja je uključila 73 bolesnika podvrgnutih TAVI zahvatu, a koji su imali primarnu ili sekundarnu MR.

Novi bodovni sustav predikcije rizika kratkoročnog i dugoročnog mortaliteta u bolesnika s teškom degenerativnom MR koji se liječe medikamentno ili kirurški, integrira različite kliničke i ehokardiografske varijable podržane novim smjernicama, a zove se MIDA (prema engl. *the Mitral Regurgitation International Database mortality risc score*).[29] U bolesnika s teškom MR i očuvanom EF lijeve klijetke pogoršanje globalnoga longitudinalnog „straina" neovisno je povezano sa smrtnošću tijekom praćenja od 8,3 godine, što pridonosi prognostičkoj korisnosti dosadašnjih prediktora poput smanjenoga funkcionalnog kapaciteta testom opterećenja.[30] Važno je naglasiti kako se u novim smjernicama kirurški zahvat na mitralnom zalistku ne preporučuje u slučaju umjerene sekundarne MR u bolesnika koji su podvrgnuti aortokoronarnom premoštenju.

Kod MR-a zbog degenerativnih promjena više se preporučuje popravak mitralnog zalistka negoli njegova zamjena, a tu preporuku sada podupiru i rezultati multicentričnih registara analiziranih uparivanjem po vjerojatnosti sklonosti.[31] Operacijski je mortalitet bio niži u grupi bolesnika u kojih je izveden popravak mitralnog zalistka (0,2 % prema 4,4 %, p < 0,001) te je i 20-godišnje preživljenje u toj grupi bilo bolje (41 % prema 24 %, p < 0,001). U liječenju sekundarne MR zahvat na subvalvularnom aparatu može se kombinirati s anuloplastikom uz primjenu prstena. U nedavnome preglednom članku u 397 bolesnika, manji je povrat MR (relativni rizik /RR/ 0,43, 95 % CI 0,27 – 0,66; p = 0,0002) i veći je stupanj pozitivne remodelacije lijeve klijetke u bolesnika koji su podvrgnuti kombiniranom zahvatu anuloplastike i intervencije na subvalvularnom aparatu.[32]

Transkateterski popravak mitralnog zalistka predominantno se izvodi MitraClip uređajem. Ipak, objavljeni su podatci o prvim humanim implantacijama Edwards PASCAL uređaja u bolesnika sa simptomatskom, teškom funkcijskom, degenerativnom ili miješanom MR.[33] Edwards PASCAL uređaj sadržava inovativni centralni dio koji omogućuju neovisno zahvaćanje jednog pa drugog kuspisa s rezultirajućim postproceduralnim rezidualnim MR od 2+ ili manjim u 22 od 23 bolesnika. Iako je studijom dokazana izvedivost popravka mitralnog zalistka Edwards PASCAL uređajem, daljnja su ispitivanja potrebna radi dobivanja podataka o dugoročnim proceduralnim i kliničkim ishodima.

Iako je dokazano da transkateterski popravak mitralnog zalistka smanjuje simptome zatajivanja srca, prognostički učinak ovakve terapije još ne postoji. Ipak, u tijeku su velike kliničke randomizirane studije, npr. COAPT (NCT01626079), francuski MITRA-FR (NCT01920698), RESHAPE-HF2 (NCT02444338), i MATTERHORN (NCT02371512).

14% of the patients providing a proof-of-concept of this integrated approach.

A study validated a risk score (The Mitral Regurgitation International Database (MIDA) mortality risk score) integrating various clinical and echocardiographic parameters endorsed by guidelines for predicting short- and long-term mortality risk in patients with severe degenerative MR either under medical or surgical treatment.[29] In patients with severe MR and preserved left ventricular EF, worsening of global longitudinal strain using speckle-tracking resting echocardiography is independently associated with mortality during 8.3 years of follow-up, providing additive prognostic utility to reduced capacity on exercise testing and other previously known predictors.[30] Importantly, in the recent guideline, MV surgery in patients with moderate secondary MR undergoing coronary artery bypass surgery is no longer recommended in the guidelines.

Mitral valve repair is recommended over MV replacement in degenerative MR and this recommendation is backed-up by multicentre registry data analysed with propensity score matching.[31] The operative mortality was lower in the MV repair group (0.2% vs. 4.4%, $P < 0.001$) and 20-year survival was better (41% vs. 24%, $P < 0.001$). In secondary MR, sub-valvular intervention may be added to annuloplasty with a ring. In a recent review of 397 patients, there was less recurrence of MR (relative risk (RR) 0.43, 95% CI 0.27–0.66; $P = 0.0002$), and more positive remodelling of the left ventricle in the group with the combined intervention as compared to those treated with just annuloplasty.[32]

Transcatheter MV repair has been dominated by the MitraClip system. However, the first-in-man study on the Edwards PASCAL system in compassionate cases with symptomatic, severe functional, degenerative, or mixed MR has been reported.[33] The Edwards PASCAL system implements a central spacer, and allows for independent leaflet grasping resulting in procedural residual MR of Grade 2+ or less in 22 of 23 patients. Although the study established feasibility of the Edwards PASCAL system, further research is needed on procedural and long-term clinical outcomes.

While transcatheter MV repair has been shown to reduce heart failure symptoms, the prognostic impact of these therapies is lacking. However, large randomised trials are ongoing, e.g. COAPT (NCT01626079), French MITRA-FR (NCT01920698), RESHAPE-HF2 (NCT02444338), and MATTERHORN (NCT02371512).

The outcome of transcatheter MV implantation in failed degenerated surgical MV prostheses (176 patients; 'valve-in-valve') and failed annuloplasty rings (72 patients; 'valve-in-ring') has been evaluated in a multicentre registry.[34] Overall technical and device success rates were acceptable, at 92.3% and 85.5%, respectively. However, compared with the valve-in-valve treatment, the valve-in-ring treatment had lower technical and device success, and was associated with more MR, life-threatening bleeding, acute kidney injury, and higher mortality.

Transcatheter MV implantation in native non-calcified MR has attracted much attention during the last 5 years. The technique has been associated with high mortality, risk of left ventricular outflow tract obstruction and prosthesis dislocation. However, a recent report on 30 selected patients with primarily functional MR and high surgical risk, transapical im-

Ishodi bolesnika liječenih transkateterskom implantacijom mitralnog zalistka ispitivani su u multicentričnom registru koji je uključio bolesnike s degeneriranim umjetnim mitralnim zalistcima (176 bolesnika, tehnika zalistak u zalistak) i neuspješnim anuloplastikama s prstenom (72 bolesnika, tehnika zalistak u prsten).[34] Cjelokupna uspješnost same tehnike i uređaja bila je prihvatljiva (92,3 % prema 85,5 %). Ipak, tehnika implantacije zalistak u prsten bila je manje uspješna, imala je veću stopu MR-a, po život opasnih krvarenja, akutnog bubrežnog zatajivanja i mortalitet u usporedbi s tehnikom implantacije zalistka u zalistak.

Mnogo je pozornosti posljednjih pet godina privukla transkateterska implantacija mitralnog zalistka u bolesnika s nativnom, nekalcificiranom MR. Tehnika je za sada povezana s visokim mortalitetom, rizikom od opstrukcije izgonskoga trakta lijeve klijetke i rizikom od dislokacije proteze. S druge strane, nedavno je objavljen izvještaj o transapikalnoj implantaciji tendinskog zalistka u 30 probranih bolesnika s primarnom funkcijskom MR i visokim kirurškim rizikom, a zahvat je bio uspješan u 28 bolesnika, bez zabilježenoga akutnoga smrtnog ishoda. Nakon 30 dana samo je jedan bolesnik imao blagu MR, dok preostali bolesnici nisu uopće imali MR te je 75 % bolesnika opisivalo samo blage simptome ili ih nije imalo.[35]

Trikuspidna regurgitacija

Metaanaliza 15 kliničkih studija koje su uključile 2840 bolesnika u kojih je učinjen i popravak trikuspidnog zalistka tijekom kirurškog zahvata na lijevostranim srčanim zalistcima utvrdila je dobrobit zbog smanjene kardiološke smrtnosti (OR 0,38, 95 % CI 0,25 – 0,58).[36] Zamjena trikuspidnog zalistka provodi se rijetko i postoji vrlo malo podataka kojima bi se usporedili mehanički i biološki zalistci. Studija iz jednog centra gdje je obavljeno 120 zahvata zamjene trikuspidnog zalistka navodi visoku učestalost smrtnosti, kako rane (21,7 %), tako i tijekom praćenja u trajanju od 7 godina (37,5 %), a nisu utvrđene razlike pri usporedbi mehaničkog i biološkog zalistka.[37]

Za bolesnike sa znatnom trikuspidnom regurgitacijom (TR) koji nisu kandidati za kirurško liječenje razvija se tehnika transkateterskih zahvata na trikuspidnom zalistku.[38] Nedavna je studija predložila cjeloviti pristup bolesnicima koji bi bili pogodni za transkatetersko liječenje bolesti trikuspidnog zalistka koji uključuje procjenu geometrije trikuspidnog anulusa i desne klijetke, dimenzije donje šuplje vene i prostorne odnose trikuspidnog zalistka i desne koronarne arterije koristeći se CT-om.[39]

Transkateterski popravak kronične teške TR primjenom MitraClip uređaja bio je predmet studije koja je uključila 64 uzastopna bolesnika koji su smatrani nepogodnima za kirurško liječenje.[40] MitraClip uređaj uspješno je implantiran u 97 % slučajeva na trikuspidnu poziciju, pri čemu je TR smanjena za barem jedan stupanj u 91 % bolesnika, bez zabilježenih smrtnih ishoda tijekom procedure. Funkcijski kapacitet i rezultat 6-minutnog testa hoda bili su mnogo bolji nakon zahvata.

Antikoagulacijska terapija

Smjernice za liječenje bolesti srčanih zalistaka iz 2017. godine ističu kako su antagonisti vitamina K (AVK) jedina preporučena antikoagulacijska terapija u bolesnika s mehaničkim zalistcima. Novi oralni antikoagulansi (NOAK) kontraindicirani su na temelju rezultata studija provedenih direktnim

plantation of the tendyne valve was successful in 28 patients with no acute deaths. At 30 days only one patient had mild MR whereas the remaining patients had no residual MR, and 75% of the patients reported mild or no symptoms.[35]

Tricuspid regurgitation

A meta-analysis including 15 studies and 2840 patients has demonstrated the benefit of TV repair during surgery for left heart valve disease, with reduced cardiac mortality (OR 0.38, 95% CI 0.25–0.58).[36] Tricuspid valve (TV) replacement is uncommon and data comparing biological and mechanical prosthesis is scarce. In a single centre study of 120 interventions with TV replacement described a high mortality rate both early (21.7%) and during mean 7 years follow-up (37.5%); no difference was found comparing mechanical and biological TV replacement.[37]

Percutaneous transcatheter TV therapy is an evolving treatment option for patients with significant tricuspid regurgitation (TR), who are not candidates for open heart surgery.[38] A recent study proposed a systematic approach to define those patients suitable for transcatheter TV devices based on evaluation of the TV annulus geometry, right ventricle, vena cava dimensions, and spatial relationships between the TV and the right coronary artery using CT.[39]

Transcatheter repair of chronic severe TR with the MitraClip system has been studied in 64 consecutive patients deemed unsuitable for surgery.[40] The MitraClip device was successfully implanted in the TV in 97% of the cases, and TR was reduced by at least one grade in 91% of the patients with no intra-procedural deaths. Functional class and 6-min walking distance improved significantly.

Anti-thrombotic therapy

The 2017 VHD guidelines states that Vitamin K antagonists (VKA) are the only recommended anticoagulant therapy in patients with mechanical valve prostheses. Novel oral anticoagulants (NOAC) are contraindicated based on the results seen with the direct thrombin inhibitor dabigatran.[41] Factor Xa inhibition acts upstream in the coagulation cascade and may therefore have an advantage by influencing both the extrinsic and contact activation coagulation pathways with minimal antagonism of existing thrombin needed to maintain haemostasis. In a porcine model with aortic heterotopic valves, short-term, intravenous apixaban treatment was associated with a reduced weight of valve thrombus as compared to warfarin and no bleeding events occurred in the apixaban group.[42] This concept is of interest given the clinical relevance of bleeding complications because of VKA.

The optimal antithrombotic regime and duration of treatment in biological prosthetic valves is not fully explored and further randomized trials are needed. Dual antiplatelet therapy is recommended for most patients after TAVI. However, a meta-analysis of four studies including 640 patients found no benefit of dual over single antiplatelet therapy regarding the risk of stroke or mortality, but an increased frequency of major and lethal bleeding events during the first 30 days after intervention.[43]

Increasing attention is being been paid to subclinical leaflet thrombosis after biological SAVR and TAVI, as well as its

inhibitorom trombina dabigatranom.[41] Inhibicija faktora Xa djeluje uzvodno u koagulacijskoj kaskadi i zbog toga može imati prednost zato što djeluje na ekstrinzičnu i kontaktnu aktivaciju koagulacijskih putova s minimalnim potrebnim antagonizmom već postojećeg trombina za održavanje hemostaze. Na svinjskom modelu s heterotopnim aortnim zalistcima, kratkotrajna, intravenska primjena apiksabana bila je povezana s manjom masom tromba na zalistku u usporedbi s varfarinom, a također nije zabilježeno krvarenje u grupi izloženoj apiksabanu.[42] Ovakav koncept privlači pozornost s obzirom na kliničku važnost krvarećih komplikacija zbog AVK-a.

Optimalno antikoagulacijsko liječenje i trajanje liječenja u bolesnika s biološkim zalistcima nije potpuno istraženo i potrebne su daljnje randomizirane kliničke studije. Dvostruko antiagregacijsko liječenje preporučuje se u većine bolesnika nakon TAVI-ja. Ipak, metaanaliza četiriju studija koje su uključile ukupno 640 bolesnika nije utvrdila dobrobit dvojnog u usporedbi s jednostrukim antiagregacijskim liječenjem u smislu smanjenja rizika od smrtnosti ili moždanog udara, nego je utvrdila veću pojavnost velikih i fatalnih krvarenja u prvih 30 dana nakon intervencije.[43]

Sve se više pozornosti pridaje supkliničkoj trombozi zalistaka nakon SAVR biološkim zalistkom i TAVI-ja te povezanosti s antikoagulacijskim liječenjem. Zadebljanje i smanjena pokretljivost kuspisa vidljivi kompjutoriziranom tomografijom nazivaju se hipoatenuirajućim zadebljanjem listića i hipoatenuacijom koja utječe na pokretljivost listića kao teži oblik. Smatra se da su oba nalaza zapravo različiti stadiji istoga fenomena, uz napomenu da zadebljanje listića utječe na njegovu pokretljivost u kasnijoj fazi procesa. Neki podatci upućuju na moguću češću hipoatenuaciju koja utječe na pokretljivost listića nakon TAVI-ja u usporedbi sa SAVR-om (13 % prema 4 %).[44] Mogući rizični čimbenik za navedene fenomene jest nedovoljno širenje samog stenta zalistka tijekom implantacije, dok se postdilatacija zalistka i njegov smještaj iznad anulusa smatraju čimbenicima koji mogu smanjiti njihovu pojavu.

Fenomen zadebljanja listića koje utječe na njegovu pokretljivost malokad dovodi do porasta gradijenta te je prava incidencija ovog fenomena podcijenjena ehokardiografijom.[44,46] Podatci iz registara pokazuju da je fenomen povezan s većom prevalencijom TIA-e, no ne i moždanog udara.[44] No, ti se podatci moraju sagledati oprezno zbog vremenske razdvojenosti između CT-a i kliničkog događaja te su potrebne prospektivne kliničke studije. Čini se kako i AVK i NOAK štite od tromboze listića zalistka te da jednostruko ili dvojno antiagregacijsko liječenje nemaju isti učinak.[44] Kada se pojavi, supklinička tromboza listića može se razriješiti primjenom AVK-a ili NOAK-a, iako je vremenska pojavnost fenomena nepoznata.[47] Također je moguć razvoj ili regresija supkliničke tromboze listića rano ili kasno nakon zamjene zalistka bez promjene u antikoagulacijskom liječenju. Ovi preliminarni podatci kompliciraju preporuke o optimalnoj antikoagulacijskoj strategiji nakon TAVR-a ili SAVR-a. Čini se kako su bolesnici zaštićeni od tromboze listića samo dok su na antikoagulacijskoj terapiji, a cjeloživotno antikoagulacijsko liječenje povezano je s povećanim rizikom od krvarenja. Trenutačne kliničke studije o antitrombotskom liječenju nakon TAVI-ja poput ARTE (NCT01559298), ATLANTIS (NCT02664649), AUREA (NCT01642134), AVATAR (NCT02735902), GALILEO (NCT02556203) i POPULAR-TAVI (NCT02247128), nadamo se, donijet će nove dokaze o optimalnom načinu liječenja.

association with antithrombotic regimes. Leaflet thickening and reduced leaflet motion on CT have been referred to as hypo-attenuating leaflet thickening (HALT) and the more severe hypo-attenuation affecting motion (HAM), respectively. Observations suggest that HALT and HAM are two stages of the same phenomenon, with leaflet thickening affecting leaflet motion at a more advanced stage. Uncontrolled data indicate that HAM may be more common after TAVI (13%) than after SAVR (4%).[44] Among several suggested risk factors, regional stent frame underexpansion has been associated with an increased risk of leaflet thickening, and post-dilatation of self-expanding transcatheter heart valves as well as a supra-annular valve position seemed to reduce the occurrence of this phenomenon.[45]

As the finding of an increase gradient is uncommon with HAM, it is conceivable that the true incidence of HAM is underestimated with the echocardiography assessment.[44,46] Registry data suggest that the phenomenon may be associated with a higher prevalence of TIA, but not stroke.[44] However, these findings must be interpreted with caution due to a temporal separation between the CT and the clinical event, and prospective clinical studies are warranted. Both VKA and NOAC seem to protect against leaflet thrombosis, though neither single or dual anti-platelet therapy have the same effect.[44] When present, the subclinical leaflet thrombosis may be resolved by VKA or NOAC; however, the temporal dynamics of these phenomena are poorly understood.[47] It is possible that subclinical leaflet thrombosis may develop or regress early or late after valve replacement despite no change in anti-thrombotic regime. These preliminary findings complicate recommendations regarding optimal anti-thrombotic therapy after TAVR or SAVR. Patients only seem to be protected against leaflet thrombosis whilst on anti-coagulation therapy, and life-long treatment is associated with an increased bleeding risk. The ongoing trials on anti-thrombotic therapy after TAVI, such as ARTE (NCT01559298), ATLANTIS (NCT02664649), AUREA (NCT01642134) AVATAR (NCT02735902), GALILEO (NCT02556203), and POPULAR-TAVI (NCT02247128), will hopefully add information regarding the optimal treatment.

Valvular disease and pregnancy

Obstructive valvular disease is associated with increased maternal and foetal risk during pregnancy especially in women with severe mitral stenosis. Results from The Registry on Pregnancy and Cardiac Disease (ROPAC), which is part of the European Observational Registry Program, also underline the importance of identifying and evaluating women with AS before pregnancy. In pregnant women with severe AS, defined as a peak gradient ≥64 mmHg, 35.3% were hospitalized because of cardiac reasons compared with 12.9% of the women with moderate AS ($P = 0.02$); the risk of heart failure during pregnancy was significantly higher in symptomatic AS patients.[48]

When valve replacement is indicated in women with childbearing potential, a biological rather than mechanical prosthesis is recommended; women with mechanical prostheses treated with VKA have a higher risk of valve thrombosis and bleeding during pregnancy combined with an increased risk for the foetus. Recently, a meta-analysis of 18 studies with 800 pregnancies evaluated four different antithrombotic regimes [VKA, low molecular weight heparin (LMWH), LMWH + VKA,

Bolesti srčanih zalistaka i trudnoća

Opstruktivna bolest srčanih zalistaka povezana je s većim rizikom za majku i fetus tijekom trudnoće, a posebno u žena s teškom mitralnom stenozom. Rezultati registra ROPAC (prema engl. *The Registry on Pregnancy and Cardiac Disease*), koji je dio EORP-a (prema engl. *the European Observational Registry Program*), također ističu i detekciju osoba s AS prije trudnoće. 35,3 % trudnica s teškom AS, definiranom kao maksimalni gradijent ≥64 mmHg, hospitalizirano je zbog kardioloških razloga, a samo 12,9 % onih s umjerenom AS (p = 0,02). Rizik od razvoja zatajivanja srca tijekom trudnoće mnogo je veći u simptomatskih bolesnica s AS.[48]

Kad se razmatra zamjena zalistka u bolesnica koje tek planiraju roditi, biološki ima prednost pred mehaničkim zalistkom; žene s mehaničkim zalistcima liječene AVK-om imaju veći rizik od tromboze zalistka i krvarenja tijekom trudnoće u kombinaciji s većim rizikom za fetus. Nedavna metaanaliza 18 kliničkih studija koje su uključivale 800 trudnoća istraživala je četiri različite antritrobmotske strategije (AVK, niskomolekularni heparin, niskomolekularni heparin + AVK, nefrakcionirani heparin + AVK) u trudnica s mehaničkim zalistcima.[49] Potvrđeno je kako je s gledišta majke AVK bolja opcija. Niskomolekularni heparin s prilagodbom doze tijekom trudnoće imao je manji rizik za fetus u usporedbi s ostalim strategijama, no fetalni je rizik bio sličan onomu u skupini koja je liječena AVK-om u dozi ≤5 mg/dan (HR 0,9, 95 % CI 0,3 – 2,4). Navedeno potvrđuje otprije poznate podatke da je teratogeni učinak varfarina ovisan o dozi. U sličnoj metaanalizi 46 studija, strategija liječenja AVK-om pokazala je najmanje komplikacija u majke, ali i najmanje živorođene djece. Sekvencijsko liječenje heparinom tijekom prvoga trimestra, praćeno liječenjem AVK-om, tijekom ostatka trudnoće nije poništilo neželjene događaje u fetusa ili novorođenčeta. Strategija liječenja niskomolekularnim heparinom povezana je s najvećim brojem živorođene djece. Sigurnost nefrakcioniranog heparina tijekom cijele trudnoće i primjene AVK-a u dozi od ≤5 mg/dan tijekom prvoga trimestra nije potvrđena.[50]

Endokarditis

Transezofagijska ehokardiografija (TEE) i dalje je preporučena slikovna metoda u dijagnosticiranju infektivnog endokarditisa (IE), a CT se može alternativno primjenjivati i u otkrivanju apscesa/pseudoaneurizmi. U maloj kliničkoj studiji (N = 49) sa slikovnim metodama u bolesnika s IE nativnih i umjetnih zalistaka, preoperativni TEE i CT uspoređivani su s morfološkim nalazom tijekom kirurškog zahvata.[51] Nisu utvrđene razlike u dijagnostičkoj senzitivnosti metoda, ali je TEE-om numerički utvrđeno više vegetacija, perforacija listića i paravalvularnih regurgitacija.

Radionuklidno oslikavanje upale koristeći se ^{18}F-fluorodeoksiglukozom ili radioaktivno obilježenim leukocitima može pomoći u otkrivanju endokarditisa umjetnih zalistaka. Veća senzitivnost i prostorna rezolucija u usporedbi sa standardnim gama-kamerama postignute su razvojem novih kadmij-cink telurid SPECT (prema engl. *single-photon emission computed tomography*) detektora, koji omogućuju bolje oslikavanje endokarditisa s pomoću radionuklida ^{111}In. Provedena je studija izvedivosti i dijagnostičke točnosti simultanog oslikavanja upale s pomoću ^{111}In označenih leukocita i perfuzije miokarda s pomoću 99nTc kako bi se lokalizirali leukociti s

and unfractionated heparin + VKA] in mechanical valves during pregnancy.[49] The study confirms previous findings that VKA is preferred from a maternal perspective. Dose-adjusted LMWH throughout the pregnancy was associated with a lower foetal risk when compared to other regimes, but the foetal risk was similar to risk in the group taken a dose of VKA ≤5 mg/day (HR 0.9, 95% CI 0.3–2.4). These results support previous findings that the teratogen effect by VKA seems to be dose-dependent. In a similar meta-analysis of 46 studies, VKA was associated with fewest maternal complications but also with fewest live births. Sequential treatment with heparin during first-trimester followed by VKA did not eliminate anticoagulant-related foetal/neonatal adverse events. Low molecular weight heparin is associated with the highest number of live births. The safety of unfractionated heparin throughout pregnancy and first-trimester VKA ≤5 mg/day remains unconfirmed.[50]

Endocarditis

Transoesophageal echocardiography (TOE) remains the recommended imaging modality for the diagnosis of infectious endocarditis (IE), whereas CT can be used as an alternative or for detection of abscesses/pseudo-aneurysm. In a small imaging study (n = 49) of patients with both native and prosthetic valve IE, preoperative TOE and CT findings were compared to those at surgery.[51] There was no difference in the diagnostic sensitivity of the two methods, but TOE identified numerically more vegetations, leaflet perforation, and paravalvular leakage.

Radionuclide imaging of inflammation with ^{18}F-fluorodeoxyglucose or radioactively-labelled white blood cells can help in the detection of prosthetic valve endocarditis. Developments with novel cadmium-zinc telluride detector single-photon emission computed tomography (SPECT) cameras provide higher count sensitivity and spatial resolution compared with standard gamma cameras; these promise enhanced ^{111}In imaging of endocarditis. A study evaluated the feasibility and diagnostic accuracy of simultaneous imaging of inflammation with ^{111}In-labelled white blood cells and myocardial perfusion with 99mTc, for localization of white blood cells relative to the valve plane in suspected endocarditis.[52] The results support the usefulness of a novel approach to increase sensitivity and accuracy of white blood cell imaging in endocarditis.

Work has also considered the risks of endocarditis in patients with prosthetic valves. In a population-based cohort study of 138 867 patients with a prosthetic valve (median follow-up 1.7 years) the incidence rate of oral streptococcal IE was 93.7/100 000 patient-years.[53] No increased rate of IE was found within three months of exposure to invasive dental procedure, but in a case crossover analysis a dental procedure was more frequent in IE periods (5.1% vs. 3.2%, OR 1.66; 95% CI 1.05–2.63; P = 0.03). In the CONCOR registry, including patients with congenital heart disease, the incidence of IE was 1.33 cases/1000 patient-years.[54] Prosthetic valves were associated with an increased risk of IE (HR 5.48, 95% CI 3.58–8.38) compared with no prosthetic valve. This increased risk was found both early and during long-term follow-up after surgery. In a registry-based observational study of both biological and mechanical aortic prostheses (mean follow-up 6.2 years), the incidence of prosthetic valve IE was 0.57%/person-year; the

obzirom na ravninu zalistka sa suspektnim endokarditisom.[52] Rezultati podupiru ovakav pristup s većom senzitivnošću i točnošću oslikavanja leukocita u endokarditisu.

Proučavan je i rizik od endokarditisa u bolesnika s umjetnim zalistcima. U kohortnoj studiji temeljenoj na skupini koja je uključila 138 867 bolesnika s umjetnim zalistcima (medijan praćenja 1,7 godina) incidencija IE-a s oralnim streptokokom iznosila je 93.7/100 000 bolesnika na godinua.[53] Nije utvrđena viša učestalost IE-a unutar 3 mjeseca od dentalnog zahvata, ali je u „crossover" analizi slučajeva dentalni zahvat bio češći u razdobljima IE-a (5,1 % prema 3,2 %, OR 1,66; 95 % CI 1,05 – 2,63, p = 0,03). U registru CONCOR, koji uključuje bolesnike s kongenitalnim srčanim greškama, incidencija IE-a iznosila je 1,33 slučaja/1000 bolesnika na godinu.[54] Umjetni zalistci nose povećani rizik od IE-a (HR 5,48, 95 % CI 3,58 – 8,38) u usporedbi s nativnim zalistkom. Povišeni je rizik prisutan rano nakon kiruškog zahvata, ali i tijekom dugotrajnoga praćenja. U opservacijskoj studiji temeljenoj na registru, a koja je uključivala biološke i mehaničke umjetne aortne zalistke (prosječno praćenje 6,2 godine), incidencija IE-a na umjetnom zalistku iznosila je 0,57 %/osobi-godini; rizik je bio najveći u prvoj godini nakon kirurškog liječenja.[55] Rizik od IE-a umjetnog zalistka veći je u grupi s biološkim umjetnim zalistcima (HR 1,54, 95 % CI 1,29 – 1,83) u usporedbi s mehaničkim umjetnim zalistcima. Ove studije potvrđuju rizik od IE-a u bolesnika s umjetnim aortnim zalistcima i podupiru daljnje preporuke antibiotske profilakse u svih takvih bolesnika.

Perspektive

Uz brzu implementaciju TAVI-ja u bolesnika s AS i uz povećani kirurški rizik, uloga TAVI-ja u bolesnika s malim kirurškim rizikom sve se više istražuje. Budući da bolesnici u kliničkim studijama imaju dulje očekivano trajanje života, te studije mogu pružiti nove informacije o trajnosti bioloških umjetnih zalistaka.

Iako transkateterske metode popravka i zamjene zalistka napreduju, dokazi intervencije, posebno u funkcijskoj MR, još uvijek ne postoje. Studije COAPT i MITRA-FR istražuju MitraClip u ovoj indikaciji i rezultati se očekuju tijekom 2018. godine. Još se istražuju i transkateterska zamjena MV-a i transkateterski popravak trikuspisnog zalistka.

risk was highest during the first year after surgery.[55] The risk of prosthetic valve IE was higher in the group with biological prostheses (HR 1.54, 95% CI 1.29–1.83) as compared with those with mechanical prostheses. These studies have confirmed the risk of IE in patients with prosthetic valves and support the continued recommendation of antibiotic prophylaxis in all such patients.

Perspectives

With the rapid adaptation of TAVI in patients with AS and increased surgical risk, the role of TAVI in patients at low surgical risk is currently being explored. Since patients in these trials have longer life-expectancy, these trials may also add important information on longevity of bioprosthetic aortic valves.

As several transcatheter repair and replacement techniques are emerging, evidence for the benefit of intervention in particular functional MR is still missing. The COAPT and French MITRA-FR trials investigate MitraClip in this setting and study results are foreseen during 2018. Furthermore, the impact of transcatheter MV replacement and tricuspidal valve repair is also under investigation.

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