Cardiologia Hungarica
2019; 49: 64–75.

The year in cardiology 2018: valvular heart disease

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Introduction

In 2018 the publications on valvular heart disease (VHD) addressed all topics – epidemiology, diagnosis, therapy and predictors of outcome – but were dominated by studies focusing on transcatheter treatment. Regarding mitral regurgitation (MR) two pivotal studies investigating transcatheter edge-to-edge repair for secondary MR as well as early clinical experience with transcatheter mitral valve replacement (TMVR) were published. Regarding aortic stenosis (AS) there is a clear trend towards the expansion of indications for transcatheter aortic valve implantation (TAVI) to intermediate and low-risk groups, bicuspid aortic valve (BAV) and failed surgically implanted bioprostheses. Tricuspid valve (TV) disease is a growing clinical problem associated with high morbidity and mortality. Isolated TV surgery has a high risk and is currently performed in a minority of patients. Novel therapies using the edge-to-edge approach or annuloplasty are being investigated.

Aortic stenosis

TAVI is rapidly evolving, and implantation numbers are steeply increasing. In Germany where all procedures are mandatorily registered in a quality control program, more than 15 000 TAVI procedures were performed in 2016. The number more than tripled since 2011 while isolated surgical aortic valve replacement (SAVR) remained relatively stable with approximately 10 000 per year being performed now much less frequently than TAVI *(Figure 1)*. Complication rates and mortality decreased continuously with overall in-hospital mortality being in 2016 for the first time similar for TAVI (2.6%) and SAVR (2.9%) despite the different risk profile of both patient groups (1). Expanding adoption of TAVI across the risk strata is widespread both in Europe and the US. Based on SURTAVI, Sapien3 Intermediate Risk and PARTNER 2A the safety and efficacy was established for intermediate risk and following the NOTION study the concept showed promising results for low-risk patients (2). Importantly surgical risk scales used for both approaches tend to overestimate mortality for TAVI patients in all the risk strata even taking into consideration that low-risk patients undergoing TAVI are younger than SAVR *(Figure 2)*. The recent FDA-approved Low-risk TAVR Trial prospectively studied the outcomes of transfemoral TAVI in the low-risk group (STS-PROM ≤3%) and compared the results to historical controls from the Society of Thoracic Surgeons (STS) database. No mortality and strokes at 30 days, low risk of paravalvular regurgitation as well as permanent pacemaker implantation (PPI) rates similar to SAVR were reported, however frailty was an exclusion criterium (3). A sub-analysis of the randomized controlled SURTAVI trial evaluating patients with STS-PROM <3% suggested that TAVI may achieve superior early clinical outcomes compared to SAVR (4). These findings support the need for an adequately powered randomized trial to compare TAVI with SAVR in patients at low operative risk. Apparently, in such a population with assumingly

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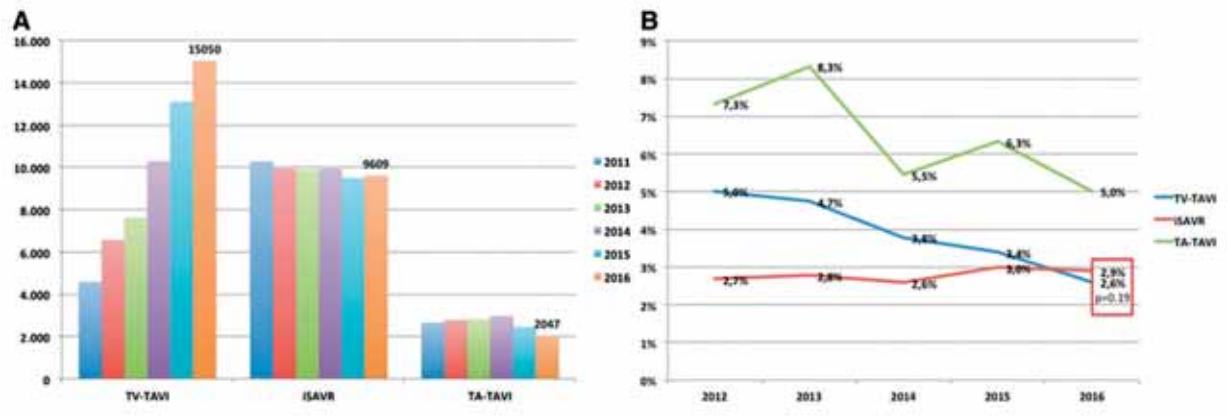

FIGURE 1. Numbers of procedures (panel A) and in-hospital mortality related to transvascular transcatheter aortic valve implantation (TAVI), transapical TAVI and isolated surgical aortic valve replacement (SAVR) (panel B). Data from the German Institute for Quality Assurance and Transparency in Healthcare (IQTIG) report (reprinted from Gaede L, et al. Eur Heart J 2018; 39: 667–675, combining Fig.1 and 3)

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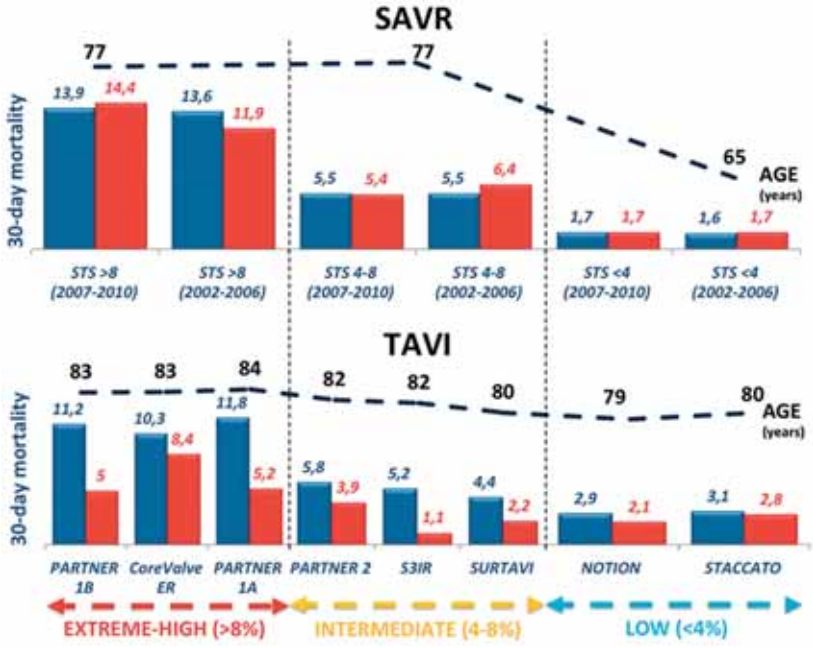

FIGURE 2. Different performance of surgical risk scores in SAVR and TAVI patients across the risk strata (reprinted from Tarantini et al. European Heart Journal, Volume 39, Issue 8, 21 February 2018, Pages 658–666, take-home-figure)

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longer life expectancy, there is a clear need for data on the long-term durability because no follow-up beyond 2 years has so far been published for this population. Ongoing trials such as PARTNER3, Evolut R Low Risk and NOTION 2 with follow up of 5-10 years will provide more data with this regard. Currently available long-term durability data for transcatheter aortic valves although promising are unfortunately limited by the poor survival of the high-risk early populations. Eltchaninoff et al. reported an incidence of structural valve deterioration (SVD) of 3.2% and bioprosthetic valve failure of 0.58% at 8 years using the new European consensus definition (5). Holy et al. estimated from their series that the rate of bioprosthetic valve failure at eight years was

7.9% for the actuarial and 4.5% for the actual analysis (6). However, long-term durability will remain one of the key concerns until we have more solid data.

One of the other concerns beyond durability is the need for PPI which is in most reports higher with TAVI than with SAVR. A recent systematic review demonstrated the highly variable risk of PPI (2.3-36.1%) due to new onset conduction abnormalities after TAVI (7). The risk tended to be lower after balloon-expandable than self-expandable valves. Procedural factors, such as the depth of implantation, predilatation, distribution of calcifications and pre-existing conduction abnormalities were important risk factors for PPI. The possible long-term impact of even mild PVL and the necessity of access to coronary arteries in patients with long life expectancy must also be considered.

Severe periprocedural complications of TAVI requiring emergent cardiac surgery (mainly annular rupture, ventricular perforation, and valve embolization) are rare but remain approximately 1% (8) – 2% (9). Early mortality remains high in such cases. Nevertheless, given these life-threatening complications, the 30-day survival rate exceeding 50% underlines the importance of an experienced and well-attuned heart team providing immediate access to surgical bailout procedures. One-year mortality remains high (78%). These numbers may also indicate that on-site cardiac surgery alone is not sufficient and the setup for emergency conversion requires further improvement. Complication rates and early mortality decrease with increasing procedure volume. In an analysis of German national quality assurance data, in-hospital mortality varied highly (0 to 16.7%) and was on average markedly higher with 5.6±5.0% in hospitals performing <50 transfemoral TAVIs annually compared to 2.4±1.0% with rather consistent results (range 0.5 to 3.7%) in hospitals with ≥200 procedures per year (10). These studies support the recommendation of performing TAVI in heart valve centers with departments of cardiac surgery on-site and sufficiently high volumes (8).

Impact on the healthcare resources utilization is an important issue given the epidemiology of aortic stenosis and currently expanding indications for TAVI. The estimated number of TAVI candidates in Europe under current indications exceeds 114,000 per year and assuming low-risk indication is accepted this number may increase to 177,000 (11) *(Figure 3).*

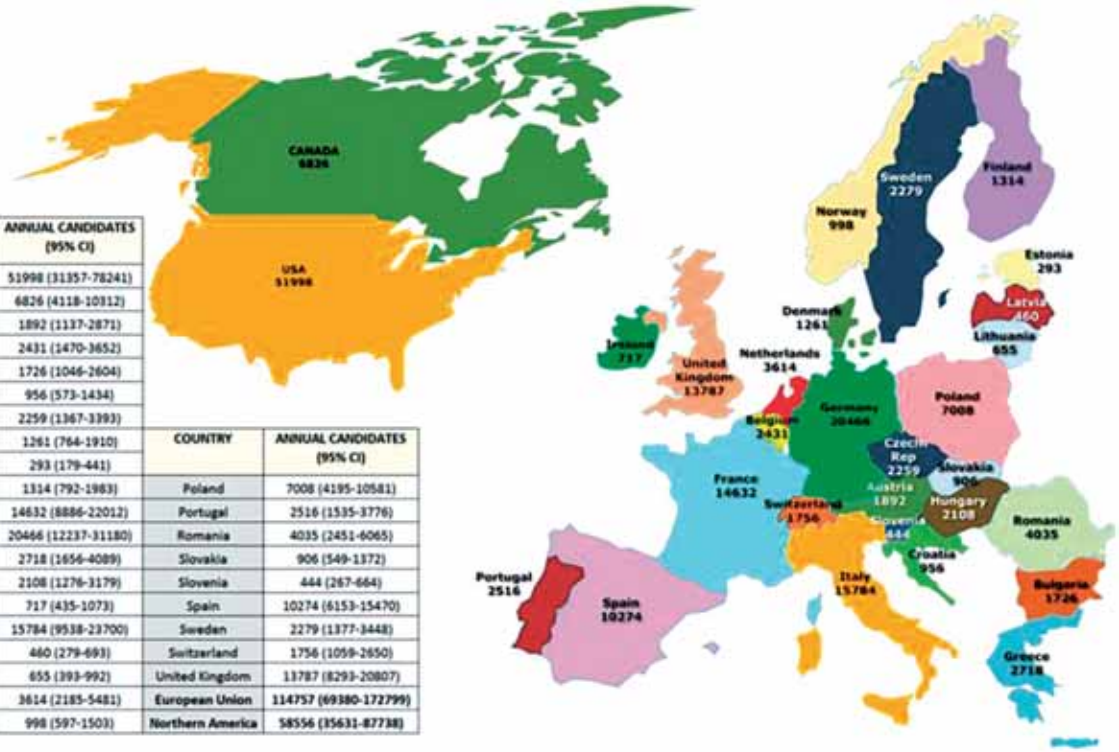
Aortic stenosis and coronary artery disease (CAD) have common risk factors, and clinically overt CAD is present in approximately half of the patients undergoing TAVI or SAVR. CAD impacts the outcomes of TAVI, but data are still lacking for recommendations whether and when to perform percutaneous coronary intervention – before, during or after TAVI (12). The usefulness of invasive physiological assessment of CAD significance in severe AS is also unclear due to the hypertrophy, increased end-diastolic pressure and impaired function of the microvasculature. However, recent data suggest that both fractional flow reserve (FFR) as well as an instantaneous valve-free ratio (iFR) have good correlation with ischemic burden in SPECT and might be useful in clinical decision making about the revascularization strategy before aortic valve intervention (13). In most centers, the revascularization is limited to large proximal vessels, but the completeness of revascularization can have a prognostic impact, and use of the residual SYNTAX score could improve the risk stratification (12, 14).

Transcatheter treatment of severe bicuspid aortic valve (BAV) stenosis is associated with procedural challenges related to large volume and asymmetrically distributed calcifications, large aortic annulus, the presence of calcified raphe and coexisting aortopathy. Such anatomy increases the risk of non-uniform valve expansion, under-expansion, aortic root injury and paravalvular leaks (PVL). Despite that, given the high prevalence of BAV in the population TAVI procedures are increasingly done in this population. Data from the German TAVI registry including 1424 patients showed reassuring clinical outcomes with similar 30-days mortality as in tricuspid valve. In patients with BAV, there was, however, a higher rate of PVL while pacemaker implantation was less frequent (15).

Transcatheter valve-in-valve implantation (ViV) has become an accepted alternative to redo surgery in patients with surgical bioprosthetic valve failure and should be considered depending on surgical risk, valve type and size (IIa, level of evidence C recommendation) (16). The STS/ACC registry provided reassuring data on the safety of ViV. Such patients should have a meticulous follow-up with echocardiography because the postprocedural gradients are higher than for native valve TAVI (16 vs. 9 mm Hg; p<0.001). The follow-up in this study was limited to one year (17). Coronary obstruction following ViV procedures occurred in 2.3% patients enrolled in the Valve-in-Valve International Data (VIVID) Registry and was more frequent in stented bioprostheses with externally mounted leaflets and stentless biological valves as well as in patients with a virtual transcatheter valve to coronary ostium distance measured by computed tomography below 4 mm (18). Delayed coronary obstruction is an infrequent (0.22%) complication of TAVI (more often in ViV procedures and with self-expanding valves) but related to a high risk of death and myocardial infarction. ViV is challenging in small surgical prostheses because of a high postprocedural gradient, and new concepts, such as using the high-pressure inflation of non-compliant balloon and fracturing of the prosthetic valve ring are evaluated (19).

The antithrombotic regimen after TAVI remains a matter of debate and results of randomized controlled trials are still awaited. In patients who required oral anticoagulation with vitamin K antagonists (VKA) for atrial fibrillation, an observational study reported significantly less major, and life-threatening bleeding complications

A



COUNTRY	ANNUAL CANDIDATES (95% CI)
USA	51998 (31357-78241)
Canada	6826 (4118-10312)
Austria	1892 (1137-2871)
Belgium	2431 (1470-3652)
Bulgaria	1726 (1046-2604)
Croatia	956 (573-1434)
Czech Republic	2259 (1367-3393)
Denmark	1261 (764-1910)
Estonia	293 (179-441)
Finland	1314 (792-1983)
France	14632 (8886-22012)
Germany	20466 (12237-31180)
Greece	2718 (1656-4089)
Hungary	2108 (1276-3179)
Ireland	717 (435-1073)
Italy	15784 (9538-23700)
Latvia	460 (279-693)
Lithuania	655 (393-992)
Netherlands	3614 (2185-5481)
Norway	998 (597-1503)

COUNTRY	ANNUAL CANDIDATES (95% CI)
Poland	7008 (4195-10581)
Portugal	2516 (1535-3776)
Romania	4035 (2451-6065)
Slovakia	906 (549-1372)
Slovenia	444 (267-664)
Spain	10274 (6153-15470)
Sweden	2279 (1377-3448)
Switzerland	1756 (1059-2650)
United Kingdom	13787 (8293-20807)
European Union	**114757 (69380-172799)**
Northern America	**58556 (35631-87738)**

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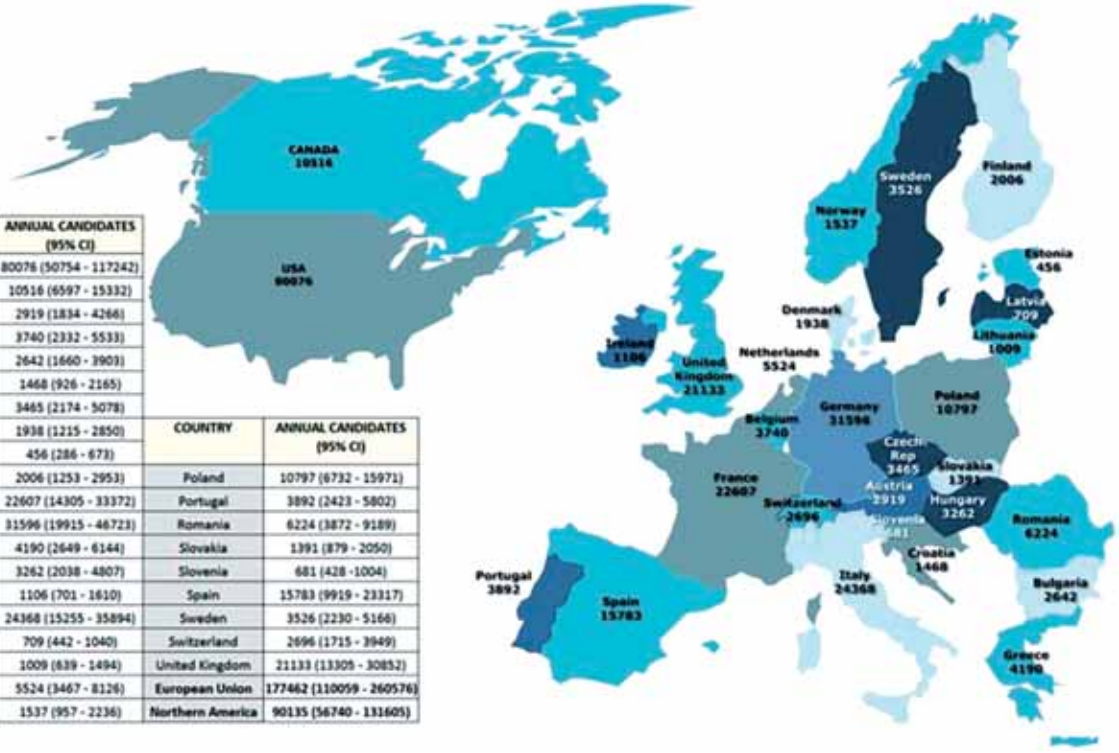

COUNTRY	ANNUAL CANDIDATES (95% CI)
USA	80076 (50754 - 117242)
Canada	10516 (6597 - 15332)
Austria	2919 (1834 - 4266)
Belgium	3740 (2332 - 5533)
Bulgaria	2642 (1660 - 3903)
Croatia	1468 (926 - 2165)
Czech Republic	3465 (2174 - 5078)
Denmark	1938 (1215 - 2850)
Estonia	456 (286 - 673)
Finland	2006 (1253 - 2953)
France	22607 (14305 - 33372)
Germany	31596 (19915 - 46723)
Greece	4190 (2649 - 6144)
Hungary	3262 (2038 - 4807)
Ireland	1106 (701 - 1610)
Italy	24368 (15255 - 35894)
Latvia	709 (442 - 1040)
Lithuania	1009 (639 - 1494)
Netherlands	5524 (3467 - 8126)
Norway	1537 (957 - 2236)

COUNTRY	ANNUAL CANDIDATES (95% CI)
Poland	10797 (6732 - 15971)
Portugal	3892 (2423 - 5802)
Romania	6224 (3872 - 9189)
Slovakia	1391 (879 - 2050)
Slovenia	681 (428 -1004)
Spain	15783 (9919 - 23317)
Sweden	3526 (2230 - 5166)
Switzerland	2696 (1715 - 3949)
United Kingdom	21133 (13305 - 30852)
European Union	**177462 (110059 - 260576)**
Northern America	**90135 (56740 - 131605)**

FIGURE 3. The estimated number of TAVI candidates in Europe under current indications and projected numbers after accepting low-risk indication (Reprinted from European Heart Journal, Volume 39, Issue 28, 21 July 2018, Pages 2635–2642, take-home figure)

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on VKA therapy only compared to those with additional single (SAPT) or dual antiplatelet therapy (DAPT). This difference was not outweighed by a reduction of embolic events thus favoring VKA monotherapy (20). In a propensity-matched analysis comparing SAPT and DAPT in 1210 patients, at 30 days, VARC mortality, major vascular complications, and major bleedings were significantly lower in the SAPT group without a difference in prosthetic heart valve dysfunction after TAVI with a balloon-expandable valve favoring aspirin monotherapy when no anticoagulation is indicated (21).

Data from the FRANCE-TAVI registry, on the other hand, showed that VKA are related to less bioprosthetic valve dysfunction in short-term follow-up (22). More research is required to define the optimal antithrombotic treatment after TAVI.

There are currently no convincing data that all patients with severe AS who have normal left ventricular function and are asymptomatic by history and during exercise testing may benefit from early valve replacement and current guidelines, therefore, recommend watchful waiting for these patients unless they present with particular risk factors (16). Retrospective analyses reporting a benefit from early surgery were mainly driven by the fact that a considerable number of patients did not undergo surgery in the conservative group when developing indications for intervention, mainly symptoms. This suggests that the worse outcome in the conservative group was primarily due to nonadherence to the guidelines. A retrospective cohort study including 300 patients with asymptomatic severe AS appears to support this assumption (23). Nonadherent patients had significantly higher mortality and rate of hospital admission for heart failure while they underwent less frequently SAVR during follow-up. A recent analysis of the Heart Valve Clinic International Database reported that in asymptomatic patients with severe AS LVEF <60% and peak aortic jet velocity >5 m/s were associated with increased all-cause and CV mortality suggesting that this population may benefit from early valve replacement (24), but more data will be required for solid recommendations.

Recent guidelines modified the indications for surgery in asymptomatic severe AS (16). A new recommendation was added that SAVR should be considered when surgical risk is low, and patients present with severe pulmonary hypertension. The negative impact of pulmonary hypertension on long-term outcome was reported once more in a study including more than 1000 patients with severe AS supporting the guidelines (25). Current guidelines do also no longer include the recommendation that surgery may be considered in asymptomatic patients with an increase in mean gradient >20 mmHg on exercise16. This was based on pathophysiologic concerns and new studies questioning this recommendation. Goublaire et al. did not find a difference in event-free survival between asymptomatic patients (no symptoms on exercise testing) with or without stress-induced mean gradient increase >20 mmHg (26).

Untreated severe AS causes on the long-term progressive damage to other heart structures. Genereux et al. accordingly classified five stages of disease: no extravalvular cardiac damage (Stage 0), left ventricular damage (Stage 1), left atrial or mitral valve damage (Stage 2), pulmonary vasculature or tricuspid valve damage (Stage 3), right ventricular damage (Stage 4). One-year mortality increased continuously from 4.4% (Stage 0) to 24.5% (Stage 4). The extent of cardiac damage was independently associated with increased mortality after AVR (27). These data emphasize once more the importance of timely intervention.

Development of myocardial fibrosis with eventual negative impact on long-term outcome of AS has been a concern for a long time. However, how to include this into management strategies remains uncertain. Treibel et al. studied 133 patients with severe symptomatic AS undergoing SAVR. Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) and extracellular volume fraction (ECV) quantification were performed as well as histological examinations. LGE correlated with collagen volume fraction but not ECV. Both, LGE and ECV correlated independently with biomarkers. ECV was also associated with worse LV remodeling, LV ejection fraction and functional capacity. Combining both improved the identification of patients at risk (28). In 116 patients with CMR repeated 1 year after AVR, focal fibrosis did not resolve while diffuse fibrosis and myocardial cellular hypertrophy regressed (29). In a study of 674 patients with severe symptomatic AS undergoing SAVR or TAVI, LGE on CMR was independently associated with late mortality (2-fold higher) (30). Although these studies provide important new insight, whether we should screen asymptomatic patients with severe AS for early signs of fibrosis to optimize the timing of surgery can still not be answered from currently available data.

Patients with paradoxical low flow, low gradient AS remain a challenging subgroup diagnostically as well as therapeutically. Many of these patients do not only have AS but other causes of LV myocardial damage, particularly arterial hypertension. Recent data suggest that cardiac amyloidosis is another associated disease one should think of. Castano and colleagues performed technetium-99 m pyrophosphate cardiac scintigraphy prospectively on patients who underwent TAVI to screen for transthyretin cardiac amyloidosis (ATTR-A). Among 151 unselected patients 16% screened positive. These patients had thicker ventricles and lower stroke volume, more severe diastolic dysfunction and lower ejection fraction (31). These findings gain even more importance in the view of a recent randomized controlled trial demonstrating that in patients with ATTR-A, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations

and reduced the decline in functional capacity and quality of life as compared with placebo (32).

Aortic regurgitation

The prevalence of aortic regurgitation (AR) is approximately 2% in patients over 70 years and increases with age. According to current guidelines, aortic valve surgery is indicated in severe AR if patients are symptomatic, or asymptomatic patients present with reduced LVEF and/or marked dilatation of the LV or with aortic aneurysm (16). In patients with high/prohibitive surgical risk transcatheter intervention remains an option, however, due to the lack of calcifications and to dilatation of the annulus the procedural challenges make acute TAVI results less predictable and associated with higher rates of PVL and prosthesis embolization. Recent data suggest that TAVI using new-generation devices (both balloon- and self-expandable) is feasible in selected high surgical risk patients with pure AR. A multicenter registry including 331 patients showed improved device success rate, less post-procedural AR with new generation valves. Post-procedural AR was a strong predictor of mortality (33).

Mitral regurgitation

The burden of mitral regurgitation (MR) is increasing with age. The data on the frequency of MR vs. AS is varying between registries. In a population-based study from the US prevalence of MR was higher than of AS (34), but the European registries EORP VHD I (2003) and VHD II (2018) demonstrated that MR was the second most frequent VHD after the AS (Iung B. et al. Late-breaking science session at ESC Congress 2018). In a community cohort study, isolated MR was common and associated with excess mortality and frequent heart failure postdiagnosis in all patient subsets, even in those with normal left ventricular ejection fraction and low comorbidity. Despite these poor outcomes, only a small minority of affected patients underwent mitral surgery (29% for primary and 5% for secondary MR) even in a community with all means of diagnosis and treatment readily available and accessible (35). This suggests that in a wider population there might be a substantial unmet need for treatment for this disorder. Educational needs and application of guidelines in the management of patients with MR were addressed in a European mixed-methods study. Based on an online survey including 115 primary care physicians and 439 cardiologists and cardiac surgeons from seven European countries, systematic auscultation was dramatically underused for the early detection of MR. Surgical therapy was underused and medical therapy overused in primary MR while optimization of medical therapy was frequently not advised in secondary MR. Indications for interventions were appropriate in most patients with primary MR but were unexpectedly frequent for secondary MR. These gaps identify important targets for future educational programs (36).

Secondary (functional) MR was reported to be associated with adverse prognosis (47% mortality over 5 years) in patients with heart failure and to be a predictor of long-term mortality after adjustment for clinical (HR 1.61, 95% CI: 1.22–2.12; P = 0.001), echocardiographic variables (HR 1.38, 95% CI: 1.03–1.84; P = 0.03), optimal medical therapy (OMT) and neurohumoral activation. This was most evident in patients with NYHA II and III, moderately reduced LVEF, and elevated NT-pro BNP. These findings suggest that repair of MR might be more effective in patients in whom the valve incompetence has the highest impact on the prognosis and is the main factor associated with the progression of the disease (37). On the other hand, there is a paucity of data on the long-term effect of surgical MV repair on the clinical outcomes of secondary MR. The widespread use of transcatheter edge-to-edge repair using the MitraClip (Abbott) system in patients with secondary MR was based on registry data showing favorable safety and clinical outcomes regarding MR reduction, and suggesting symptomatic improvement and ventricular remodeling. The efficacy was, however, lower for secondary than for primary MR and the predictors of adverse outcomes were device failure, low LVEF, and tricuspid regurgitation (38, 39). There has been agreed that the definite role of transcatheter repair of secondary MR in clinical practice can only be elucidated in randomized clinical trials, and two of these were now recently published presenting divergent results.

MITRA-FR enrolled 304 patients with heart failure, severe secondary MR, and reduced left ventricular ejection fraction (15-40%) who were on OMT and CRT as indicated (40). They were randomly assigned 1:1 to additional MitraClip therapy or continued OMT alone. The procedure was performed with a low complication rate and high effectiveness. At discharge, 91.9% had MR ≤2+. Nevertheless, there was no difference for the primary endpoint – death or unplanned re-hospitalization for heart failure at 12 months (54.6% versus 51.3% for interventional and conservative treatment, respectively; death, 24.3% versus 22.4%; re-hospitalization, 48.7% versus 47.4%). NYHA class improved in both groups and was similar at 12 months. The study has the strength of a randomized trial with 99% follow-up regarding the primary endpoint and that it is an industry independent academic trial. The weakness is that a significant amount of follow-up data on echocardiographic outcome and functional status at 12 months were missing. The subgroup analyses in this trial showed consistently no effect of this therapy across pre-specified subgroups.

The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) study enrolled 614 patients with ischemic (60,7%) and non-ischemic (39,3%) heart failure (HF) and moderate-severe or severe secondary MR and were symptomatic (NYHA class II-IV) despite maximally tolerated doses of OMT and CRT (36,5%) as indicated by guidelines (41). Patients were randomly assigned to the MitraClip procedure (n=302) or OMT alone (n=312). It showed a significant reduction of the primary endpoint of rehospitalization due to HF at two-years (35.8% vs. 67.9%, HR 0.53; 95% CI: 0.40 to 0.70, p<0.001) with the number needed to treat (NNT) to prevent 1 hospitalization of 3.1. There was also a significant reduction of all-cause mortality at 2 years, (29.1% vs. 46.1%, HR 0.62; 95% CI: 0.46–0.82, p<0.001) and improvement of the quality of life, functional capacity, improvement of MR and reduction of LVEDV (prespecified secondary endpoints).

There were differences between the MITRA-FR and COAPT with regard to the sample size (304 vs. 614 patients) and duration of follow-up for primary end-point evaluation (12 vs. 24 months). The primary endpoint in COAPT was all hospitalizations for HF (including recurrent events) and in MITRA.FR composite of death from any cause or unplanned hospitalization for HF. Regarding inclusion criteria, the definition of MR differed (effective regurgitant orifice area ≥20 mm^2 and/or regurgitant volume >30 mL vs. ≥30 mm^2 and >45 mL), as well as of LVEF (15–40% vs. 20–50%) and LV size. This resulted in on average larger ventricles (mean end-diastolic volume 135 mL/m^2 vs. 101 mL/m^2) and less severe MR (effective regurgitant orifice area 31±10 vs. 41±15 mm^2) while LVEF was similar (33±7 vs. 31±7%). Although the technical success rate in MITRA-FR was good compared to previous observational studies, it tended to be even higher in the COAPT study. Also, the enrolment strategy was different with central eligibility committee evaluating current treatment in every patient in the COAPT and more inclusive, real-life approach in MITRA-FR trial which could result in the observed improvement in the control arm in the latter study. Although these differences may have influenced outcomes, it remains unclear how the results of the two trials could differ so fundamentally. More studies will be required to resolve this controversy and identify the patient characteristics that make a benefit from valve repair in secondary MR likely. The ongoing RESHAPE-HF2 (NCT02444338) and Matterhorn (NCT02371512) trials will likely help clarify the role of this technology in secondary MR.

In contrast to edge-to-edge repair, direct annuloplasty systems aim to achieve surgical-like results in the secondary MR by reducing the dilatation of the mitral annulus and correct the malcoaptation of the leaflets using undersized adjustable rings implanted by the transseptal catheter-based approach. A recent study by Messika-Zeitoun et al. investigated the safety and efficacy of the CardiobandTM Mitral Valve Reconstruction System (Edwards Lifesciences) in patients with HF (majority NYHA III-IV) and secondary MR. The technical success rate was 97% and in 52/60 patients a significant reduction of annulus diameter and MR severity (66% mild or less in-hospital and 61% at one year). The recurrence rate was 22% in one year. Importantly periprocedural complications (tamponade, VF, stroke, and MI) and anchor detachments were noted in the

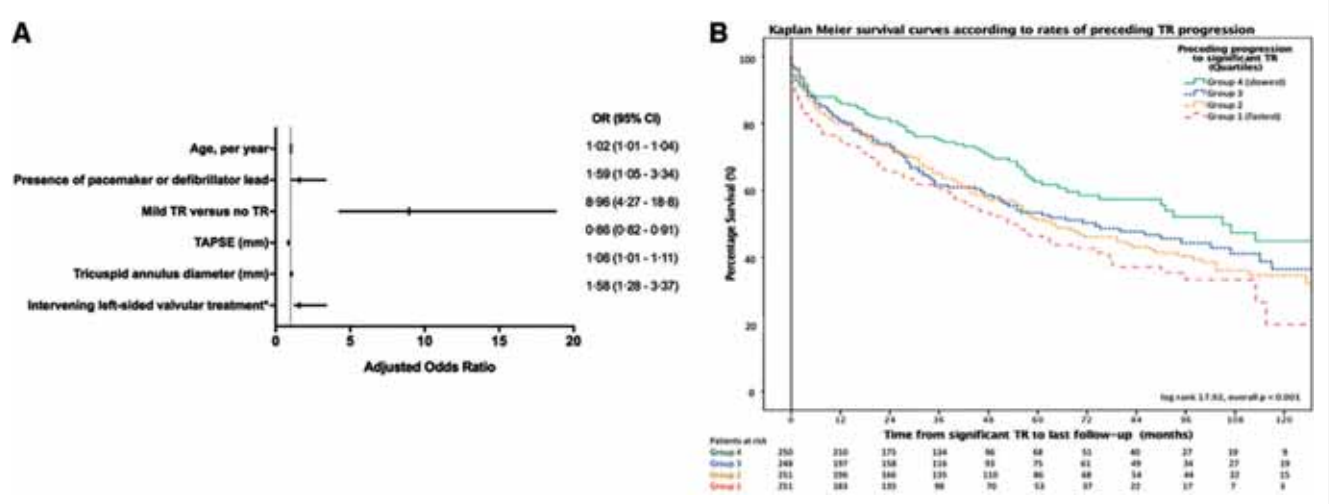

FIGURE 4. Independent predictors of the fast vs. slow development of tricuspid regurgitation (panel A) and event-free survival according to the rate of progression of TR (Group 1: ≤1.2 years; Group 2: 1.3–4.7 years; Group 3: 4.8–8.9 years; Group 4: ≥9.0 years) (panel B) (reprinted from Prihadi EA, et al. Eur Heart J 2018 Oct 14; 39(39): 3574–3581.)

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first cohort treated patients. This technology alone or in combination with edge-to-edge repair seems effective however the long-term clinical outcomes require further studies (42).

Persistent reduction of MR probably requires not only the intervention targeting the leaflets or annulus alone but either combination of both approaches or ultimately implantation of the transcatheter mitral valve (TMVR). The early experience was hampered with valve thrombosis and regurgitation, but the improvement of the design and preprocedural planning allowed better outcomes. As reported by Bapat et al. TMVR with self-expandable transapical valve [Intrepid, Medtronic] with bovine pericardial leaflets in 50 patients with high or extreme operative risk proved feasible and effective in providing symptomatic relief. It was also safe with no periprocedural strokes or reinterventions (43). The ongoing APOLLO trial which is planned to include trans-septal TMVR will provide important data for this technology. A trans-septal approach mitigating the use of high-profile transapical catheters is likely to improve the safety.

In severe primary MR, management of asymptomatic patients with preserved LV and no atrial fibrillation or pulmonary hypertension remains a matter of debate. *Zilberzac et al.* prospectively followed 280 such patients with a watchful waiting strategy for a median of 8 years. Compared with the age- and a gender-matched general population expected cumulative survival and early survival rates were even better in the study population. One third was still event-free after 10 years (44). These data support watchful waiting. However, it has to be emphasized that these patients had regular follow-up visits every 6 months in an expert center and the results may only be expected in such a setting.

Mitral stenosis

The concept of implantation of balloon-expandable valves (Sapien, Edwards) in high/prohibitive risk patients with severe mitral annular calcification (MAC) was based on case series and registries. *Guerrero et al.* reported 1-year follow-up of 105 patients enrolled in multicenter TMVR in MAC Global Registry. Although the technical success rate was high and lead to significant symptomatic improvement, there was substantial mortality related to hemodynamically significant LVOT obstruction in 11.2% of patients such an approach need to be further evaluated and rigorous preprocedural planning is crucial (45).

Tricuspid regurgitation

Tricuspid regurgitation is a significant clinical problem affecting in Europe approximately 300,000 patients yearly (46). There is a growing recognition of this disease and novel therapeutic options. Fast progression of TR has an adverse impact on survival, and key risk factors for fast TR progression have been identified (Figure V) (47). It is accepted that tricuspid valve (TR) repair during left-sided valve intervention is beneficial in terms of reduced mortality, however increasing number of patients with MR deemed inoperable have also tricuspid regurgitation (TR). In such cases, transcatheter repair on MV does not address the TV pathology and is ineffective in abating the symptoms of right heart failure. The concept of simultaneous or staged transcatheter TV repair using the MitraClip has been proven feasible and safe, however technically challenging. This approach requires careful preprocedural planning with angio-CT and expert TOE guidance during the procedure (48). Other transcatheter devices, such as PASCAL (edge-to-edge repair system), Cardioband (direct annuloplasty) or caval approach (one or two TAVI devices implanted within the stents in caval veins) have been recently tested with promising early results (reduction of TR severity, improved symptoms) in selected high risk patients (49, 50, 51). The majority of patients are treated on a compassionate basis and have multiple comorbidities, and the impact of TR repair requires further evaluation. The TriValve (Transcatheter Tricuspid Valve Therapies) registry evaluated 106 high-risk patients treated with multiple transcatheter devices and showed safety, moderate (62%) procedural success and reduction of HF symptoms (52).

Not only secondary TR coexisting with the disease of other valves remains a significant clinical problem, but also isolated TV disease which confers an increased risk of mortality and shows increasing prevalence. Isolated TV surgery is associated with a high perioperative risk (in-hospital mortality of 8.8%) and does not diminish over time despite the growing number of surgical procedures (53). Similarly to MV interventions, the key step is patient selection. At the current stage, the most appropriate would be high surgical risk patients without RV failure and pulmonary hypertension. Finally, it has to be emphasized that for secondary TR similar to secondary MR, only its association with worse outcome has been demonstrated while it remains uncertain whether its reduction by intervention can improve outcome.

Non-valve specific issues

Paravalvular regurgitation (PVL) is an uncommon complication of surgical valve replacement requiring repair in 2-5% of cases. Repeated surgery is associated with significant risk. Transcatheter closure is a valid treatment option after exclusion of active endocarditis in patients with acceptable anatomy. However, data on the periprocedural and long-term outcomes were based

on the registries using heterogenous definitions (16). Recently, the PVL Academic Research Consortium set standards for the assessment of disease severity, data collection, and updated endpoint definitions (54).

Diagnosis of prosthetic valve endocarditis (PVE) remains challenging. A multicenter study including 160 patients with suspicion of PVE confirmed the diagnostic value of visual and quantitative assessment of FDG PET/CT in this setting and highlights the importance of early implementation in the diagnostic work-up to prevent confounding effects of low inflammatory activity due to prolonged antibiotic therapy. Recent valve implantation was not a significant predictor of false positive interpretations, but surgical adhesives used during implantation were (55, 56).

The incidence of Infectious endocarditis (IE) in the UK is estimated to be 36.2/million/year. The risk factors of mortality in IE patients are the previous history of IE, prosthetic valve, and history of valve repair (57). Recent data from the Danish nationwide registries allowed improved identification of IE risk factors in moderate and high-risk populations in comparison to the general population. There was a stepwise increase of IE risk in these populations. The risk factors for IE in moderate risk group were VHD, an implantable device, hypertrophic cardiomyopathy and the risk of IE was higher than the general population but lower than in high-risk group (58, 59).

In a randomized, noninferiority, multicentre trial, 400 adults in stable condition who had endocarditis on the left side of the heart caused by *Streptococcus, Enterococcus Faecalis, Staphylococcus aureus, or coagulase-negative Staphylococci* treated for at least 10 days with intravenous antibiotics were assigned to either continued intravenous or to switch to oral treatment. The primary composite outcome of all-cause mortality, unplanned surgery, embolic events, or relapse of bacteraemia occurred in 12.1% versus 9.0% confirming noninferiority of switching to oral treatment. These findings could have major impact on clinical practice (60).

Pulmonary hypertension (PH) may persist after correction of VHD. It is then associated with increased morbidity and mortality. Whether targeted PH treatment is effective in this setting remains uncertain. In a multicentric, randomized, placebo-controlled trial including 200 patients with successful valve replacement or repair procedure at least 1 year before inclusion, a mean pulmonary artery pressure still ≥30 mmHg (57% with a resistance > 3 Wood Units, i.e., combined post and pre-capillary PH) were assigned to sildenafil 40mg three times daily or placebo for 6 months. The primary endpoint was a composite clinical score combining death, hospital admission for heart failure, change in functional class, and patient global self-assessment. Patients on sildenafil had a significantly worse outcome indicating that this treatment cannot be recommended for this patient group (61).

Perspectives

There is a growing awareness of the burden of VHD worldwide, and the adoption of minimally invasive treatment options will be expanding thanks to new device technologies and progress of imaging. Mitral and tricuspid valve interventions are gaining momentum in high risk and inoperable patients but will need to overcome more technical challenges than aortic valve interventions due to the more complex and variable anatomy.

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