VALVULAR HEART DISEASE

The year in cardiology: valvular heart disease
The year in cardiology 2019

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SAHeart 2020;17:60-68

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INTRODUCTION

After decades as a Cinderella discipline, valvular heart disease (VHD) now occupies the centre stage of cardiovascular medicine. Changing societal demographics and an ageing population (with increasing prevalence of degenerative disease), advances in imaging and the explosion of interest in transcatheter interventional techniques (supported by a series of landmark clinical trials) have attracted clinicians, researchers, engineers, device manufacturers and investors, and transformed the landscape of clinical management. In many senses, 2019 has been a leap year for VHD.

EPIDEMIOLOGICAL TRENDS

The changing demography of VHD and its impact on clinical management were highlighted by the EURObservational Research Programme VHD II Survey,[1] a contemporary registry of 7 247 patients (4 483 hospitalised, 2 764 outpatients) with VHD treated at 222 centres in 28 nations. Key findings included the rising age of patients with VHD in comparison with a similar survey performed in 2005,[2] a high concordance with guideline recommendations for patients with aortic valve disease (though less so for mitral valve disease where referral for intervention was frequently delayed), and the progressive emergence of transcatheter interventions (aortic stenosis 39%, mitral regurgitation 17%).

DIAGNOSTIC IMAGING

Multimodality imaging is of fundamental importance in VHD for initial diagnosis, monitoring of disease progression (valve lesion and associated myocardial remodelling response), planning of transcatheter and surgical intervention, and subsequent follow-up.

The valve

Echocardiography remains the first-line imaging modality in VHD. An investigation of inter-observer reproducibility of peak velocity and mean gradient measurements in patients with aortic stenosis (based on 20 echocardiographic examinations assessed by 25 different observers) demonstrated superior reproducibility of peak velocity compared with mean gradient assessment (coefficient of variation 10.1% vs. 18.0%; $p<0.001$), suggesting that peak velocity should be the preferred measure for tracking the progression of aortic stenosis.[3] Asymptomatic patients with a peak velocity >5m/s and ejection fraction <60% have increased mortality [even after aortic valve replacement (AVR)] and early intervention should be considered in these high-risk patients.[4]

European Society of Cardiology (ESC) guidelines recommend computed tomography (CT) calcium scoring to assess the severity of aortic stenosis when echocardiographic measurements are discordant.[5] Advances in this field include clear guidance on optimal scoring of valve calcification[6] and a large international multicentre study confirming the diagnostic accuracy of this method and its power to predict disease progression and clinical events.[7]

Positron emission tomography (PET) imaging using ^{18}F-fluoride as a marker of calcification activity may detect early bioprosthetic valve degeneration before it is evident on echocardiography or CT (Figure 1). Indeed, one study demonstrated histological validation of increased tracer uptake by bioprosthetic leaflets as a marker of degeneration and the only independent predictor for future valve dysfunction.[8] However, the potential for the integration of these findings into clinical practice remains uncertain.

The myocardium

Myocardial damage secondary to VHD is being increasingly investigated using novel echocardiographic and cardiovascular

magnetic resonance (CMR) approaches. In primary mitral regurgitation (MR), for example, myocardial fibrosis identified on CMR is closely associated with increased incidence of ventricular arrhythmias,[9] while impaired echocardiographic global longitudinal strain (threshold ≥20.6%) is associated with adverse long-term prognosis in subjects undergoing surgery.[10]

Left ventricular mechanical dispersion assessed using speckle tracking echocardiography demonstrated incremental prognostic value for all-cause mortality in 630 patients with aortic stenosis [hazard ratio (HR) 1.10 (95% confidence interval, CI 1.04 - 1.15) per 10ms increase; p<0.001].[11] Similarly, reduced endocardial, mid-myocardial, and epicardial longitudinal strain predicted symptomatic status in 211 patients with severe aortic stenosis, whilst endocardial longitudinal strain provided an independent predictor of cardiovascular mortality.[12] Extending this concept, a four-stage system for the echocardiographic grading of cardiac damage in 735 patients with asymptomatic moderate or severe aortic stenosis provided incremental prognostic information over and above standard clinical variables.[13]

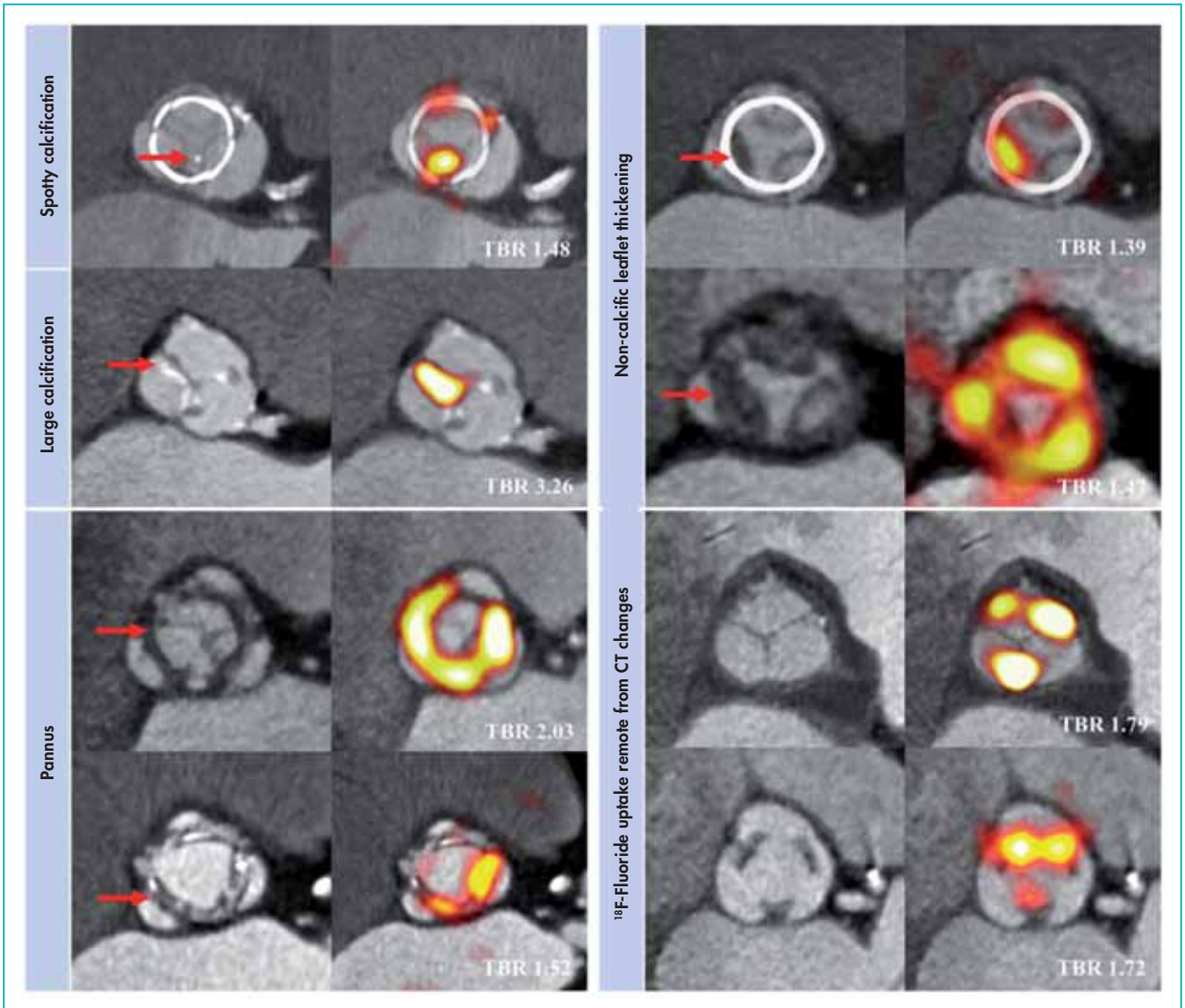

FIGURE 1: ***In vivo*** **^{18}F-fluoride positron emission tomography and computed tomography imaging of patients with bioprosthetic aortic valves.**
Baseline computed tomography (left) and ^{18}F-fluoride positron emission tomography (right) images from patients with bioprosthetic aortic valves. En-face computed tomography images of bioprosthetic aortic valves showing spotty and large calcification (top left), circumferential pannus (bottom left), and non-calcific leaflet thickening suggestive of thrombus (top right) (all identified by red arrows). Hybrid en-face positron emission tomography-computed tomography images in the same patients: Increased bioprosthetic ^{18}F-fluoride activity (red/yellow) colocalise with computed tomography abnormalities in each patient. ^{18}F-fluoride activity was also commonly observed remote from leaflet changes on computed tomography (bottom right). Target-to-background values are annotated on the hybrid positron emission tomography-computed tomography images (white text). Reproduced with permission from Blackman DJ, et al.[8]

Myocardial fibrosis is the major driver of left ventricular decompensation in aortic stenosis and may be directly visualised using CMR.[14] Replacement fibrosis progresses rapidly once established, persists following valve replacement, and is associated with poor long-term prognosis (Figure 2).[15,16] The ongoing EVOLVED trial (NCT03094143) will determine whether prompt AVR/transcatheter aortic valve implantation (TAVI) can improve clinical outcomes in asymptomatic patients with severe aortic stenosis and evidence of early fibrosis.

DEVELOPING MEDICAL THERAPIES

Unlike other major cardiovascular conditions, effective medical therapies are lacking for VHD. Intense research has focused upon identifying novel therapeutic targets, particularly in aortic stenosis. Among 367 703 UK BIOBANK participants, obesity was associated with increased risk of aortic stenosis, thereby underlining the potential importance of weight reduction as a preventive strategy.[17]

Preclinical studies have highlighted the role of platelet activation in the progression of aortic stenosis,[18] while Lp(a) is associated with increased aortic valve calcification, faster progression of aortic stenosis, and increased risk of intervention or death,[19] and provides an extremely promising therapeutic target. Statins increase Lp(a), however,[20] and tailored treatment may prove necessary.

Calcification is the major driver of progressive aortic stenosis and the target of novel imaging technologies and potential therapeutic strategies, including the ongoing SALTIRE II (NCT02132026) and BASIK II (NCT02917525) randomised controlled trials.[21] A Swedish population study of over 1 million subjects confirmed the association between aortic stenosis and chronic kidney disease, presumably related to altered calcium and phosphate metabolism,[22] while a non-randomised study of 2 785 patients demonstrated greater reduction in left ventricular volumes, hypertrophy, and cardiovascular mortality associated with the use of renin-angiotensin system inhibitors following TAVI.[23] Randomised controlled trials are now required.

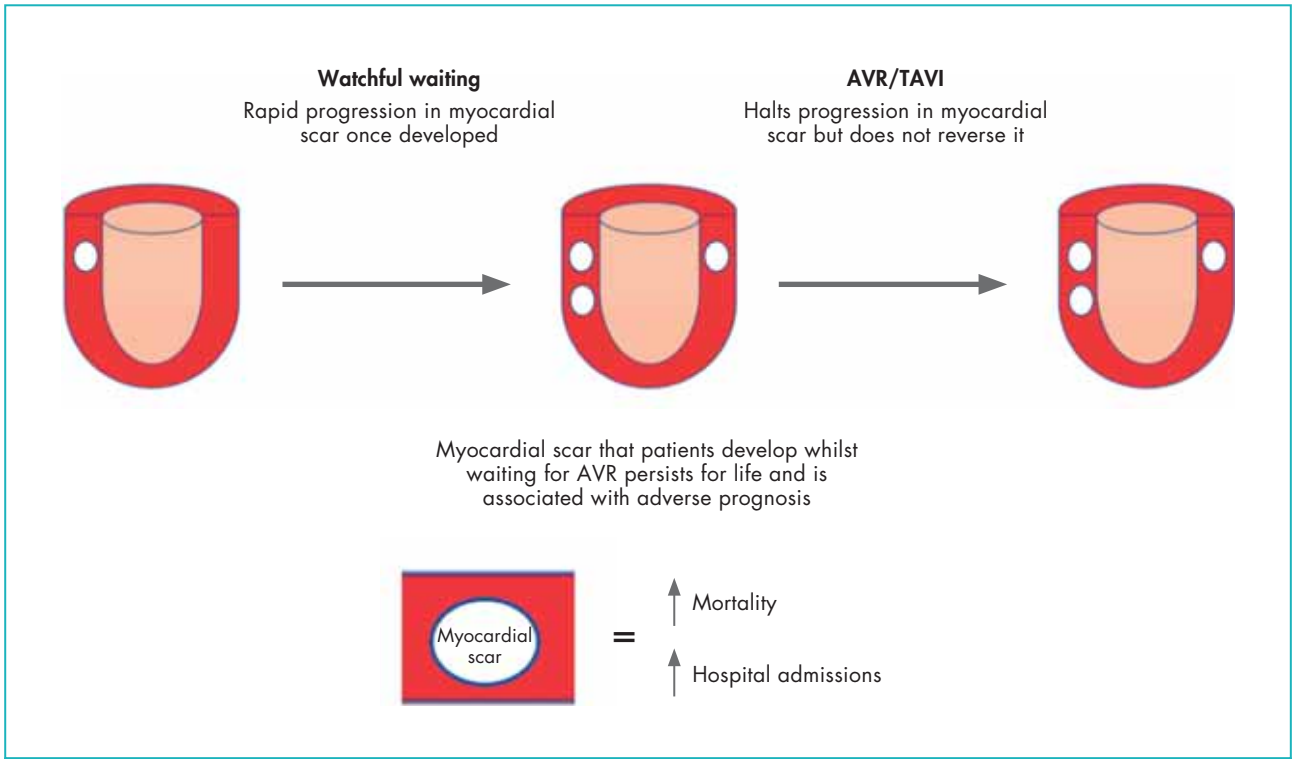

FIGURE 2: Myocardial scar in aortic stenosis.
Cardiovascular magnetic resonance late gadolinium enhancement allows detection of non-infarct pattern replacement fibrosis (white areas) in patients with severe aortic stenosis. This myocardial scar is associated with multiple markers of left ventricular decompensation and progresses rapidly until aortic valve replacement or transcatheter aortic valve implantation is performed. Although these interventions halt the development of further scar, replacement fibrosis that develops whilst awaiting intervention is irreversible, persists lifelong and is associated with dose-dependent impact on long-term prognosis.

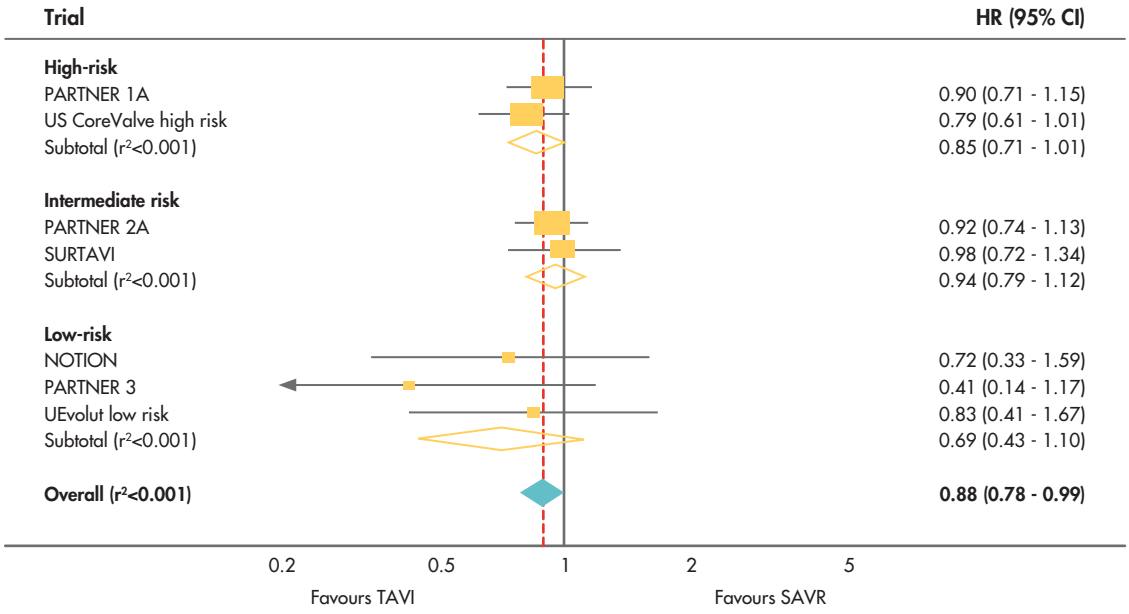

FIGURE 3: Meta-analysis comparing transcatheter aortic valve implantation and surgical aortic valve replacement up to 2-year follow-up for the primary outcome of all-cause mortality stratified by baseline surgical risk.
Reproduced with permission from Siontis GCM, et al.[26]

TRANSCATHETER INTERVENTION

The aortic valve

Transcatheter aortic valve implantation in low surgical risk patients

In 2019, an important evidence gap for TAVI was closed following publication of 2 landmark trials[24,25] comparing TAVI and surgical aortic valve replacement (SAVR) in patients at low surgical risk.

In the PARTNER 3 trial,[24] 1 000 patients with symptomatic severe aortic stenosis at low surgical risk were randomly assigned to undergo SAVR or TAVI with the balloon-expandable Edwards SAPIEN 3 transcatheter heart valve (THV). Those with a bicuspid valve or high-risk anatomical features for either procedure were excluded. The primary endpoint (a composite of death, stroke, or rehospitalisation) was tested for non-inferiority as well as superiority in the as-treated population. At 1 year, the primary endpoint was significantly lower in the TAVI group than in the SAVR group (8.5% vs. 15.1%, p<0.001 for non-inferiority; HR 0.54, 95% CI 0.37 - 0.79; p=0.001 for superiority), principally driven by reduced rates of rehospitalisation. There were no significant differences in major vascular complications, need for new permanent pacemaker implantation, or more than mild paravalvular regurgitation.

Similarly, in the Evolut Low Risk Trial,[25] 1 468 patients with symptomatic, severe aortic stenosis at low surgical risk were randomly assigned to undergo SAVR or TAVI with the self-expanding CoreValve, Evolut-R, or Evolut Pro THV (Medtronic, USA). At 24 months, the estimated incidence of the primary endpoint (a composite of death or disabling stroke) was 5.3% in the TAVI group and 6.7% in the SAVR group [difference -1.4%; 95% Bayesian credible interval for difference (BCI) -4.9 - 2.1; posterior probability of non-inferiority >0.999]. At 30 days, TAVI patients had lower incidence of disabling stroke (0.5% vs. 1.7%; 95% BCI -2.4 - -0.2), acute kidney injury (0.9% vs. 2.8%; 95% BCI -3.4 - -0.5), and atrial fibrillation (7.7% vs. 35.4%; 95% BCI -31.8 - -23.6), but higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%; p<0.05) and pacemaker implantation (17.4% vs. 6.1%; 95% BCI 8.0 - 14.7).

Alongside previous landmark studies, these results complete the evidence trail comparing TAVI and SAVR in all surgical risk categories and establish TAVI as a treatment for severe aortic stenosis irrespective of surgical risk. Furthermore, meta-analysis of the 8 020 patients enrolled in the 7 randomised trials across the entire spectrum of surgical risk demonstrated a significant reduction of 1-year all-cause mortality with TAVI compared to SAVR (HR 0.88, 95% CI 0.78 - 0.99, p=0.03) and lower risk of stroke (HR 0.81, 95% CI 0.68 - 0.98, p=0.03; Figure 3).[26] These results have already translated into routine clinical practice in several European nations, as demonstrated by analysis of the German national aortic valve replacement registry (GARY).[27] Comparison of 14 487 SAVR patients and

6 062 TAVI patients at low surgical risk demonstrated superior in-hospital and 30-day survival for TAVI compared to SAVR (98.5% vs. 97.3%, p=0.003; 98.1% vs. 97.1%, p=0.014; respectively), with equivalent survival at 1 year (90.0% vs. 91.2%, p=0.16).

These favourable outcomes of TAVI indicate that surgical risk estimation is no longer the basis to guide the choice between TAVI and SAVR. Heart teams should now weigh clinical and anatomic characteristics to identify the best treatment option for individual patients, with transfemoral TAVI replacing SAVR as the default therapy for symptomatic severe aortic stenosis. Future research will need to address remaining uncertainties and options for further improvement in outcomes, including evaluation of TAVI in younger and asymptomatic patients (patients enrolled in the low-risk trials summarised above had a mean age of 74 years), assessment of THV durability using predefined clinical and echocardiographic assessment (5-year follow-up in the major randomised controlled trials has already demonstrated low rates of structural valve deterioration compared with SAVR, but longer-term data and larger patient numbers remain essential),[28-31] more detailed evaluation of TAVI in patients with bicuspid aortic valve disease and concomitant coronary artery disease, continued measures to reduce the need for permanent pacemaker implantation, definition of the optimal short- and long-term regimes of antithrombotic therapy, and the institutional and operator standards required to achieve clinical outcomes that match those in the randomised controlled trials.[32]

Stroke and transcatheter aortic valve implantation

Stroke is a rare, but potentially devastating complication of TAVI that impacts quality of life, independent living and survival. Cerebral protection devices (CPDs) are intended to reduce the risk of cerebral embolism by capturing or deflecting debris during the TAVI procedure. A patient-level propensity-matched analysis[33] of the SENTINEL US IDE trial,[34] the CLEAN-TAVI trial,[35] and the SENTINEL-Ulm study,[36] showed that TAVI with a dual-filter CPD (Claret Medical Inc., CA, USA) was associated with a significantly lower rate of procedural stroke compared with unprotected procedures (1.9% vs. 5.4%, odds ratio 0.35, 95% CI 0.17 - 0.72, relative risk reduction 65%, p=0.0028). However, this pooled analysis contained data from a non-randomised study[36] and significant reduction in stroke with the use of CPD has yet to be shown in a major randomised trial.

Comparison of different transcatheter aortic valve implantation devices

Data directly comparing different TAVI devices are scarce. In the SCOPE I trial,[37] the self-expanding Symetis ACURATE Neo valve (Boston Scientific, USA) was randomly compared to the SAPIEN 3 balloon-expandable valve (Edwards Lifesciences, CA, USA) in 739 patients. The primary endpoint (all-cause mortality, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary obstruction requiring intervention, acute kidney injury, rehospitalisation for valve-related symptoms or congestive heart failure (HF), valve-related dysfunction requiring repeat procedure, moderate or severe prosthetic valve regurgitation, or prosthetic valve stenosis within 30 days of the procedure) occurred in 87 (24%) and 60 (16%) of patients in the ACURATE Neo and SAPIEN 3 groups, respectively. Non-inferiority criteria for the ACURATE Neo were not met [absolute risk difference 7.1% (upper 95% CI 12.0%), p=0.42], and secondary analysis demonstrated that superiority of the SAPIEN 3 THV (95% CI for risk-difference, -1.3% - -12.9%; p=0.016) was driven by lower rates of acute kidney injury [3 (0.8%) vs. 11 (3%)] and moderate or severe prosthetic aortic regurgitation [10 (2.8%) vs. 34 (9.4%)]. Outcomes of the SCOPE II trial, comparing the self-expanding Evolut (Medtronic, USA) and balloon-expandable SAPIEN 3 (Edwards Lifesciences, CA, USA) THVs in similar fashion are keenly awaited.

Valve-in-valve transcatheter aortic valve implantation in small surgical bioprostheses

Valve-in-valve TAVI in small surgical bioprostheses can result in high residual gradients that are associated with increased morbidity and mortality, and bioprosthetic valve fracture (BVF) improves residual gradients in this setting. In a multicentre registry of 75 patients,[38] BVF led to a final mean transvalvular gradient of 9.2 ± 6.3mmHg, with superior haemodynamic outcomes when BVF was performed immediately after (rather than before) THV implantation (8.1±4.8mmHg vs. 16.9 ± 10.1mmHg; p<0.001). No aortic root disruptions or coronary occlusions were observed. This emerging concept and the associated BASILICA technique[39] (electrocautery-induced laceration of the bioprosthetic valve leaflets in patients at high risk of coronary obstruction) require comparison with re-do surgery in patients with structural valve deterioration affecting small surgical bioprostheses.

The mitral valve

The conflicting results of the COAPT[40] and MITRA-FR[41] randomised controlled trials evaluating the safety and efficacy of transcatheter edge-to-edge repair using the MitraClip device in patients with symptomatic HF and moderate-severe secondary mitral regurgitation MR despite medical therapy, generated considerable discussion, with almost 20 editorial articles attempting to address subtle differences between the studies (Table 1) and their implementation in clinical practice.[42] Meanwhile, extended observations from both studies

TABLE 1: Key differences between the COAPT and MITRA-FR trials.
Reproduced with permission from Praz F, et al.[42]

	Primary endpoint	MITRA-FR All-cause death and hospitalisation for CHF at 1 year	COAPT All hospitalisations for CHF within 2 years (including recurrent events)
Key exclusion criteria	Heart failure severity	NYHA class <II	NYHA class <II ACC/AHA stage D heart failure
	Left ventricular dimensions	No exclusion criteria	LVESD >70mm
	Coronary artery disease	CABG or PCI performed within 1 month	Untreated coronary artery disease requiring revascularisation
	Right ventricle	No exclusion criteria	Right-sided congestive heart failure with moderate or severe right ventricular dysfunction
	Pulmonary disease	No exclusion criteria	COPD with home oxygen therapy or chronic oral steroid use Estimated or measured PAP >70mmHg
Principal baseline characteristics	Number of patients screened	450	1 576
	Number of patients enrolled (ITT)	304	614
	Mean age (years)	70 ± 10	72 ± 12
	Mean LVEF (%)	33 ± 7	31 ± 10
	MR severity (EROA, cm^2)	0.31 ± 0.10	0.41 ± 0.15
	Mean indexed LVEDV (mL/m^2)	135 ± 35	101 ± 34
Safety and efficacy endpoints in the intervention arm	Complications[a] (%)	14.6	8.5
	No implant (%)	9	5
	Implantation of multiple clips (%)	54	62
	Post-procedural MR grade ≤2+ (%)[b]	92	95
	MR grade ≤2+ at 1 year (%)[b]	83	95
	Hospitalization for CHF at 1 year (%)	49	38
	30-day mortality (%)	3.3	2.3
	1-year mortality (%)	24	19

ACC = American College of Cardiology, AHA = American Heart Association, BNP = brain natriuretic peptide, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, EROA = effective regurgitant orifice area, ITT = intention to treat, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, MR = mitral regurgitation, NT-proBNP = N-terminal pro brain natriuretic peptide, PAP = pulmonary artery pressure.
[a]MITRA-FR definition of pre-specified serious adverse events: device implant failure, transfusion or vascular complication requiring surgery, ASD, cardiogenic shock, cardiac embolism/stroke, tamponade, urgent cardiac surgery.
[b]According to ESC/EACTS guidelines[5] in MITRA-FR and AHA/ACC Guidelines[43] in COAPT.

showed no change in the findings of MITRA-FR, with no impact of MitraClip implantation on all-cause mortality or HF hospitalisation at 24-month follow-up,[44] while the benefits of MitraClip implantation in COAPT were even more pronounced at 3-year follow-up [composite endpoint of death and HF rehospitalisation 58.8% vs. 88.1%, HR 0.48 (95% CI 0.39 - 0.59), p<0.001; number needed to treat 3.4 (95% CI 2.7 - 4.6)].[45] A proposed pathophysiological model of "proportionate" and "disproportionate" MR[46] based upon the relationship between left ventricular end-diastolic volume and effective regurgitant orifice area, and its disruption in patients with ventricular dyssynchrony or papillary muscle dysfunction, may explain these disparities and awaits prospective validation. Cost-effectiveness analysis of COAPT at 2 years confirmed a higher cost of intervention overall ($73 416 vs. $38 345, p<0.001; predominantly related to the price of the MitraClip device), but acceptable economic value based upon current US thresholds (incremental cost-effectiveness ratio $40 361 per life-year gained, $55 600 per quality-adjusted life-year gained).[47]

Although large-scale clinical experience (>100 000 patients) and outcome data are only available for MitraClip edge-to-edge repair, the Carillon Mitral Contour system (Cardiac Dimensions, Kirkland, WA, USA) was also investigated in a randomised sham-controlled study (REDUCE-FMR) among patients receiving guideline-directed medical therapy.[48] At 12 months, indirect annuloplasty using this system was associated with a significant fall in MR regurgitant volume (the primary endpoint) accompanied by reduction in left ventricular volumes and improvement in paired 6 minute walking distance and New York Heart Association (NYHA) functional class. However, the trial was not powered for clinical endpoints and the reported reduction in MR regurgitant volume (22%)

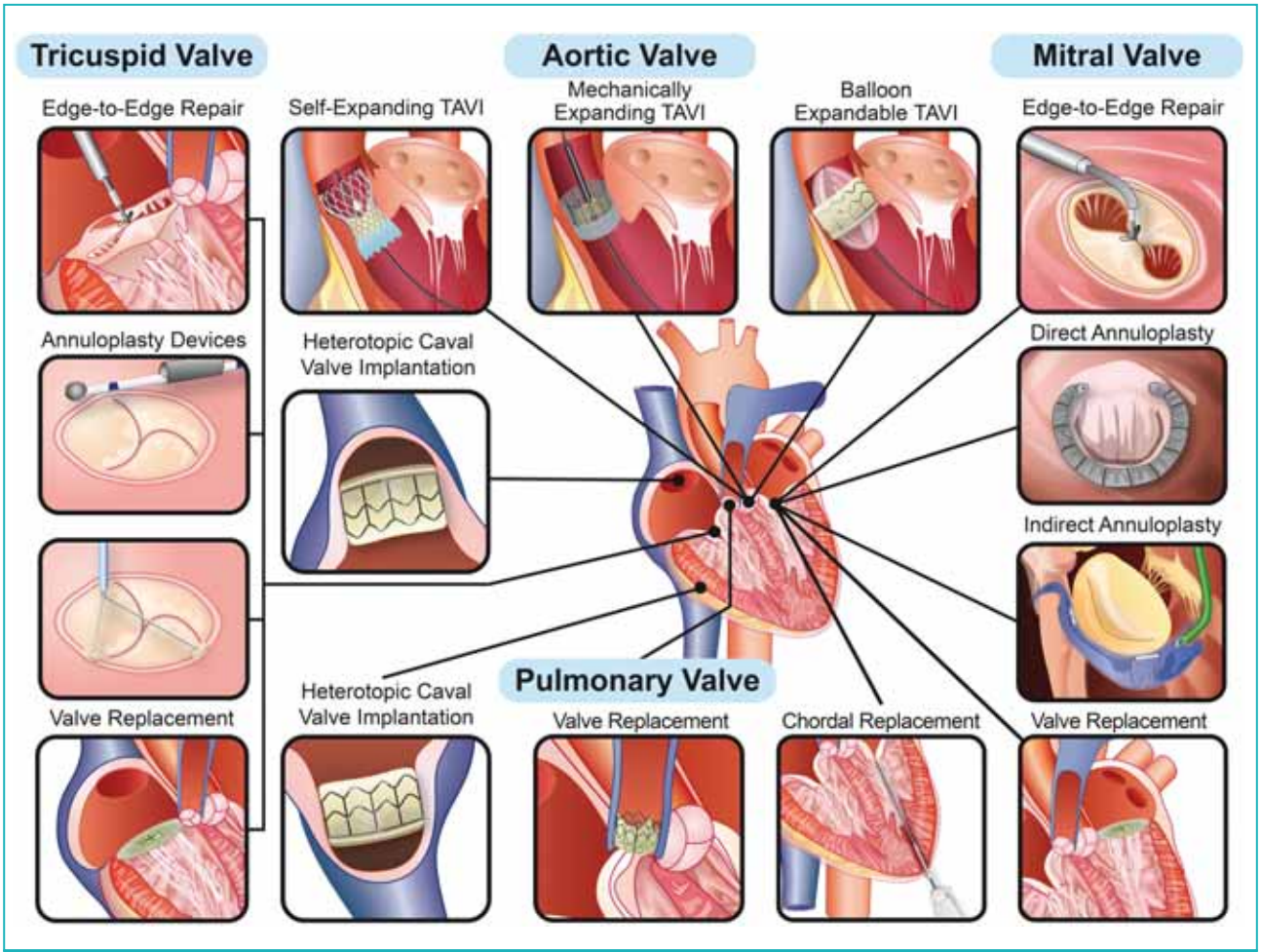

FIGURE 4: The scope of transcatheter intervention for valvular heart disease in 2019.

was modest compared to that typically achieved following MitraClip edge-to-edge repair (60% - 70%).[49]

Meanwhile, the evidence supporting surgical intervention for secondary mitral regurgitation remains weak. Mitral annuloplasty, the most commonly used technique for surgical mitral valve repair, reduces MR, improves symptoms and results in reverse left ventricular remodelling in the short-term. However, it remains unclear whether these outcomes are durable or reduce mortality, although low rates of recurrent MR (28%) were recently reported at 10-year follow-up in a single-centre study.[50] Further high-quality studies will be required to refine selection criteria for the various medical and interventional treatment options in this high-risk group, to explore indications for MitraClip beyond the current evidence base, and to investigate the role of other transcatheter devices (annuloplasty, combined repair techniques, valve replacement).

The tricuspid valve

Transcatheter strategies for tricuspid disease remain in their early stages. Anatomical challenges include the large annulus, paucity of valve/annular calcification, adjacency of the right coronary artery, and fragility of the valve tissue. Current approaches under investigation in feasibility and early phase clinical trials include edge-to-edge repair, coaptation enhancement, annuloplasty, heterotopic caval valve implantation, and percutaneous tricuspid valve replacement.[51] The supporting dataset is substantially smaller than for mitral interventions (which is itself limited), although promising early outcomes have been demonstrated with the MitraClip device.[52,53] Although recent studies have suggested potential advantages of transcatheter intervention compared with medical therapy,[54] major questions that need to be addressed by future trials include whether earlier intervention for tricuspid regurgitation may be beneficial, and whether combined mitral and tricuspid procedures improve procedural success and clinical outcomes.

The pulmonary valve

Twenty years since the first-in-human procedure, transcatheter pulmonary valve implantation (TPVI) has become the gold standard for treatment of pulmonary conduit dysfunction. In a

retrospective multicentre analysis of 845 patients undergoing TPVI with the Melody™ valve (Medtronic, USA),[55] the composite endpoint of TPVI-related events (death, reoperation, or reintervention >48 hours after TPVI) occurred with an incidence of 4.2% per person per year (95% CI 3.7 - 4.9), confirming procedural efficacy in a large cohort of congenital heart disease patients. Long-term risk of infective endocarditis is a concern in this setting and preventive measures are essential.[56]

INFECTIVE ENDOCARDITIS

The prospective EURO-ENDO registry of 3 116 adult patients (156 hospitals, 40 countries) with infective endocarditis confirmed persistent adverse outcomes (in-hospital mortality 17%, embolic complications 21%) despite advances in imaging, antibiotic therapy, and earlier surgery.[57] Predictors of mortality included Charlson index, creatinine >2mg/dL, congestive HF, vegetation length >10mm, presence of abscess or cerebral complications, and failure to undertake surgery when indicated according to ESC guidelines. Management by a multidisciplinary team and early, aggressive surgery are essential to improve outcomes.

Diagnosis of prosthetic valve endocarditis is frequently difficult and ESC guidelines recommend ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging in challenging cases.[58] Among 173 patients with left-sided endocarditis, diagnosis using ^{18}F-FDG PET/CT was associated with a significantly higher rate of the primary endpoint [death, recurrent endocarditis, HF, non-scheduled cardiovascular hospitalisation, new embolic event; HR 2.7 (1.1 - 6.7), p=0.04] in those with prosthetic valve infection, while moderate-intense valve uptake was associated with new embolic events [HR 7.5 (1.2 - 45.2), p=0.03].[59]

CONCLUSIONS

Recent advances in the management of VHD achieved by open collaboration between cardiologists and cardiac surgeons have been remarkable. Ongoing innovation, a multidisciplinary Heart Team approach to the management of individual patients, and its delivery via a network of specialist valve centres,[60] will further transform the dismal prognosis associated with the condition. Worldwide extension of these advances to low- and middle-income countries (where VHD remains endemic) is the next urgent priority.

Conflict of interest: R.K.B.: proctor for Boston Scientific, consultant for Edwards Lifesciences and speakers' fees and educational grants from Medtronic and Abbott. M.D.: none to declare. B.P.: speakers' fees and educational grants from Edwards Lifesciences.

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