Godina 2021. u kardiovaskularnoj medicini: bolesti srčanih zalistaka

The year in cardiovascular medicine 2021: valvular heart disease

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Uvod

Sve veću zastupljenost bolesti srčanih zalistaka, pogotovo u starijoj populaciji, struka je prepoznala, ali je u općoj populaciji osviještenost još uvijek nedovoljna. S obzirom na sve veći broj nekirurških intervencijskih metoda liječenja, povećao se broj znanstvenih istraživanja u području valvularnih bolesti koja je dovela do znatnog povećanja broja objavljenih znanstvenih radova tijekom protekle godine. Velik broj tih radova pridaje važnost upravo intervencijskom liječenju, kao i usporedbi ishoda pri kirurškom i medikamentnom liječenju. Naglasak je također stavljen na patofiziologiju, poboljšanje dijagnostičkih algoritama, stratifikaciju rizika te određivanje optimalnoga vremena za intervenciju. I europsko (ESC/

Introduction

The increasing burden of valvular heart disease (VHD)—in particular in an ageing population—is recognized by medical experts, although there is less awareness of these conditions by the general public and relevant stakeholders. Together with emerging nonsurgical interventional treatment options, this has led to intense research interest in VHD with an enormous number of publications during the last year. Many of these publications address interventional treatment, including technical refinements and outcomes compared with surgery or medical therapy. In addition, attention has focused on pathophysiological aspects, improved diagnosis, risk stratification, and optimal timing for intervention. Im-

EACTS) i američko (ACC/AHA) kardiološko društvo objavilo je nove smjernice za liječenje bolesti srčanih zalistaka (**slika 1A**).[1,2] Ovaj kratki pregled ne može izdvojiti sve promjene u novim smjernicama niti navesti svaki znanstveni napredak u protekloj godini. Stoga je izabrano nekoliko članaka koji su odraz širokog raspona sve većeg broja znanstvenih istraživanja uz nadu da će pobuditi interes za daljnje pretraživanje literature.

portantly, new guidelines for the management of VHD have been published by both the ESC/EACTS and ACC/AHA (**Figure 1A**).[1,2] This short overview can neither address all changes in the guidelines nor acknowledge all appreciable research efforts over this year. Thus, we have selected a few papers as examples that reflect the breadth of ongoing research, with the expectation that interested readers will find additional articles using online searches.

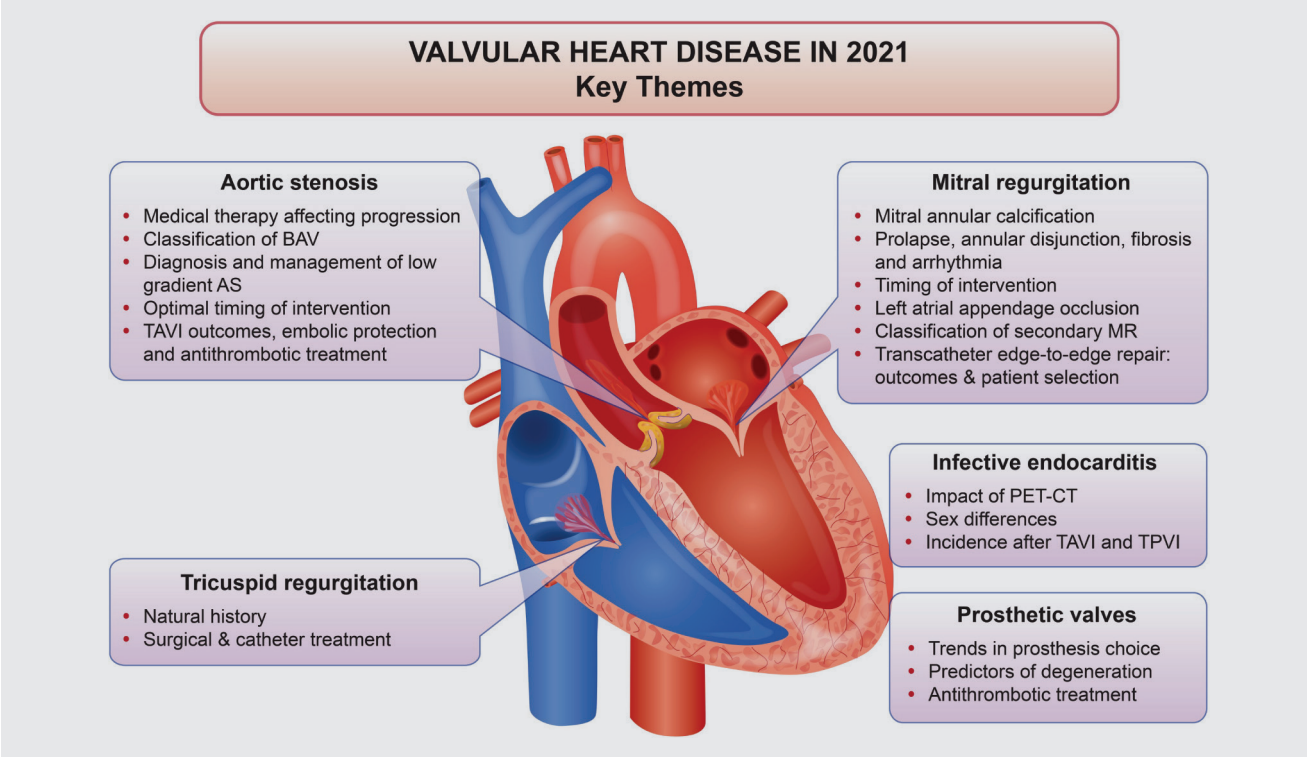

FIGURE 1A GRAPHICAL ABSTRACT. Valvular heart diseases in 2021. (from Baumgartner H, Iung B, Messika-Zeitoun D, Otto CM. The year in cardiovascular medicine 2021: valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):633-640. doi: 10.1093/eurheartj/ehab885, by permission of OUP on behalf of the ESC).

Aortalni zalistak

PATOFIZIOLOGIJA

Ima sve više dokaza o postojanju terapije koja može utjecati na kalcificirajuću aortalnu stenozu (AS). Pretklinička i opservacijska istraživanja pokazala su da bi cijena pregradnje i osteoblastične diferencijacije intersticijskih stanica u srčanim zalistcima mogla imati važnu ulogu, no u dvostruko slijepom randomiziranom kliničkom ispitivanju ni denosunab ni alendronična kiselina nisu pokazali učinak na progresiju kalcifikacije aortalnog zalistka.[3] Lee *i sur.*[4] u retrospektivnoj analizi bolesnika sa šećernom bolešću i blagom do umjerenom AS objavili su da su inhibitori dipeptidil peptidaze-4 s povoljnim farmakokinetskim i farmakodinamskim svojstvima bili povezani sa manjim rizikom od progresije AS-a. Perez de Isla i *sur.*[5] ustanovili su povećanu incidenciju zamjene aortalnog zalistka (AVR) u bolesnika s porodičnom hiperkolesterolemijom (FH) na temelju podataka iz istraživanja *SAFEHE-*

Aortic valve

PATHOPHYSIOLOGY

There is increasing evidence that disease-modifying therapies for calcific aortic stenosis (AS) may be possible. Preclinical and observational studies had suggested that bone turnover and osteoblastic differentiation of valvular interstitial cells are important contributory mechanisms but in a double-blind randomized controlled trial (RCT) neither denosumab nor alendronic acid was shown to affect the progression of aortic valve calcification.[3] Lee et al.[4] reported in a retrospective analysis of patients with diabetes and mild-to-moderate AS that dipeptidyl peptidase-4 inhibitors with favourable pharmacokinetic and pharmacodynamic properties were associated with lower risk of AS progression. Pérez de Isla et al.[5] reported a higher incidence of aortic valve replacement (AVR) in patients with familial hypercholesterolaemia (FH) based on data from SAFEHEART–a long-term prospective cohort

ART – prospektivne kohortne studije koja je uključivala 5022 ispitanika. Analiza Coxovom regresijom pokazala je povezanost između FH-a i zamjene aortalnog zalistka (HR: 3,89; 95 % interval pouzdanosti (CI): 1,20 – 12,63; P = 0,024) sa starijom dobi, prethodno dokazanom aterosklerotskom kardiovaskularnom bolešću, arterijskom hipertenzijom, povećanim LDL kolesterolom i Lp(a), pri čemu su se dob i Lp(a) pokazali neovisno prediktivnima, što upućuje na to da redukcija LDL kolesterola i Lp(a) te adekvatna kontrola arterijske hipertenzije mogu usporiti progresiju AS-a u bolesnika s FH-om. Navedena istraživanja ostaju samo na pretpostavkama, a daljnja su istraživanja potrebna radi procjene novih terapijskih mogućnosti.

DIJAGNOZA

Dijagnosticiranje teške AS, kao i identifikacija bolesnika koji bi imali dobrobit od liječenja, ostaje izazovna kada je riječ o *low-gradient* AS-a. Mosleh *i sur.*[6], primjenom metode uparivanja prema rezultatu sklonosti (engl. *propensity score matching*), utvrdili su podjednaku korist od transkateterske implantacije aortalne valvule (TAVI) i u bolesnika s *high-gradient* AS-a i u onih s paradoksalnom *low-flow – low-gradient* AS. Metaanaliza koja je uključila 32 istraživanja pokazala je podjednaku korist od AVR-a u bolesnika s klasičnom *low-flow – low-gradient* AS, paradoksalnom *low-flow – low-gradient* AS, čak i *normal-flow – low-gradient* AS (HR za mortalitet od svih uzroka 0,41 – 0,42).[7] Suprotno tomu, Freitas-Ferraz *i sur.*[8] objavili su da trećina bolesnika s paradoksalnom *low-flow – low-gradient* AS nema koristi od intervencije. Bienjounetti-Boudreau *i sur.*[9] utvrdili su da među bolesnicima s *low-gradient* AS žene imaju lošije preživljenje u usporedbi s muškarcima, moguće kao posljedica manje zastupljenosti AVR-a, što izaziva zabrinutost u vezi s postavljanjem pravilne dijagnoze i kliničkim odlučivanjem u takvih bolesnica. Spomenuta istraživanja ističu važnost integriranog pristupa, uključujući i dodatne parametre kao kvantifikaciju kalcifikacije zalistka, kada je posrijedi *low-gradient* AS[1] kako bi se izbjegli i pretjerano i nedovoljno liječenje. Takav integrirani pristup mogao bi biti adekvatan i za bolesnike s *normal flow – low-gradient* AS.

Međunarodni konsenzus o nomenklaturi i klasifikaciji kongenitalne bikuspidalne aortalne valvule i aortopatije bio bi koristan za kliničku, kiruršku, intervencijsku i znanstvenu svrhu.[10]

ODREĐIVANJE TRENUTKA ZA INTERVENCIJU

Nove ESC/EACTS i ACC/AHA smjernice i dalje preporučuju AVR samo u selekcioniranih bolesnika s asimptomatskom AS, iako se rezultati randomiziranih kliničkih istraživanja koja su u tijeku još uvijek iščekuju.[1,2] Nedavno su objavljeni rezultati istraživanja *AVATAR* (*Aortic Valve ReplAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis*).[11] Među 157 bolesnika s teškom asimptomatskom AS (uključujući negativan test opterećenja) koji su nasumično podijeljeni u skupine s ranim kirurškim ili konzervativnim liječenjem, kirurška skupina imala je mnogo manju incidenciju primarnoga zajedničkog ishoda (ukupna smrtnost, akutni infarkt miokarda, moždani udar ili hospitalizacija zbog akutnog popuštanja srca). Ovi rezultati zahtijevaju potvrdu u većim istraživanjima s duljim vremenom praćenja ako se uzme u obzir zajednički ishod i problem izdržljivosti valvula tijekom bolesnikova života. Prema trenutačno valjanim smjernistudy of a population with and non-affected relatives including a total of 5022 subjects. Cox regression analysis demonstrated an association between FH and AVR [hazard ratio (HR): 3.89; 95% confidence interval (CI): 1.20–12.63; P=0.024], with older age, previous atherosclerotic cardiovascular disease, hypertension, increased LDL-cholesterol Lp(a) —years, and elevated Lp(a) being independently predictive of an event suggesting that reduction in LDL-cholesterol and Lp(a) together with control of hypertension could retard the progression of AS in FH. All these studies, however, remain only hypothesis generating, and further research is required to evaluate potential treatment options.

DIAGNOSIS

The diagnosis of severe AS and identification of patients who benefit from intervention remains challenging in the setting of lowgradient AS. Mosleh et al.[6] reported a similar benefit of transcatheter aortic valve implantation (TAVI) in patients with high-gradient AS and paradoxical low-flow–low-gradient AS using propensity score matching. A meta-analysis including 32 studies found the similar benefit of AVR in patients with classical low-flow–lowgradient AS, paradoxical low-flow–low-gradient AS, and even normal flow–low-gradient AS (HR for all-cause mortality 0.41–0.42).[7] Conversely, Freitas-Ferraz et al.[8] reported that one-third of patients with paradoxical low-flow–low-gradient AS failed to benefit from intervention. Bienjounetti-Boudreau et al.[9] reported that in patients with low-gradient AS, women had lower survival compared with men, possibly related to a lower rate of AVR, raising concerns about correct diagnosis and clinical decision-making for women in this setting. These studies emphasize the importance of an integrated approach, including additional parameters such as quantification of valve calcification, in the setting of low-gradient AS[1] to avoid both, over- or undertreatment. An integrated approach also may be appropriate in patients with normal flow–lowgradient AS.

Availability of the international consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy will be helpful for clinical, surgical, interventional, and research purposes.[10]

TIMING OF INTERVENTION

The updated ESC/EACTS and ACC/AHA guidelines continue to recommend AVR only in selected patients with asymptomatic AS although results from ongoing RCTs are awaited.[1,2] Recently, the results of the AVATAR (Aortic Valve ReplAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis) Trial were published.[11] In 157 patients with severe asymptomatic AS (including a negative exercise test) who were randomly allocated to early surgery or conservative treatment, the surgical group had a significantly lower incidence of the primary composite endpoint (all-cause mortality, acute myocardial infarction, stroke or unplanned hospitalization for heart failure). These findings require confirmation in larger studies and over a longer follow-up time, given the use of a combined endpoint and the issue of valve durability over the patient's lifetime. In the current guidelines, the thresholds where intervention should be considered (Class IIa recommendation) in asymptomatic patients with severe AS were lowered to left ventricular ejection fraction (LVEF),55% and peak transvalvular velocity ≥5 m/s in surgical low-risk patients[1] (**Figure 1B**).

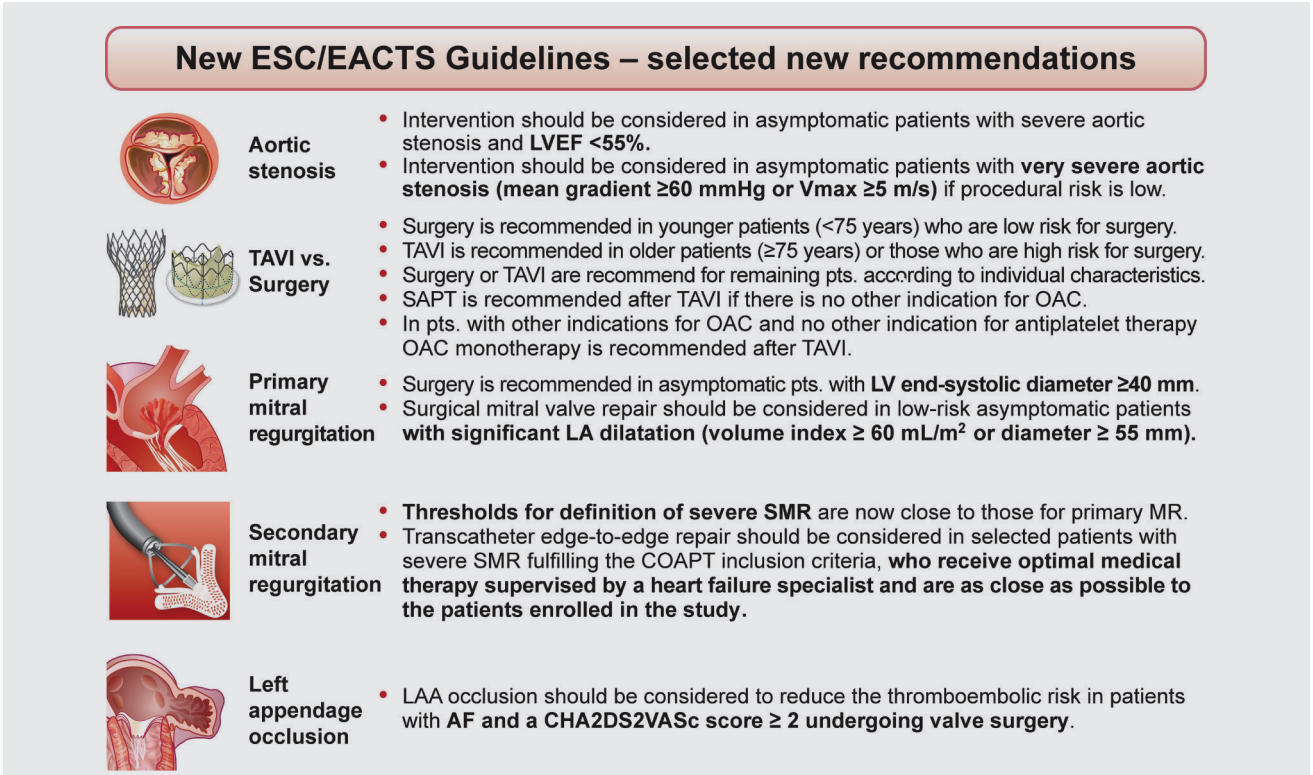

FIGURE 1B. Selected important new recommendations in the 2021 ESC/EACTS guidelines for the management of valvular heart disease. Reproduced with permission from Vahanian *et al.*[1]. (from Baumgartner H, Iung B, Messika-Zeitoun D, Otto CM. The year in cardiovascular medicine 2021: valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):633-640. doi: 10.1093/eurheartj/ehab885, by permission of OUP on behalf of the ESC).

cama, pragovi kada bi se trebala razmotriti intervencija (razina preporuke II. A) u asimptomatskih bolesnika s teškom AS sniženi su na ejekcijsku frakciju lijeve klijetke (LVEF) <55% i maksimalnu transvalvularnu brzinu ≥ 5 m/s u bolesnika s niskim kirurškim rizikom[1] (**slika 1B**).

Jean *i sur.*[12] prikazali su da je umjereni stupanj AS-a u bolesnika sa zatajivanjem srca (HF) i sniženom LVEF povezan sa znatnim rizikom od smrtnosti. AVR, a posebice TAVI, tijekom praćenja pokazali su bolje preživljenje, što podržava potrebu procjene učinka rane transkateterske AVR u randomiziranim kliničkim istraživanjima.

Bolesnici u kojih je postavljena indikacija za AVR moraju biti pravodobno zbrinuti, što potvrđuju i rezultati istraživanja koje je pokazalo znatnu smrtnost bolesnika na listama čekanja i za kiruršku i za transkatetersku AVR.[13]

VRSTA INTERVENCIJE

Izbor između TAVI-ja i kirurške AVR (SAVR) i dalje ostaje težak za bolesnike koji su prikladni za obje metode liječenja. U metaanalizi trenutačno dostupnih kliničkih randomiziranih istraživanja Zhang *i sur.*[14] kao mogući problem ističu dugoročne ishode nakon TAVI-ja. Dok su dvogodišnji rezultati za ukupnu smrtnost, kombinirani ishod ukupne smrtnosti i moždanog udara te kardiovaskularne smrtnosti bili podjednaki za obje metode liječenja, rezultati nakon 2 – 5 godina praćenja išli su u prilog kirurškog liječenja. Ovakvi se rezultati mogu

Jean et al.[12] reported that in a series of patients with heart failure (HF) and reduced ejection fraction, moderate AS was associated with a marked incremental risk of mortality. Aortic valve replacement, and especially TAVI during follow-up, was associated with improved survival supporting the realization of RCTs to assess the effect of early transcatheter AVR in these patients.

Patients with established indication for AVR require timely treatment. This was once more emphasized by a study reporting significant mortality on the waiting list for surgical as well transcatheter AVR.[13]

TYPE OF INTERVENTION

The choice between TAVI and surgical AVR (SAVR) remains a matter of controversy in patients suitable for both interventions. In a meta-analysis of currently available RCTs, Zhang et al.[14] raise concerns regarding the long-term outcome of TAVI. While 2-year results for all-cause mortality, the combined endpoint of all-cause mortality and stroke, and cardiovascular mortality were similar for the two modalities, 2- to 5-year results favoured surgery. Possible explanations for this observation include higher rates of more than mild paravalvular regurgitation and conduction disturbances (pacemaker requirement, left bundle branch block) after TAVI which may affect long-term, but not short-term, outcomes. The 2-year analysis of PARTNER 3 (balloon-expandable TAVI vs. SAVR

dijelom objasniti većim rizikom od znatnih paravalvularnih regurgitacija i smetnji provođenja (potreba za implantacijom elektrostimulatora srca, blok lijeve grane) nakon TAVI-ja, što može utjecati na dugoročne, ali ne i kratkoročne ishode. Dvogodišnja analiza rezultata istraživanja *PARTNER 3* (*balloon-expandable TAVI* vs. *SAVR in low-risk patients*) pokazala je znatnu razliku u korist TAVI-ja što se tiče zajedničkog ishoda (smrtnost, moždani udar i rehospitalizacija zbog HF), ali nije dosegnula statističku značajnost za smrtnost i moždani udar zajedno.[15] Osmogodišnji rezultati istraživanja *NOTION*[16] (studije s najdužim vremenom praćenja za kliničko randomizirano ispitivanje, većinom s bolesnicima niskoga kirurškog rizika) nisu pokazali razliku u ukupnoj smrtnosti (**slika 2**)[17] ili u zajedničkom ishodu od ukupne smrtnosti, moždanog udara i infarkta miokarda. Hemodinamski su rezultati diskretno, ali ipak mnogo bolji za TAVI s nižom stopom strukturne deterioracije valvule, iako to može biti posljedica viših rezidualnih gradijenata u kirurškoj skupini bolesnika. Za klinički relevantan ishod zatajenja protetičkog zalistka (smrt povezana sa zalistkom, teška strukturna deterioracija zalistka, reintervencija na zalistku), nije bilo značajne razlike između ispitivanih skupina. Spomenuto je ispitivanje pokazalo neinferiornost za TAVI dugoročno, ali uz nekoliko ograničenja (mali broj bolesnika, nepotpuni ehokardiografski nalazi, znatan udio kirurških valvula sa suboptimalnim rezultatima). Zbog toga se i dalje trebaju prikupljati dugoročni podatci, a proširenje indikacije za TAVI u mlađih niskorizičnih bolesnika još uvijek treba razmatrati s oprezom. I dalje ostaje pitanje izdržljivosti valvula zbog povećanog rizika od paravalvularnih regurgitacija i smetnji provođenja koje su jednim dijelom uvjetovane vrstom valvule. Rezultati za balonom širećeu Edwardsovu valvulu druge generacije bili su lošiji u usporedbi s kirurškom valvulom, dok je treća generacija valvula bila neinferiorna.[18]

in low-risk patients) found a decreasing but still significant difference in favour of TAVI for the composite of death, stroke, and rehospitalization for HF but no longer a significant difference for death or stroke alone.[15] The 8-year results of the NOTION trial16—so far the longest follow-up for an RCT with the majority of patients included being at low surgical risk—continue to show no difference in all-cause mortality (**Figure 2**)[17] or the composite of all-cause mortality, stroke, and myocardial infarction. Haemodynamic results were slightly but still significantly better for TAVI with a lower rate of structural valve deterioration although the latter was driven by the higher residual gradients in the surgical group. For the more clinically relevant endpoint of prosthetic valve failure (valve-related death, severe structural valve deterioration, or valve re-intervention), there was no difference between study groups. This trial supports non-inferiority of TAVI in the long-term but has several limitations (small patient numbers, incomplete echo data and no core lab, and a significant proportion of surgical valve types with known suboptimal results). Therefore, long-term data still need to be collected carefully and the extension of TAVI to younger low-risk patients must be considered with caution. In addition to higher rates of paravalvular regurgitation and conduction disturbances the issue of valve durability, which appears to be valve specific, remains a concern. For the balloon-expandable Edwards valve, the performance of the second generation was worse than for the surgical valve while the third generation was non-inferior.[18]

Potentially limited access to the coronary arteries after TAVI also remains a matter of concern. Although high success rates for the cannulation of coronaries have been reported, in particular for short stent-frame prosthesis, failure of percutaneous coronary intervention (PCI) was close to 10%[19,20] and must be ex-

FIGURE 2. Please see Figure 2 in the original article.

Još jedan problem jest mogući ograničen pristup koronarnim arterijama nakon TAVI-ja, pri čemu se neuspjeh perkutane koronarne intervencije (PCI) bilježi u gotovo 10 % slučajeva[19,20], a znatan se porast očekuje nakon ponovnog TAVI-ja.[21] Bolesnici s infarktom miokarda s elevacijom ST-segmenta nakon TAVI-ja imali su mnogo dulje *door-to-balloon* vrijeme i 4 puta veći rizik od neuspjele PCI s lošijim ishodom u usporedbi s bolesnicima bez TAVI-ja.[22]

Trenutačno aktualne ACC/AHA smjernice proširile su kriterije za podijeljeno donošenje odluke (*heart team* i bolesnik koji razmatraju prednosti i nedostatke TAVI-ja i SAVR-a) za bolesnike u dobi od 65 i 80 godina ili očekivanim životnim vijekom od 10 do 20 godina.[2] Smjernice ESC/EACTS nešto su konzervativnije te preporučuju SAVR u svih niskorizičnih bolesnika mlađih od 75 godina (IB), a TAVI za bolesnike od 75 godina ili starije ili bolesnike s visokim kirurškim rizikom (IA), dok su preostali bolesnici ostavljeni za individualnu procjenu.[1]

pected to markedly increase after redo-TAVI.[21] Patients with ST-elevation myocardial infarction after TAVI had a significantly longer door-to-balloon time and a four-fold higher PCI failure rate associated with poor outcome compared with patients without TAVI.[22]

Current ACC/AHA guidelines opened the range where individual shared decision-making (heart team and patient weigh individual advantages and disadvantages of TAVI and SAVR) to patients between age 65 and 80 years or life expectancy 10–20 years, respectively. [2] The ESC/EACTS guidelines remained more conservative recommending SAVR for all low-risk patients younger than 75 years (IB) and TAVI for patients 75 years and older or patients at high surgical risk (IA) while leaving the remaining patients for individual decision.[1]

KOMPLIKACIJE NAKON TRANSKATETERSKE IMPLANTACIJE AORTALNE VALVULE

Iako je rizik od moždanog udara relativno nizak nakon TAVI-ja, ta komplikacija i dalje ostaje jedna od najozbiljnijih pa se stoga intenzivno ispituju uređaji za zaštitu od embolijskih incidenata koji bi mogli dodatno smanjiti taj rizik. U jednoj metaanalizi u više od 70 % bolesnika dokazano je manje moždano oštećenje nakon TAVI-ja što je bilo povezano s povećanim rizikom od rane kognitivne disfunkcije, ali s još nepoznatim dugoročnim posljedicama.[23] Uređaji za zaštitu od cerebralnih embolijskih događaja nisu smanjili učestalost ni broj ozljeda po bolesniku, a nekoliko istraživanja također nije uspjelo pokazati smanjenje neželjenih događaja primjenom tih uređaja.[24-26]

Na temelju rezultata nekoliko kliničkih randomiziranih istraživanja, nakon postupka TAVI trenutačno se preporučuje primjena jednog antiagregacijskog lijeka u bolesnika u kojih ne postoji druga indikacija za antikoagulantnu ili dvojnu antiagregacijsku terapiju te primjena oralne antikoagulantne terapije u bolesnika koji za to imaju otprije postavljenu indikaciju, a bez indikacije za drugu antiagregacijsku terapiju.[27]

Antikoagulancije koji nisu antagonisti vitamina K (NOAK) mogu biti dobra zamjena za varfarin,[28,29] iako su neka istraživanja pokazala veći rizik od krvarenja.[30] Jedno je istraživanje pokazalo superiornost klopidogrela u odnosu prema acetilsalicilatnoj kiselini kod monoterapije.[31] U drugom istraživanju s niskorizičnim bolesnicima varfarin je bio povezan s manje supkliničkih valvularnih tromboza bez povećanog rizika od krvarenja.[32] Uzimajući u obzir još nerazjašnjen učinak supkliničkih valvularnih tromboza, rutinska primjena antikoagulantne terapije u takvih bolesnika ostaje upitna.

Znatna rezidualna mitralna regurgitacija (MR) nakon postupka TAVI ima negativan učinak na ishod[33] te bi perkutana intervencija na mitralnom zalistku mogla poboljšati simptome i ishode[34], ali za to su potrebna daljnja klinička istraživanja.

Bolesti mitralnog zalistka

KALCIFICIRAJUĆA BOLEST MITRALNOG ZALITSKA

Kalcificirajuća bolest mitralnog zalistka (CMVD) posljedica je kalcifikacije mitralnog anulusa (MAC) koja se proširi na zalistke te može uzrokovati mitralnu stenozu (MS), MR ili oboje. Najčešće je riječ o starijim bolesnicima, dominantno o ženama s brojnim komorbiditetima.[35] Takvi su bolesnici često neliječeni, iako simptomatski s lošim ishodima koji su precipitirani težinom bolesti (površina zalistka / gradijent) i plućnom hipertenzijom. Drugo je istraživanje potvrdilo neovisni prognostički učinak transmitralnoga gradijenta neovisno o težini MR-a.[36] Transmitralni se gradijent se lako mjeri, ali jako ovisi o hemodinamskim uvjetima (udarni volumen i frekvencija srca). Kada se gradijent prilagodi tim parametrima, dobije se bolja dijagnostička podudarnost za težinu MS-a, a pragovi od 4 i 6 mmHg za umjerenu i tešku MS pružaju bolju stratifikaciju rizika nego uobičajeno primjenjivani pragovi od 5 i 10 mmHg.[37] Budući da je kirurški zahvat visokorizičan, razvijaju se transkateterske intervencije na mitralnom zalistku, no i one nose povećan rizik od smrtnosti, opstrukcije izlaznoga trakta lijeve klijetke (LVOT) i paravalvularnih regurgitacija.[38]

COMPLICATIONS AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION

Although the stroke rate has become relatively low after TAVI, it remains one of the most devastating complications and embolic protection devices that may potentially further reduce this risk are intensively investigated. In a meta-analysis, more than 70% of patients had evidence of silent brain injury after TAVI which was associated with increased incidence of early cognitive dysfunction but still unclear long-term effects.[23] Cerebral embolic protection devices reduced the volume but did, however, not affect the incidence and the number of injuries per patient. Several other studies could so far not demonstrate a reduction in clinical event rates with the use of protection devices.[24–26]

After TAVI, the current recommendation is to use single platelet therapy in patients without other indication for oral anticoagulation or dual antiplatelet therapy, and to use oral anticoagulation only in those with established indication and no other indication for antiplatelet therapy, based on results from several RCTs.[27]

Non-vitamin K antagonist oral anticoagulants (NOACs) may be a good alternative to warfarin when oral anticoagulation is indicated[28,29] although a recent RCT reported a higher bleeding rate.[30] One study reported that clopidogrel may be superior to aspirin for single antiplatelet therapy.[31] In another RCT of low-risk patients, warfarin was associated with less subclinical valve thrombosis without increased bleeding risk.[32] However, considering the still unclear impact of subclinical valve thrombosis, the use of routine anticoagulation remains questionable even in these patients.

Significant residual mitral regurgitation (MR) after TAVI has been shown once more to have negative impact on outcome[33] and percutaneous mitral valve repair may then improve symptoms and outcome,[34] but further prospective studies will be required to prove this concept.

Mitral valve disease

CALCIFIC MITRAL VALVE DISEASE

Calcific mitral valve disease (CMVD) is due to mitral annular calcification (MAC) that extends into the leaflets and can present as mitral stenosis (MS), MR, or a combination of both. Patients with CMVD are mostly elderly, with a strong female predominance and multiple comorbidities.[35] They are often left untreated even when symptomatic and experienced a poor outcome predicted by severity of the disease (valve area/gradient) and pulmonary artery pressure. The independent prognostic value of the transmitral gradient—irrespective of MR degree—was confirmed in a second study.[36] Transmitral gradient is easy to measure but is dependent on haemodynamic conditions (stroke volume and heart rate). The projected gradient, adjusting for these two parameters, improved diagnostic concordance for MS severity and thresholds of 4 and 6 mmHg for moderate and severe MS provided a better risk stratification than the commonly used thresholds of 5 and 10 mmHg.[37] Surgery is high risk, and transcatheter mitral valve interventions have emerged as an alternative but remain associated with high mortality and expose to left ventricular outflow tract (LVOT) obstruction and paravalvular regurgitation.[38] Acceptable procedural and clinical outcomes

Prihvatljivi proceduralni i klinički ishodi mogli bi se postići primjenom preventivnih strategija (alkoholna septalna ablacija) kao u prospektivnom registru *MITRAL*, ali dvije trećine bolesnika morale su biti isključene zbog velikog rizika od opstrukcije LVOT-a, embolizacije proteze ili obojega.[39]

PROLAPS MITRALNOG ZALISTKA, DISJUNKCIJA MITRALNOGA PRSTENA, FIBROZA I ARITMIJE

U 400 bolesnika s prolapsom mitralnog zalistka (MVP) nađena je fibroza (s prevalencijom od 28 %) procijenjena na osnovi kasnog nakupljanja gadolinija (LGE) na magnetnoj rezonanciji (CMR), više u području bazalne inferolateralne stijenke i papilarnih mišića, što je bilo povezano s težinom MR-a, remodelacijom lijeve klijetke (volumen i masa), ventrikularnim aritmijama i povećanim rizikom od neželjenih kardiovaskularnih događaja.[40] Povezanost između LGE-a i ventrikularnih aritmija izraženija je u bolesnika bez MR-a ili s blagom do umjerenom MR nego u bolesnika s teškim stupnjem MR-a, što podržava patofiziološku hipotezu kako je abnormalnost mitralne valvule koja uzrokuje do fibroze više odgovorna za ventrikularne aritmije nego sama MR. Prijavljena je povezanost između disjunkcije mitralnog prstena (MAD), redundantnih zalistaka i dvokuspisne MVP / Barlowljeve bolesti s ventrikularnim aritmijama[41,42], a rizik od smrtnosti povećava se s težinom ventrikularnih aritmija, pogotovo ako su konzervativno liječene.[41] Ipak, povezanost između MAD-a i smrtnosti ostaje nerazjašenjena.[43] Kada su bolesnici sa strukturno zdravim srcem bili podvrgnuti CT-u, prevalencija MAD-a bila je iznimno visoka (96 %).[44] Osim toga, prevalencija MAD-a vrlo varira, ovisno o slikovnoj metodi. Transtorakalna ehokardiografija ima dobru specifičnost, ali nisku osjetljivost u usporedbi s MRI-jem i transezofagealnom ehokardiografijom (TEE).[45] Velika prospektivna istraživanja nužna su da bi se standardizirale definicija i metodologija procjene za MAD te bolje definirao aritmološki rizik od MVP-a i MAD-a, kao i moguća uloga LGE-a u postavljanju indikacije za operaciju u bolesnika s teškom primarnom MR.

ODREĐIVANJE TRENUTKA ZA INTERVENCIJU

U asimptomatskih bolesnika s primarnom MR i Smjernice ESC/EACTS i ACC/AHA preporučuju operaciju kada promjer lijeve klijetke na kraju sistole dosegne 40 mm (prethodno 45 mm).[1] Europske smjernice također ističu važnost uvećanja lijeve pretklijetke (≥60 mL/m^2 ili ≥55 mm) u asimptomatskih bolesnika u sinusnom ritmu s očuvanom sistoličkom funkcijom i dijametrom lijeve klijetke na kraju sistole <40 mm ako je kirurški rizik nizak i vjerojatnost reparacije velika, a operacija se provodi u specijaliziranom centru za srčane zalistke (razina preporuke II. A). Američke smjernice reparaciju zalistka smatraju razumnom u asimptomatskih bolesnika s teškom MR, lijevom klijetkom uredne veličine i funkcije te niskim kirurškim rizikom i reparabilnom valvulom, neovisno o veličini lijeve pretklijetke.

ANTIKOAGULACIJSKA TERAPIJA I MOŽDANI UDAR

Istraživanje *LAOOS III* (*The Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke*) ispitivalo je učinkovitost i sigurnost istodobnog zatvaranja aurikule lijeve pretklijetke (LAA) (u usporedbi s nezatvaranjem LAA) u bolesnika s fibrilacijom atrija (FA) i CHAD2DS2-Vasc skorom ≥2

could be achieved using pre-emptive strategies (alcohol septal ablation) as in the MITRAL prospective registry, but two-thirds of patients had to be excluded because of high risk of LVOT obstruction, prosthesis embolization, or both.[39]

MITRAL VALVE PROLAPSE, MITRAL ANNULAR DISJUNCTION, FIBROSIS, AND ARRHYTHMIA

In 400 patients with mitral valve prolapse (MVP) enrolled in two centres, myocardial replacement fibrosis—late gadolinium enhancement (LGE) assessed using cardiac magnetic resonance imaging (CMR)—was common (prevalence 28%), preferentially located in the basal infero-lateral wall and papillary muscle, was associated with MR severity, left ventricular (LV) remodelling (LV volume and mass), ventricular arrhythmia, and with an increased risk of cardiovascular events (incremental to echocardiographic information). [40] Interestingly, the relationship between LGE and ventricular arrhythmia was more pronounced in patients with no/mild or moderate MR than in patients with severe MR favouring the pathophysiologic hypothesis that abnormalities of the mitral valve apparatus lead to fibrosis responsible for ventricular arrhythmia rather than a causal role of MR. An association between mitral annular disjunction (MAD), leaflet redundancy or bileaflet MVP/ Barlow disease, and ventricular arrhythmia has been reported[41,42] and mortality rate increased with ventricular arrhythmia grade especially under conservative management.[41] However, the relationship between MAD and mortality remained unclear.[43] When assessed in patients with structurally normal heart who underwent a CT scan, the prevalence of MAD was reported to be very high (96%).[44] In addition, the prevalence of MAD widely varied according to the imaging technique. Transthoracic echocardiography (TTE) exhibited a good specificity but a low sensitivity compared with MRI or transoesophageal echocardiography (TEE).[45] Large prospective studies are strongly needed to standardize the definition and methodology of MAD measurement and to better define the arrhythmogenic risk of MVP and MAD as well as the potential role of LGE to guide indications for surgery in patients with severe primary MR.

TIMING OF INTERVENTION

In asymptomatic patients with primary MR, both the ESC/EACTS and ACC/AHA guidelines now recommend surgery when LV endsystolic diameter reaches 40 mm (previously 45 mm).[1] The ESC/ EACTS guidelines also emphasize the importance of left atrium enlargement (≥60 mL/m2 or ≥55 mm) in asymptomatic patients in sinus rhythm with preserved EF and LV end-systolic diameter ,40 mm if surgical risk if low and likelihood of repair high when surgery is performed in a Heart Valve Centre (Class IIa recommendation). The ACC/AHA guidelines consider valve repair reasonable in asymptomatic patients with severe MR, normal LV size and function, low surgical risk and a repairable valve, regardless of the left atrial size.

ANTICOAGULATION AND STROKE

The Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke (LAOOS III) trial has evaluated the efficacy and safety of concomitant left atrial appendage (LAA) occlusion (vs. no occlusion) in patients in atrial fibrillation and a CHAD2DS2-Vasc score ≥2 undergoing cardiac surgery, of whom 36% had a mitral valve procedure.[46] The trial showed a reduction of the risk of stroke or systemic embolic event [4.8 vs. 7.0%, HR=0.67 (0.53–0.85), P=0.0010] in those with LAA occlusion.

koji su podvrgnuti kardiokirurškom zahvatu, od čega je 36 % bolesnika imalo zahvat na mitralnom zalistku.[46] Istraživanje je pokazalo redukciju rizika od moždanog udara i sistemskih embolijskih događaja (4,8 prema 7,0 %, HR = 0,67 (0,53 – 0,85), P = 0,0010) u bolesnika u kojih je izvedeno zatvaranje LAA. U skladu s ovim podatcima, trenutačne američke i europske smjernice smatraju da u bolesnika s bolesti srčanih zalistaka i FA-om koji se podvrgavaju kardiokirurškom zahvatu treba razmotriti ligaciju ili eksciziju LAA, kao i kirurško izolaciju plućnih vena ili *maze* proceduru.

SEKUDARNA MITRALNA REGURGITACIJA – PRAGOVI I PROGNOSTIČKI ČIMBENICI

Brojna su istraživanja potvrdila povezanost između sekundarne mitralne regurgitacije (SMR) i neželjenih ishoda, čak i u slučaju blage MR.[47-49] Nove su europske smjernice prihvatile kriterije za definiciju teške SMR (američke smjernice to su učinile prije) koji uključuju efektivnu površinu regurgitacijskog ušća (EROA) ≥40 mm^2 ili regurgitacijski volumen ≥60 mL, pritom prihvaćajući i niže kriterije (EROA ≥30 mm^2 ili RV ≥45 mL) ako je površina regurgitacijskog ušća eliptična ili u *low-flow* hemodinamskim uvjetima. Glavni razlog za ovu promjenu jest nedostatak dokaza da kirurško ili transkateterske liječenje poboljšava ishod u bolesnika s manjom efektivnom površinom regurgitacijskog ušća ili manjim volumenom (npr. umjerena MR).[50,51]

The data support current ACC/AHA and ESC guidelines that LAA ligation or excision, along with surgical pulmonary vein isolation or a maze procedure, are reasonable in patients with VHD and AF who are undergoing surgical intervention.

SECONDARY MITRAL REGURGITATION – THRESHOLDS AND PROGNOSTIC IMPACT

Multiple recent studies have confirmed the association between secondary mitral regurgitation (SMR) and adverse outcome even with only mild MR.[47–49] However, the new ESC/EACTS guidelines have adopted the definition for severe SMR (as ACC/AHA guidelines have done before) of an effective regurgitant orifice ≥40 mm^2 or regurgitant volume ≥60 mL acknowledging that a lower threshold (effective regurgitant orifice ≥30 mm^2 or regurgitant volume ≥45 mL) may be applied, especially if the effective regurgitant orifice is elliptical or in low-flow conditions. The main reason supporting this change is the lack of evidence that surgical or transcatheter treatment improved outcome in patients with lower effective regurgitant orifice or regurgitant volume (i.e. moderate MR).[50,51]

FIGURE 3. Please see Figure 3 in the original article.

TRANSKATETERSKE INTERVENCIJE NA MITRALNOM ZALISTKU

U istraživanju *COAPT* bolesnici koji su bili randomizirani u skupinu kojoj je primijenjena transkateterska *edge-to-edge* tehnika reparacije mitralnog zalistka (TEER) pokazali su veću stopu preživljenja, niži mortalitet i bolji oporavak funkcionalnoga statusa u usporedbi sa skupinom bolesnika na optimalnoj medikamentnoj terapiji prema smjernicama uz znatnu redukciju težine MR-a tijekom razdoblja od 3 godine (**slika 3**)[52]. Važni prognostički čimbenici u ispitanika iz istraživanja *COAPT* uključivali su plućnu hipertenziju, težinu trikuspidalne regurgitacije (TR), NYHA funkcionalni razred, rezultat *Kansas City Cardiomiopathy* upitnika i 6-minutni test hoda.[53-57] Važnost ovih parametara, kao i disfunkcija desne klijetke potvrđeni su i u opservacijskim istraživanjima.[58] Međutim, mitralni TEER bio je koristan čak i u bolesnika s lošim prognostičkim čimbenicima ako je postignuta znatna redukcija težine MR-a. Važno je napomenuti da su hospitalizirani bolesnici s teškom plućnom hipertenzijom ili umjerenom do teškom disfunkcijom desne klijetke bili isključeni iz istraživanja COAPT.[59]

Koncept proporcionalne/disproporcionalne MR predložen je kao okvir da bi se uskladili rezultati istraživanja *COAPT* i *MITRA-FR*. U subanalizi *COAPT-a*, mala podskupina bole-

TRANSCATHETER MITRAL VALVE INTERVENTIONS

In the COAPT trial, patients randomized to mitral transcatheter edge-to-edge repair (TEER) continued to show a higher event-free survival, lower mortality, and higher functional improvement compared with guideline-directed medical therapy, with a sustained reduction in MR severity through 3 years (**Figure 3**)[52]. Important prognostic factors identified in the COAPT population include pulmonary hypertension, tricuspid regurgitation (TR) severity, NYHA functional class, Kansas City Cardiomyopathy Questionnaire score, and 6 min walk distance.[53–57] The importance of these parameters and of right ventricular dysfunction have also been reported in observational studies.[58] However, mitral TEER still was beneficial, even in patients with poor prognostic factors, as long as a significant reduction in MR severity was achieved. It is worth noting that non-ambulatory patients, as those with severe pulmonary hypertension or moderate/severe right ventricular dysfunction were excluded from the COAPT study.[59]

The concept of proportionate/disproportionate MR has been proposed as a framework to reconcile the discordant results of the COAPT and MITRA-FR studies. In a sub-analysis of COAPT, a small subgroup of COAPT patients—resembling

snika, slična onima uključenima u istraživanju *MITRA-FR*, nije pokazala poboljšanje u ishodima ukupne smrtnosti niti hospitalizacija zbog HF-a tijekom 24 mjeseca, ali su ipak pokazali znatno poboljšanje individualiziranih ishoda.[60] S druge strane, nije dokazana korist od intervencijskog liječenja u podskupini bolesnika iz istraživanja *MITRA-FR* s takozvanom disproporcionalnom MR ili u „COAPT prikladnih bolesnika".[61,62]

U subanalizi *COAPT-a* smanjenje težine MR-a nakon 30 dana povezano je s poboljšanim ishodima tijekom dvogodišnjeg razdoblja praćenja neovisno o tome je li smanjenje težine MR-a postignuto TEER-om ili medikamentnom terapijom. Iznenađujuće je da je potonja skupina imala MR težine +2 ili manju nakon 30 dana.[63] Opservacijska su istraživanja potvrdila prognostički učinak težine rezidualne MR (kao i trajanja reducirane MR),[64,65] pogotovo u bolesnika bez uznapredovale bolesti (dilatacija lijeve klijetke / disfunkcija desne klijetke), što pokazuje da je dobrobit od intervencijskog liječenja upitna u bolesnika s uznapredovalom bolešću.[66]

Iako još uvijek nije potpuno jasno zašto su rezultati tih dviju randomiziranih kliničkih studija u tolikom neskladu, nedavno objavljene europske i američke smjernice preporučuju TEER s razinom preporuke II. A, ako nema potrebe za istodobnim kirurškim liječenjem u bolesnika s teškom SMR koji ispunjavaju *COAPT* uključujuće kriterije na optimalnoj medikamentnoj terapiji pod nazorom specijalista za HF i koji su, prema karakteristikama, vrlo slični bolesnicima koji su bili uključeni u istraživanje.[1,2]

S obzirom na rastući broj učinjenih TEER procedura u svijetu, liječenje i ishod bolesnika s neuspješnim TEER (oko 30 % u stvarnome životu) od velikog je interesa. U *STS* bazi podataka pronađena su 463 bolesnika s neuspješnim TEER-om koji su podvrgnuti elektivnome kardiokirurškom zahvatu u razdoblju između 2014. i 2020. godine.[67] Tridesetodnevna smrtnost bila je 10,6 %, a stopa reparacije 5 %. Bez obzira na to što je velik dio bolesnika s neuspješnim TEER-om liječen konzervativno, ti su podatci bitni jer se indikacije za TEER proširuju na mlađe bolesnike s nižim kirurškim rizikom.

U međunarodnom *VIVID* registru (*Valve In Valve*) objavljeni su srednjoročni klinički, hemodinamski i ehokardiografski ishodi kod postupaka mitralne *valve in valve* (ViV) (N = 857) i *valve in ring* (ViR) (N = 222) koje su obavljeni u razdoblju između 2006. i 2020. godine u 90 centara diljem svijeta.[68] Podaci iz Registra ukazuju da su MS i MR česte i da su povezane s lošijim ishodom. Rane komplikacije i srednjoročno preživljenje bili su mnogo lošiji kod ViR nego ViV procedura. STS/ACC transkatetersko liječenje bilježi rane i jednogodišnje rezultate ViV procedura primjenom *Sapien 3®* u kohorti od 1529 bolesnika.[69] U većine je bolesnika postignuto znatno i postojano poboljšanje funkcionalnog statusa, no srednji je gradijent prosječno bio 7 mmHg, što se podudara s podatcima iz registra *VIVID*. Transseptalni pristup povezan je s nižim jednogodišnjim mortalitetom nego transapikalni pristup (16 % prema 22 %, P = 0,03).

RIJEČ OPREZA

Postoji zabrinutost oko moguće ozljede jednjaka zbog duljine trajanja TEE koja je nužna pri izvođenju kompleksnih transkateterskih procedura. U 50 bolesnika izvedena je gornja endoskopija prije i nakon same intervencije te je pokazala visoku razinu mogućnosti nastanka nove ozljede jednjaka (86 %),

those patients enrolled in MITRA-FR did indeed not achieve improvement in allcause mortality or HF admissions at 24 months. However, they still had a significant benefit on patient-centred outcomes.[60] On the other side, no benefit of the intervention was observed in MITRA-FR subgroups of patients with the so-called disproportionate MR or 'COAPT-eligible patients'.[61,62]

In a sub-analysis of COAPT, reduced MR at 30 days was associated with improved outcome through 2-year follow-up regardless whether the MR reduction was achieved by TEER or medical therapy. Surprisingly, one-third in the latter group had grade +2 or less at 30 days.[63] Observational studies have confirmed the prognostic impact of residual MR severity (as well as of durable MR reduction),[64,65] especially in patients with less advanced disease (LV dilatation/RV dysfunction) suggesting that in those with advanced disease the benefit of the intervention remains uncertain.[66]

Although the reasons for the discrepant results between the two RCTs are still not fully understood, the recently released ESC/EACTS and ACC/AHA guidelines recommend TEER with a Class IIa, in the absence of the need for concomitant surgery, in selected patients with severe SMR fulfilling the COAPT inclusion criteria, who receive optimal medical therapy supervised by an HF specialist and are as close as possible to the patients actually enrolled in the study.[1,2]

With the increasing number of TEER performed worldwide, the management and outcomes of patients with failed TEER (up to 30% in real-life) is of utmost interest. In the STS database, 463 patients with failed TEER who underwent a non-urgent cardiac surgery were identified between 2014 and 2020.[67] Thirty-day mortality was 10.6% and repair rate only 5%. Even if most patients with failed TEER are likely conservatively managed, these data are critical as TEER indications are extending to lower risk and younger patients.

The Valve In Valve International Data Registry (VIVID) reported the mid-term clinical, haemodynamic, and echocardiographic outcome of mitral valve in valve (ViV) (N=857) and valve in ring (ViR) (N=222) performed between 2006 and 2020 across 90 centres worldwide.[68] This registry showed that residual MS and regurgitation were common and associated with worse outcome. Immediate complications and mid-term survival were markedly worse in ViR than in ViV. The STS/ACC transcatheter valve therapy reported immediate and 1-year results of ViV implantation with the Sapien 3® in a cohort of 1529 patients.[69] Most patients experienced significant and sustained functional improvement but as noted in the VIVID registry, the mean gradient was in average 7 mmHg. Transeptal access was associated with a lower 1-year mortality rate than transapical access (16 vs. 22%, P=0.03).

A WORD OF CAUTION

There are concerns about potential oesophageal injury due to the duration of TEE imaging needed to guide complex transcatheter procedures. A systematic upper endoscopy was performed before and after intervention in 50 patients (mainly TEER and LAA occlusion) showing a high rate of new oesophageal injury (86%), often complex (haematoma and mucosal laceration) predicted by longer procedural time, suboptimal image quality, and pre-existing oesophageal lesions.[70] With the growing number of interventions requiring TEE guidance in an ageing population with frequent comorbidities, frequent use of an-

nerijetko kompleksne (hematom i laceracija mukoze), s većim rizikom što postupak dulje traje, kod suboptimalnih ehokardiografskih prikaza i preegzistentnih ozljeda jednjaka.[70] Uzimajući u obzir sve veći broj intervencija koje zahtijevaju TEE nadzor u sve starijih bolesnika s brojnim komorbiditetima te sve češćom primjenom antikoagulantne i anagregacijske terapije, potreban je razvoj alternativnih pristupa, kao i preventivnih mjera kako bi se umanjio rizik od gastrointestinalnih komplikacija.

Bolesti trikuspidalnog zalistka

TEŽINA TRIKUSPIDALNE REGURGITACIJE I KLINIČKI ISHODI

Postoje brojni dokazi kako je teška TR povezana s višim rizikom od neželjenih kardiovaskularnih događaja, što je i prikazano u nekoliko istraživanja u protekloj godini. Primjerice, u monocentričnom američkom registru bolesnika s učinjenim CMR-om tijekom razdoblje od 10 godina, Zhan *i sur.*[71] pronašli su 547 bolesnika sa sekundarnom (funkcionalnom) TR nakon isključenja bolesnika s FA, primarnom bolesti trikuspidalnog zalistka, remodeliranom desnom klijetkom, implantiranim uređajima i visokorizičnim stanjima poput transplantiranog srca ili metastatskog karcinoma.[71] U tih 547 bolesnika regurgitacijski volumen ≥45 mL ili regurgitacijski udio ≥50 % svrstao je bolesnike u podskupinu visokog rizika (**slika 4**), pri čemu je svaki porast za 10 mL u regurgitacijskom volumenu bio povezan s prilagođenim HR-om od 1,15 (95 % CI: 1,04 – 1,26) za smrtnost koja se temelji na multivarijatnoj analizi koja je uključivala kliničke i biventrikularne slikovne parametre.

ticoagulant or antiplatelet agents, this study shows the need to develop alternative approaches and preventive measures to minimize gastro-intestinal complications.

Tricuspid valve disease

TRICUSPID REGURGITANT SEVERITY AND CLINICAL OUTCOMES

There is ample evidence that more severe TR is associated with a higher risk of adverse cardiovascular outcomes as exemplified in several studies over the last year. For example, in a single US centre registry of patients undergoing CMR over a 10-year time span, Zhan et al.[71] identified 547 patients (mean age 60 years, 53% male) with secondary (functional) TR, after excluding those with atrial fibrillation, primary tricuspid valve (TV) disease, confounding causes of right ventricular remodelling, implanted cardiac electronic devices, and medical conditions with competing risk such as heart transplantation or metastatic cancer.[71] In these 547 patients, a regurgitant volume ≥45 mL or a regurgitant fraction ≥50% identified a high-risk subgroup (**Figure 4**) with each 10 mL increase in TR regurgitant volume associated with an adjusted HR of 1.15 (95% CI: 1.04–1.26) for death based on multivariable analysis that included clinical and biventricular imaging parameters.

FIGURE 4. Please see Figure 4 in the original article.

KIRURŠKO LIJEČENJE TRIKUSPIDALNE REGURGITACIJE NIJE IDEALNO

Klinički ishodi nakon izolirane operacije trikuspidalnog zaliska (TV) nisu dobri. U multicentričnoj francuskoj bazi podataka od 5661 bolesnika koji su bili podvrgnuti operaciji TV-a u razdoblju od 10 godina, njih 466 (8 %) je imalo izoliranu TV proceduru (reparacija u 41 %, bioprotetički zalistak u 57 % i mehanički zalistak u 2 % slučajeva).[72] Otprilike polovica bolesnika imala je sekundarnu a druga skupina primarnu TR (najčešće kao posljedicu endokarditisa) s većom unutarbolničkom smrtnošću (14 % prema 6 %) i nižim petogodišnjim preživljenjem i manjim brojem rehospitalizacija zbog HF (62 % prema 75 %), pri čemu je glavna odrednica ishoda klinička slika, a ne etiologija/mehanizam.

Nedavne randomizirana klinička istraživanja ispitivala su učinak istodobne operacije TV-a i MV-a zbog degenerativne MR u bolesnika s blagom do umjerenom TR i dilatacijom anulusa.[73] Bolesnici u kojih je izvedena operacija na TV-u imali su manju učestalost primarnih ishoda (reoperacija zbog TR-a,

SURGICAL MANAGEMENT FOR TRICUSPID REGURGITANT IS NOT IDEAL

Clinical outcomes with isolated TV surgery are poor. In a multicentre French administrative database of 5661 patients who underwent TV surgery over a 10 year period, 466 (8%) were an isolated TV procedure (repair in 41%, bioprosthetic valve in 57%, and mechanical valve in 2%).[72] About one-half patients had secondary vs. primary TR (most often due to endocarditis) with higher in-hospital mortality (14 vs. 6%) and lower 5-year survival rates free of HF readmission (62% vs. 75%), but the main determinant of outcome was the clinical presentation and not the aetiology/mechanism.

The effect of concomitant TV repair during mitral valve surgery for degenerative MR in patients with moderate TR or less-than-moderate TR but with annular dilation was studied in a recent RCT.[73] Patients with TV repair had a lower incidence of a primary-endpoint event (reoperation for TR, progression of TR by two grades or severe TR, or death) at 2 years.

progresija TR-a za dva stupnja, teška TR ili smrt) u razdoblju od dvije godine. Ovi rezultati pokazuju korist od operacije TV-a u smanjenju TR-a kroz vrijeme, no dugoročno je praćenje potrebno da bi se ustanovilo nadmašuje li klinička korist od smanjenja TR-a gotovo 6 puta veći rizik od potrebe za implantacijom trajnoga elektrostimulatora srca.

TRANSKATETERSKE INTERVENCIJE

Nekoliko transkatereskih uređaja može se primijeniti za smanjenje stupnja težine TR-a s prihvatljivim rizikom ranih i srednjoročnih komplikacija.[74] No teško je odrediti bolesnike koji bi imali koristi od takvih zahvata. Iako je ehokardiografija i dalje primarni modalitet za identifikaciju bolesnika s teškim stupnjem TR-a i procjenu anatomske pogodnosti za transkateterski pristup, noviji podatci pokazuju da su i hemodinamski parametri važni u odabiru bolesnika. U međunarodnom multicentričnom istraživanju koje je obuhvatilo 236 bolesnika u kojih je izvedena transkateterska reparacija TV-a, jednogodišnje je preživljenje bilo samo 38 % u onih s prekapilarnom plućnom hipertenzijom u usporedbi s 92 % u onih bez plućne hipertenzije i 78 % u onih s postkapilarnom plućnom hipertenzijom.[75]

POTREBA ZA RANDOMIZIRANIM KLINIČKIM ISPITIVANJIMA

Iako postoje brojni dokazi da je teži stupanj TR-a povezan s većim rizikom od neželjenih ishoda, ipak je sve manje dokaza kako intervencije za smanjenje TR-a imaju učinka u prevenciji tih neželjenih ishoda. Je li TR marker povećanog rizika ili postoji izravna uzročno-posljedična veza između stupnja težine TR-a i ishoda koji je neovisan o pridruženim bolestima poput bolesti mitralnog zalistka, plućne hipertenzije, aritmija i disfunkcije desne klijetke? Potrebna su randomizirana ispitivanja koja bi uspoređivala operativno i transkatetersko liječenje TV-a te optimalno medikamentno liječenje.

Infektivni endokarditis

Dijagnoza infektivnog endokarditisa (IE) protetičkog zalistka olakšana je primjenom pozitronske emisijske tomografije uz uporabu 18F-fluorodeoksiglukoze (^{18}F-FDG-PET/CT). Prema rezultatima prospektivne multicentrične studije dizajnirane za procjenu dijagnostičkog i terapijskog učinka ^{18}F-FDG-PET/CT , dijagnostička je klasifikacija poboljšana u 24 % bolesnika s IE-om protetičkog zalistka i 6 % bolesnika s IE-om nativnog zalistka, dok je terapijski pristup promijenjen je u 21 %, odnosno 31 % bolesnika.[76] Unatoč manje učestalom nakupljanju u miokardu, ekstrakardijalno nakupljanje utječe na liječenje bolesnika s IE-om nativnog zalistka.

U multicentričnoj kohorti među 3451 bolesnikom s IE-om žene su bile starije i češće su imale izoliran stafilokok nego muškarci.[77] Operativno je liječenje manje zastupljeno u žena (38 % prema 50 %). Unutarbolnička smrtnost bila je veća u žena (33 % prema 26 %), kao i smrtnost prilagođena dobi (HR: 1,25, 95 % CI: 1,07 – 1,47). Ovi rezultati upućuju na moguće spolno determinirane razlike u liječenju IE-a.

Među 134 717 provedenih postupaka TAVI, godišnja incidencija IE-a iznosila je 0,87 %.[78] Smrtnost je bila 46 % nakon godine dana s trostrukim porastom u prilagođenim analizama. Moždani se udar pojavio se u 10 % oboljelih kao komplikacija kod IE-a nakon TAVI-ja i povezan je sa znatnim porastom jednogodišnje smrtnosti.[79]

The reduction was driven by less frequent progression of TR. These findings demonstrate the efficacy of TV repair in the reduction of TR over time. However, long-term follow-up based on clinical endpoints is needed to determine if clinical benefit of TR reduction outweighs the almost six-fold higher risk of needing a permanent pacemaker.

TRANSCATHETER INTERVENTIONS

Several types of transcatheter devices can be used to reduce the severity of TR with an acceptable low rate of immediate- and midterm complications.[74] However, it remains challenging to select patients most likely to benefit from these procedures. Although echocardiography remains the primary modality for identifying patients with severe TR and evaluating whether anatomy is amenable to a transcatheter repair procedure, more recent data suggest that haemodynamic parameters provide additional information in patient selection. In an international multicentre study of 236 patients undergoing transcatheter tricuspid repair, 1-year survival was only 38% in those with pre-capillary dominant pulmonary hypertension compared with 92% in those without pulmonary hypertension and 78% in those with post-capillary pulmonary hypertension.[75]

NEED FOR RANDOMIZED CONTROLLED TRIALS

Although there is ample evidence that more severe TR is associated with a higher risk of adverse outcome, there is less evidence that interventions to reduce TR severity prevent those adverse outcomes. Is TR simply a marker of increased risk or is there direct cause–effect relationship between TR severity and outcome that is independent of associated disease such as mitral valve disease, pulmonary hypertension, arrhythmias, and right ventricular dysfunction? Randomized controlled trials of TV surgery and transcatheter intervention, compared with optimal medical therapy and to each other, are needed.

Infective endocarditis

Diagnosis of prosthetic infective endocarditis (IE) is improved with 18 fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging. In a prospective multicentre study designed for assessing the diagnostic and therapeutic impact of ^{18}F-FDG-PET/CT, diagnostic classification was upgraded in 24% of patients with prosthetic IE and 6% with native IE.[76] Therapeutic management was changed in 21 and 31% of patients, respectively. Despite less frequent cardiac uptake, extracardiac uptake has an impact on the management of patients with native IE.

In a multicentre cohort of 3451 patients with IE, women were older and had more frequent staphylococcal IE than men.[77] Surgery was less frequently performed in women (38 vs. 50%), including in propensity-matched cohorts. In-hospital mortality was higher in women (33% vs. 26%), as was age-adjusted mortality (odds ratio: 1.25, 95% CI: 1.07–1.47). These findings draw attention on possible sex-related differences in the management of IE.

Among 134 717 TAVI procedures in Medicare patients with 1868 cases of IE, the annual incidence of IE was 0.87%.[78] Mortality was 46% at 1 year and was increased three-fold in adjusted analysis. Stroke complicated 10% of IE after TAVI and was associated with a strong increase in 1-year mortality.[79]

Podatci iz multicentričnog registra koji uključuje 2476 bolesnika u kojih je izvedena transkateterska zamjena pulmonalnog zalistka pokazuju da IE nije rijedak uz godišnju incidenciju od 2,2 %.[80] Mlađa dob, prethodni IE i veći gradijenti, ali ne i vrsta zalistka, povećavaju rizik od razvoja IE-a.

Protetički zalistci

Prema analizi 253 100 AVR-a i 284 962 MVR-a izvedenih u SAD-u između 2008. i 2017. godine vidljivo je smanjenje udjela mehaničkih zalistaka s 45 na 17 % na aortalnoj te sa 60 na 29 % na mitralnoj poziciji.[81] Smanjenje učestalosti primjene mehaničkih zalistaka vidljivo je u svim promatranim dobnim skupinama i izraženije je nakon 2010. godine, što može biti odraz promjena u smjernicama[2], kao i sve veće dostupnosti transkateterskih ViV procedura. Kontraindikacija za primjenu NOAK-a kod mehaničkih zalistaka temelji se na malom istraživanju II. faze u kojoj se rabio inhibitor faktora IIa. Potrebna su randomizirana klinička istraživanja koja bi uspoređivala primjenu inhibitora faktora Xa s varfarinom te potencijalno imale odraza na kliničku praksu.[82]

Kvantifikacija kalcifikacije bioprotetičkoga aortalnog zalistka koristeći se CT-om može predvidjeti naknadnu degeneraciju bioprotetičkog zalistka i kliničke ishode, što je proučavano u skupini od 204 bolesnika s medijanom od 7 godina nakon SAVR-a.[83] Kvantifikacija bioprotetičke kalcifikacije može pomoći u identifikaciji bolesnika koji su pod povećanim rizikom od degeneracije zalistka. ^{18}F-natrijev fluorid (^{18}F-NaF) marker je aktivnosti kalcifikacije zalistka i rane degeneracije bioprotetičkog zalistka. U prospektivnom istraživanju među 47 bolesnika u kojih je izveden TAVI te među 57 bolesnika koji su bili podvrgnuti SAVR-u nakupljanje ^{18}F-NaF na PET/CT bilo je neovisni prediktivni čimbenik za naknadnu degeneraciju kod transkateterski i kirurški implantiranih aortalnih bioproteza.[84] Nije bilo značajne razlike u opsegu kalcifikacije između TAVI-ja i kirurških zalistaka. Zanimljivo je da je spomenuto istraživanje pokazalo stalnu aktivnost kalcifikacije nativnoga aortalnog zalistka izvan TAVI proteze.

Antitrombotska terapija nakon biološke AVR i dalje je upitna pa su osvježene preporuke za ranu antikoagulantnu terapiju.[1,2] Primjena varfarina u 9539 bolesnika bila je povezana s nižim rizikom od ishemijskoga moždanog udara (HR: 0,49; 95 % CI: 0,35 – 0,70) i bilo kojega tromboembolijskog incidenta nego antiagregacijska monoterapija, ali uz povećan rizik od hemoragičnog moždanog udara (HR: 1,94; 95 % CI: 1,07 – 3,51) i velikih krvarenja.[85] Potrebna su randomizirana istraživanja radi bolje procjene dobrobiti i rizika.

Randomizirano istraživanje *RIVER* ispitivalo je primjenu NOAK-a u bolesnika s bioprotetičkim mitralnim zalistkom i FA jer su bolesnici s bioprotezama bili isključivani ili slabo zastupljeni u prethodnim istraživanjima.[86] U 1005 bolesnika rivaroksaban je bio neinferioran varfarinu glede primarnoga zajedničkog ishoda povezanog sa smrtnošću, neželjenih kardiovaskularnih događaja i velikih krvarenja u razdoblju od jedne godine (**slika 1B**). Lijekovi iz skupine NOAK-a sada mogu biti preporučeni uz višu razinu dokaza u bolesnika s bioprotetičkim zalistcima.[1]

Pogled u budućnost

Godina 2021. donijela je važne nove poglede na patofiziologiju, dijagnozu i liječenje bolesti srčanih zalistaka, ali i dalje osta-

A multicentre registry totalling 2476 patients who underwent transcatheter pulmonary valve replacement confirmed that IE was frequent, with an annual incidence of 2.2%.[80] Younger age, prior IE, and high gradient, but not the type of prosthesis increased the risk of IE.

Prosthetic valves

In an analysis of 253 100 AVR and 284 962 mitral valve replacements performed in the USA between 2008 and 2017, the percentage of mechanical prosthesis decreased from 45 to 17% in aortic position and from 60 to 29% in mitral position.[81] Decreased use of mechanical prostheses was observed in all age groups and was more pronounced after the mid-2010s, which may reflect changes in guidelines[2] and the growing availability of transcatheter ViV procedures. The contra-indication of NOACs for mechanical prosthesis is based on a single small Phase II study using a factor IIa-inhibitor. A randomized trial comparing a Xa-inhibitor with warfarin in aortic prostheses is thus needed and might have an impact on practices.[82]

The quantification of aortic bioprosthetic leaflet calcification using CT predicts subsequent bioprosthesis degeneration and clinical events, as assessed in a series of 204 patients evaluated a median of 7 years after SAVR.[83] The quantification of bioprosthetic calcification may help identify patients at high risk of valve degeneration and serve as a surrogate endpoint for future studies. 18F-sodium fluoride (^{18}F-NaF) is a marker of valve calcification activity and of early bioprosthetic leaflet degeneration. In a prospective study on 47 patients treated by TAVI and 51 patients treated by SAVR, ^{18}F-NaF PET/CT uptake was an independent predictive factor of subsequent degeneration of transcatheter and surgically implanted aortic bioprostheses.[84] There was no difference in the magnitude of degeneration between TAVI vs. surgical valves. Interestingly, this study also showed ongoing calcification activity in the native aortic valve outside the TAVI prosthesis.

Antithrombotic therapy after bioprosthetic AVR remains debated and recommendations on early anticoagulation have been upgraded.[1,2] In a nationwide analysis of 9539 patients, exposure to warfarin was associated with a lower incidence of ischaemic stroke (HR: 0.49; 95% CI: 0.35–0.70) and any thromboembolism than single antiplatelet therapy, at the expense of an increased risk of haemorrhagic stroke (HR: 1.94; 95% CI: 1.07–3.51) and major bleeding.[85] Difficulties in the analysis of risk–benefit analysis highlight the need for randomized trials.

The randomized trial RIVER filled an important gap is the use of NOACs in patients with a mitral bioprosthesis and in atrial fibrillation since patients with bioprosthesis were excluded or underrepresented in previous trials.[86] In 1005 patients, rivaroxaban was non-inferior to warfarin for a primary composite endpoint of death, major cardiovascular events, or major bleeding at 1 year (**Figure 1B**). NOACs can now be recommended with higher levels of evidence in patients with a bioprosthesis.[1]

Outlook

This year brought important new insights in pathophysiology, diagnosis, and treatment of VHD but left and raised important questions to be addressed in the future. Fortunately, there are several ongoing trials which already work on this. Better un-

ju mnoga neriješena pitanja. Nasreću, u tijeku je još nekoliko kliničkih istraživanja. Od velike je važnosti razumijevanje razvoja valvularnih bolesti i mogućnosti utjecaja na njihovu progresiju. Točna dijagnoza, dobar odabir bolesnika koji bi mogli imati koristi od intervencije te pravodobno liječenje veoma su važni općenito, ali posebice kod sekundarne MR i TR. Sve dostupniji transkateterski intervencijski postupci zahtijevaju daljnju evaluaciju učinkovitosti i sigurnosti u usporedbi s kirurškim i optimalnim medikamentnim liječenjem. S obzirom na stalno rastuću istraživačku aktivnost, napredak se svakako očekuje.

derstanding of the development of VHD and how to interfere with its progression remains a critical issue. Correct diagnosis, proper selection of patients who benefit from intervention, and appropriate timing remain important issues in general and in particular in secondary mitral and TR. Emerging catheter interventional treatment options require further evaluation of efficacy, safety, and outcome compared with surgical treatment or optimal medical treatment. The field of research is definitely expanding, and progress based on ongoing research expected.

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