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Special article

The year in cardiovascular medicine 2021: valvular heart disease

Helmut Baumgartner[1]*, Bernard Iung[2], David Messika-Zeitoun[3], and Catherine M. Otto[4]

[1] *Department of Cardiology III—Adult Congenital and Valvular Heart Disease, University Hospital Muenster, Albert-Schweitzer-Campus 1, Building A1, Muenster 48149, Germany*
[2] *Department of Cardiology, Bichat Hospital, APHP, Université de Paris, Paris, France*
[3] *Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Canada*
[4] *Division of Cardiology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA*

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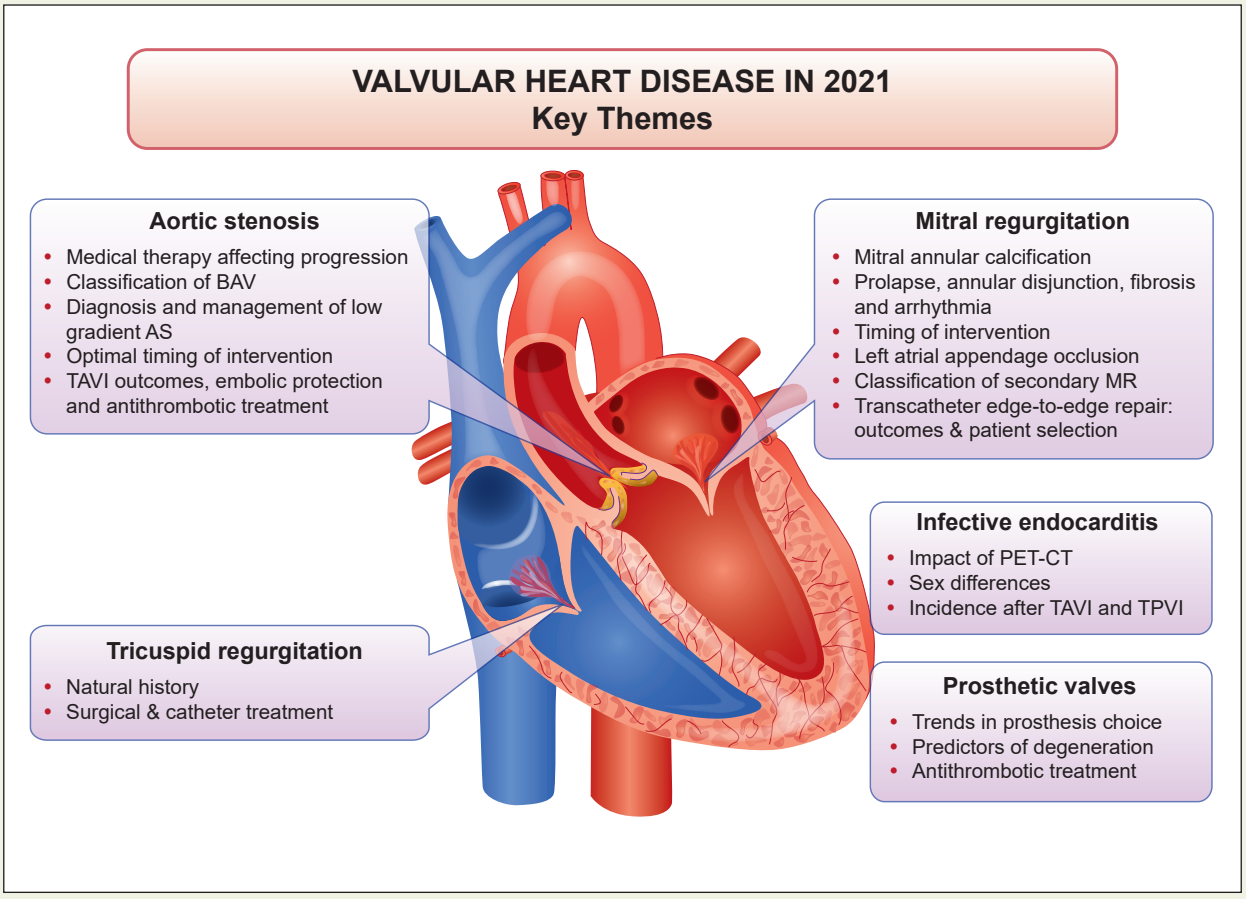
* Corresponding author. Tel: +49 251 46110, Fax: +49 251 46109, E-mail: helmut.baumgartner@ukmuenster.de



Graphical Abstract

Keywords: Valvular heart disease • Review • Aortic stenosis • Mitral regurgitation • Tricuspid regurgitation • Infective endocarditis • Prosthetic heart valve

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 non-surgical 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. Importantly, new guidelines for the management of VHD have been published by both the ESC/EACTS and ACC/AHA.[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.

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

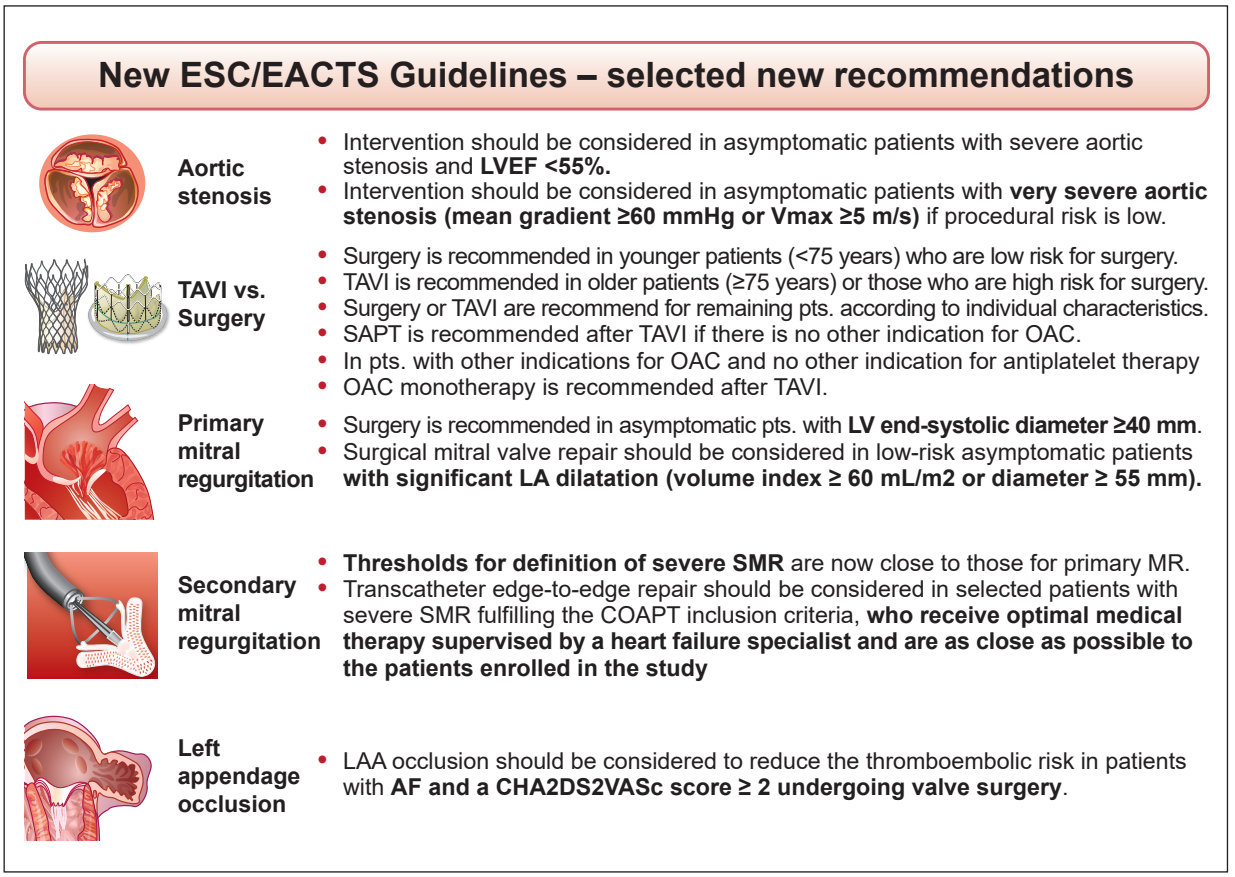


Figure 1 Selected important new recommendations in the 2021 ESC/EACTS guidelines for the management of valvular heart disease. Reproduced with permission from Vahanian *et al*.,[1] by permission of OUP on behalf of ESC.

incidence of aortic valve replacement (AVR) in patients with familial hypercholesterolaemia (FH) based on data from SAFEHEART—a long-term prospective cohort study 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 low-gradient 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–low-gradient 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–low-gradient 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 1*).

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 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 trial[16]—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 – see in original*) 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 expected 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]

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 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 end-systolic diameter reaches 40 mm (previously 45 mm).[1] The ESC/EACTS guidelines also emphasize the importance of left atrium enlargement (≥60 mL/m^2 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 $CHAD_2DS_2$-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. 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]

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 – see in original*). 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 those patients enrolled in MITRA-FR did indeed not achieve improvement in all-cause 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 (VIV-ID) 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 VIV-ID 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 anticoagulant 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 – see in original*) 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.

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 (re-operation for TR, progression of TR by two grades or severe TR, or death) at 2 years. 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 mid-term 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, extra-cardiac 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]

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. ^{18}F-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 under-represented 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 1*). 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 understanding 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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