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The year in cardiovascular medicine 2020: valvular heart disease

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Introduction

Valvular heart disease (VHD) is one of the most rapidly changing disciplines in cardiovascular medicine. During the past year, important basic research has provided new insight into disease mechanisms and identified new potential targets for pharmacological treatment. Despite the unequivocal impact of COVID-19 on global research and management of VHD (1), the results of landmark clinical trials with percutaneous devices have become available. Aspects of adjuvant medical therapies after device implantation have also been clarified. Technical improvements in next-generation valvular medical devices are taking place in parallel, showing promising preliminary clinical results. As the risk related to interventional procedures and their consequences is becoming lower, new opportunities for an earlier treatment arise. The most important achievements during 2020 are summarized herein.

Epidemiological issues and risk stratification of valvular heart disease

Rheumatic heart disease is still a major cause of VHD worldwide. In this regard, a trend towards a decrease in its incidence in the Americas has been reported. Between 1990 and 2017, the burden of mortality due to rheumatic heart disease has decreased from 88.4 to 38.8 years of life lost per 100 000 population in these regions. Importantly, this positive trend has taken place in parallel to the reduction in income-related inequalities (2). In western countries, degenerative-calcific disease is the leading aetiology of VHD. Population-based epidemiological data from the multi-ethnic study of atherosclerosis (MESA) have shown a direct association between mitral annular calcification (MAC) and the risk of peripheral artery disease and stroke (3, 4). Severe MAC progresses towards the valve leaflets, leading to progressive mitral stenosis (MS). MAC-related MS has recently been recognized as a major hemodynamic problem and its natural history is progressively being better understood. A large retrospective series of 200 patients demonstrates that patients with MAC-related MS are frequently symptomatic, present with a high burden of comorbidities and have impaired survival (5).
Regarding aortic stenosis (AS), registry data from the nationwide Australian echocardiographic database show that patients with moderate disease (i.e. a pressure gradient of >20 mmHg) are at an increased risk of cardiovascular and all-cause mortality (6). This finding could be a consequence of limited sensitivity of cur-

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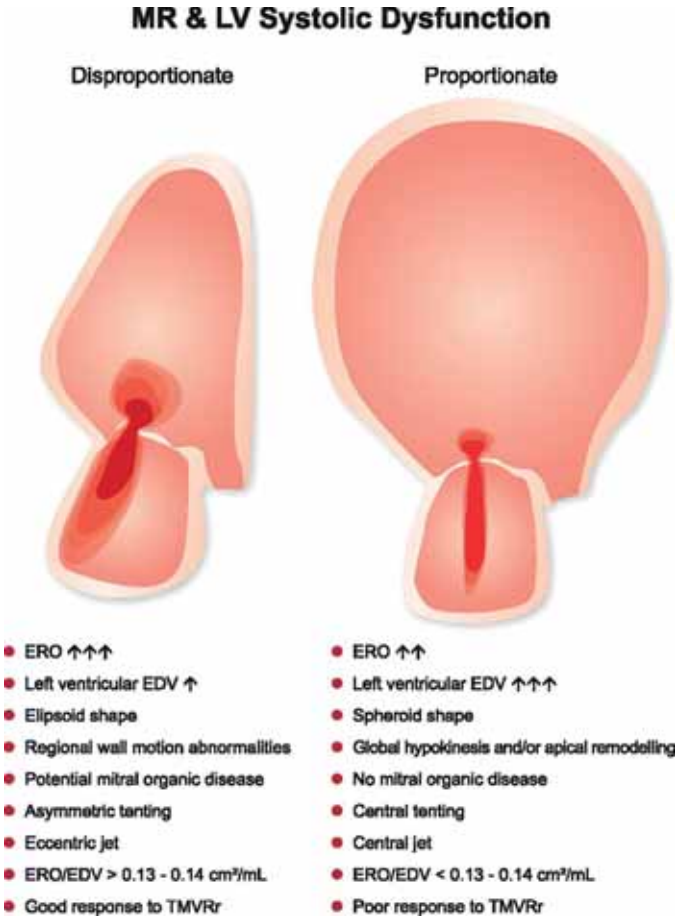

GRAPHICAL ABSTRACT Proposed framework for classifying coexisting mitral regurgitation and severe LV systolic dysfunction. This framework is based on ancillary analyses of randomized clinical trials and prospective validation is pending. ERO: effective regurgitant orifice. EDV: end-diastolic volume. TMVr: transcatheter mitral valve repair.

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rent severity criteria, and prospective data are required before it can be incorporated in recommendations for patient management. In this regard, levels of brain natriuretic peptides (BNPs) provide physicians with incremental prognostic information in all sources of VHD but particularly AS (7). However, the relationship between BNP levels and risks in AS seems more complex than previously understood. In an ancillary analysis of the Placement of AoRTic TraNscarthetER Valve Trial II (PARTNER II), the relationship between baseline BNP levels and 2-year all-cause and cardiovascular mortalities followed a J-shaped pattern *(Figure 1)* (8). Importantly, the hazard ratio for cardiovascular mortality was 2.3–4.4 for patients with a BNP value of <50 pg/mL compared to those with reference levels (50–100 pg/mL). The biological basis of this association is uncertain, but abnormally low levels of BNP could express an inability of the myocardium to compensate for the pressure overload by means of hypertrophy.

The burden of tricuspid regurgitation (TR) in the community remains poorly studied. Population data from the Olmsted County (Minnesota, USA) demonstrated an overall prevalence of moderate or severe TR of 0.55%. Although most cases of TR are secondary to left-heart disease, isolated TR is present in 8.1% of subjects and independently related to mortality (9). The bases of the relationship between secondary TR and left-heart diseases have been investigated. Interestingly, atrial fibrillation induces annular remodeling even in the absence of left-heart disease (10). In patients with heart failure and reduced EF (HFrEF), secondary TR is a very frequent finding. Although TR in HFrEF is associated with a more severe presentation, with atrial fibrillation and pulmonary hypertension, it is an independent predictor of clinical outcomes (11). In patients with degenerative mitral regurgitation (MR), moderate or severe functional TR also predicts mortality, independently from baseline confounders (12).

The bacteriological profile of endocarditis is continuously evolving due to population aging, increasing car-

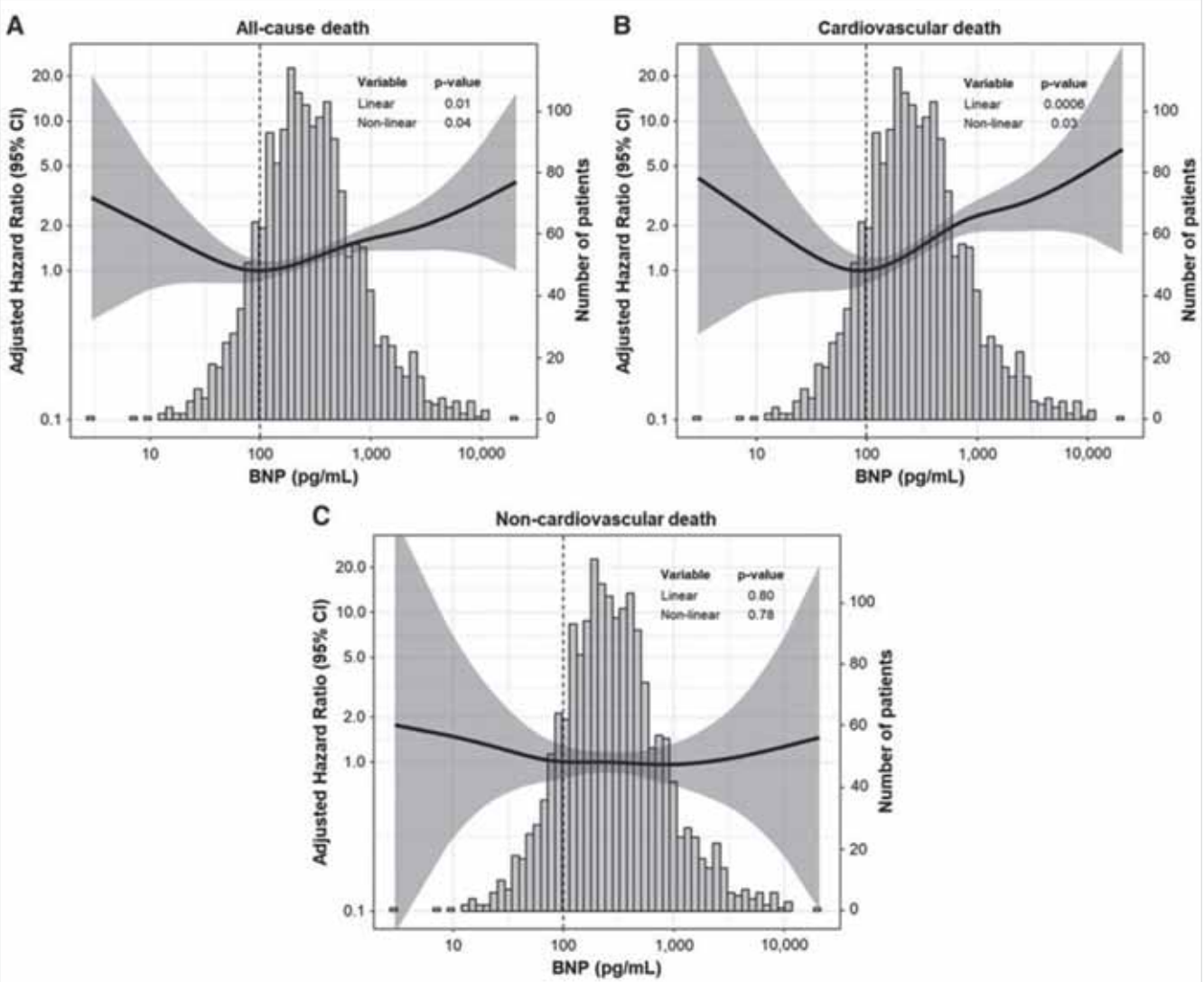

FIGURE 1. Nonlinear relationship between plasma BNP levels and 2-year clinical outcomes of patients in the PARTNER II trial and registry. Multivariable Cox proportional hazards regression using a spline function to model log-transformed baseline B-type natriuretic peptide as a continu- ous metric for (A) all-cause death; (B) cardiovascular death; and (C) non-cardiovascular death, at 2 years. BNP, B-type natriuretic peptide (reproduced with permission from Ref. 8).

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diac instrumentation, and device implantation. A contemporary European series shows that 40% of cases of endocarditis are now caused by infections of intracardiac devices and prostheses (13). Despite improvements in antimicrobial therapies and technical advances in imaging and microbiological diagnosis, in-hospital mortality is still 17% (13). Enterococcal endocarditis is health care-related in ~50% of cases, characteristically in elderly patients with concomitant degenerative valve disease and comorbidities such as chronic HF and lung disease (14). Enterococcus spp. are the most common microorganisms involved in endocarditis in TAVI (transcatheter aortic valve implantation) prostheses and are related to a considerable mortality and risk of stroke (15). However, data from the PARTNER trial suggest that the incidence and predictors of endocarditis are similar in percutaneously and surgically implanted aortic valve prostheses (16, 17).

Molecular and cellular mechanisms of valvular heart disease

In mitral valve prolapse syndrome, leaflet morphological changes take place in parallel to increased mechanical stress acting on the valve and the subvalvular apparatus. However, whether anatomical remodeling is the cause or consequence of abnormal valve biomecha-

nics remains unclear. In an elegant ex vivo biomechanical experiment, normal leaflet tissue was subjected to increased mechanical stresses ex vivo. As a resultant, superimposed tissue proliferated on the atrial side of the mitral leaflets, demonstrating that biomechanical-biological transduction plays a major role in mitral valve prolapse syndrome (18).

Although statins have failed to slow the disease progression of established AS, the relationship between AS and plasma lipids remains controversial. Mendelian randomization is a particularly well-suited methodology to test causality in this type of associations. Genetic data from 188 577 patients from the UK Biobank database were analysed for 157 genetic variants known to be associated with plasma lipid levels (19). Remarkably, the odds ratio per 0.98 mmol/L of LDL-cholesterol was 1.52 (95% CI (confidence interval) 1.22–1.90) for developing AS, whereas no association was observed between plasma levels and aortic or MR. This study strongly demonstrates a causal association between lifetime exposure to high cholesterol levels and the risk of symptomatic AS. Identifying novel metabolic pathways involved in AS is a matter of continuing research, and two important studies have been reported this year. In a murine model of AS, inhibition of microRNA significantly attenuated aortic valve calcification and its consequences (flow acceleration, LV (left ventricle) hypertrophy) (20). Zinc transporter molecules have been proven as regulators of valvular interstitial cell calcification in vitro (21). This finding, combined with the identification of a significant reduction in serum levels of zinc in patients with calcific AS, suggests a role of zinc metabolism in early valve degeneration (21). Acquired somatic mutations in haematopoietic precursors is increasingly being reported in several chronic conditions. Patients with AS show an age-related prevalence of acquired somatic mutations in haematopoietic lineages related with pro-inflammatory leucocyte subsets, up to a prevalence of nearly 53% in >90-year-old TAVI candidates (22). Remarkably, identifying these somatic mutations predicted poor survival despite successful valve implantation. These four mechanistic studies open the door to potential pharmacological interventions at the primordial and advanced phases of calcific AS (18).

Imaging

Ultrasound remains the cornerstone technique for guiding AS patient management, whereas the role of computed tomography (CT) and cardiac magnetic resonance (CMR) is rapidly increasing (24). Grading the severity of AS relies on peak-jet velocity, the mean pressure gradient and aortic valve area (25). Unfortunately, cut-off values of these three parameters should be reconciled, as inconsistencies are frequent, particularly in patients with low-flow condition (26). In this regard, mean transvalvular flow rate (27), or sex-specific thresholds of stroke-volume index (40 mL/m² for men and 32 mL/m^2 for women) (28) may be most valuable for risk assessment. Beyond these conventional indices of severity, additional metrics are still being proposed. The first-phase ejection fraction (the proportion of stroke volume ejected before peak-jet velocity) may be of value in unselected AS patients but has also shown to be related to vascular hemodynamics (29). The sensitivity of CMR to detect and quantify myocardial fibrosis can be exploited to stratify the impact of AS on the LV, using late gadolinium-enhancement, direct T1 mapping, or estimation of the extracellular volume (30–32). The relationship between fibrosis and outcomes has been confirmed in 100 patients undergoing myocardial biopsies after TAVI, demonstrating a direct relationship between histological findings and mortality (33). As bone scintigraphy is progressively being performed in patients with AS, the diagnosis of concomitant amyloidosis is increasing. Although this association is found in roughly 13% of patients referred for TAVI, observational data suggest similar benefit from intervention in AS patients with and without amyloidosis (34).

Timing of intervention

The multicentric Korean RECOVERY randomized clinical trial compared early surgery vs. conservative care in 145 asymptomatic patients with very severe AS (AVA ≤0.75 cm^2 with velocity ≥4.5 m/s or mean transaortic gradient ≥50 mmHg) (35). With an operative mortality of zero, the study demonstrated a 91% reduction in cardiovascular death at a median follow-up of 6.2 years (hazard ratio, 0.33; 95% CI: 0.12–0.90). These results must, however, be viewed with caution. The difference in mortality was primarily driven by the difference in sudden cardiac deaths (11% vs. 0%). This rate is much higher than in other reports, and 6 of the 8 deaths occurred in patients who had become symptomatic but did for unclear reasons nevertheless not undergo valve replacement. Thus, the results of ongoing trials such as the EARLY-TAVI trial and others must be awaited before changing treatment strategies in asymptomatic patients with severe AS.

Transcatheter interventional treatment

Aortic valve stenosis

A global registry of 867 658 interventions for AS performed in the USA between 2003 and 2016 shows that the number of patients undergoing valve replacement is linearly increasing in all ranges of age with TAVI accounting in 2016 for >40% of the procedures (36). Unfortunately, results of the EAPCI-Atlas Project demonstrate that in Europe the national access to TAVI is very heterogeneous and closely related to national

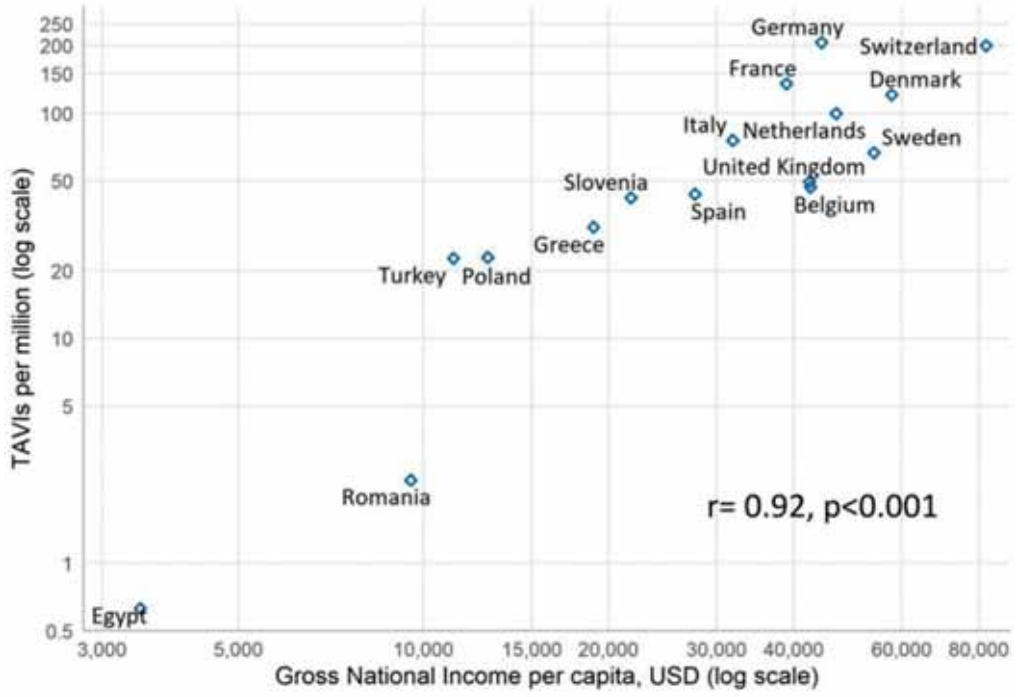

FIGURE 2. Relationship between gross national income and the usage of TAVI in selected countries. Data show the usage of TAVI per million inhabi- tants by gross national income per capita (2016 or least available year; reproduced with permission from Ref. 23).

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economic resources *(Figure 2)* (23). Nevertheless, the trend towards preference of percutaneous over surgical strategies will continue to increase as long-term results of TAVI are becoming available. In a meta-analysis of four randomized controlled trials (RCTs) comparing TAVI and surgical valve replacement in 2887 low-risk patients (mean age 75.4 years, mean STS score 2.3%), TAVI was associated with a significantly lower all-cause and cardiovascular mortality, lower rates of new-onset atrial fibrillation, life-threatening bleeding and acute kidney injury but higher rates of moderate/severe paravalvular regurgitation and pacemaker implantation (37). No difference was found for major vascular complication, endocarditis, aortic valve re-intervention, and symptom improvement. When considering to expand a preference for TAVI to surgical low-risk and younger patients one needs, however, to take into account that
(i) these RCTs included selected patients in particular excluding patients with bicuspid valves and with anatomic features increasing the risk for either procedure,
(ii) data on long-term durability are still limited,
iii) higher rates of left bundle branch block, pacemaker implantation and more than mild aortic regurgitation (AR) have an increasing impact when treating patients with longer life expectancy, and (iv) options for future repeat re-interventions may be limited.
Although recently reported 8-year data show a very low incidence of structural deterioration (moderate 3.0%, severe 1.6%) and late failure (2.5%) of percutaneously implanted prostheses (38), currently available durability and re-intervention data must be viewed with caution considering the very high mortality in the studies with now available long-term data and the higher threshold for re-intervention in this population. Five-year data of patients from the intermediate-risk PARTNER 2 trial show no difference in the incidence of death or disabling stroke between the percutaneous and the surgical groups and comparable valve performance but confirm once more excess mortality in patients with more than mild paravalvular AR (39). A meta-analysis demonstrates the association of new-onset persistent left bundle branch block and of pacemaker implantation after TAVI with a significantly worse outcome regarding heart failure and survival (40). In patients with bicuspid aortic valves (typically not included in RCT), observational registries using new generation TAVI devices show a slightly lower rate of procedural success, more frequent residual regurgitation (2.7% vs. 2.1%, $P < 0.001$), but outcomes comparable to patients with tricuspid valves (41). Short- and long-term outcomes are related to the degree of raphe and leaflet calcification (42). Regarding device selection, the compariSon of secOnd-generation seLf-expandable vs. balloon-expandable Valves and gEneral vs. local anaesthe-

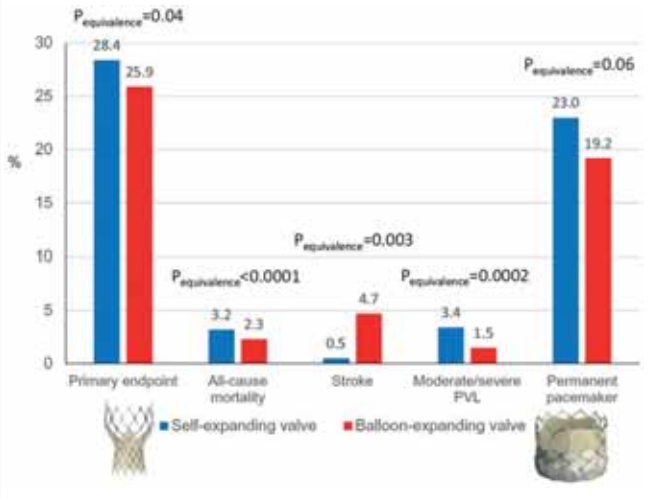

FIGURE 3 Results of the SOLVE-TAVI trial comparing 30-day out- comes of second-generation self-expanding and balloon-expanding percutaneous valves. PVL, paravalvular leakage (reproduced with permission from Ref. 43).

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sia (SOLVE-TAVI) trial was an open-label randomized equivalence clinical trial comparing new generation models of self-expandable and balloon-expandable transcatheter valves. For the composite of all-cause mortality, stroke, permanent pacemaker implantation, and paravalvular leakage (PVL) at 30 days, the two prostheses were reported to be equivalent. The lower over-all mortality and lower PVL rate of the balloon-expandable valve were counterbalanced by a higher stroke rate and pacemaker rates were similar for both valves in this trial *(Figure 3)* (43). The stroke rate of 4.7% and pacemaker rate of 19% for the balloon-expandable valve are, however, unusually high and in contrast to the large volume of data available from RCTs and registries of this valve. Two propensity-matched analyses of large registries looking not only at 30-day but on average 1–2-year outcomes reported indeed lower pacemaker and moderate/severe PVL rates, as well as lower mortality and rehospitalization for heart failure for the balloon-expandable valve (44, 45). Compared to these two prostheses, the Portico device delivered larger valve areas and lower mean gradients, but it was associated with higher rates of vascular complications and mortality at 30 days (46).

Mitral regurgitation

In the field of transcatheter mitral valve repair (TMVr) for secondary MR, new data are being helpful for reconciling the discordant results of the COAPT and the MITRA-FR clinical trials (47). Ancillary analyses of these two clinical trials have suggested the utility of the proportionate vs. disproportionate classification of MR in patients with severe LV systolic function. Patients with disproportionate MR would show larger effective regurgitant orifice areas, more eccentric regurgitant jets, less dilated ventricles, more frequently abnormal regional wall motion and may benefit most of TMVr. Patients with proportionate MR would have less severe regurgitation, more central jets, and severely and diffusedly impaired ventricles and are less prone to improve after TMVr (Graphical abstract) (48). The best criterion for discriminating disproportionate and proportionate MR would be a regurgitant orifice/end-diastolic volume ratio of > or <0.13–0.14 mm^2/mL, respectively. However, this framework must be further validated (49), as it is based on pooled secondary analyses and has not been confirmed when the MITRA-FR data were analysed in this respect (50). Although the 5-year follow-up is pending, intermediate-term data of the COAPT trial show that acute results predict improved outcomes at 2 years (51). On the other hand, the 2-year results of MITRA-FR confirmed no difference in all-cause mortality and unplanned hospitalization for heart failure (52). A planned individual participant data meta-analysis from both trials and the ongoing RESHAPE II trial will hopefully help to better identify those patients most likely to respond to secondary MR intervention.

Tricuspid regurgitation

The field of percutaneous tricuspid valve repair is evolving rapidly, as outcome data are being reported and novel transcatheter devices are becoming available. Data of the TriValve Registry including 472 patients with mostly secondary TR treated with different transcatheter techniques in 22 centres and control cohorts of 2 large retrospective registries enrolling medically managed patients were used for a propensity-score matched analysis (268 pairs) that showed improved survival and a reduced rate of rehospitalizations in the intervention group (53). However, we have learned from secondary MR that RCTs will be required to determine the effect of secondary TR treatment on outcome. A specific device for edge-to-edge repair of the tricuspid valve has undergone successful clinical testing with excellent implant success and favourable imaging and functional outcomes at 6 months (54). Also, short-term data of the percutaneous annuloplasty approach are promising (55). As expected, pulmonary hypertension (defined by an invasive systolic pulmonary pressure >50 mmHg) is an important predictor of poor outcomes in patients undergoing percutaneous tricuspid valve repair with the MitraClip system (56). In this population, echocardiography shows important limitations to estimate pulmonary pressure. Remarkably, it is the group with a false negative ultrasound diagnosis of pulmonary hypertension that shows the poorest outcomes (56). Consequently, further studies are needed to clarify the baseline characteristics that may be useful to predict treatment futility.

Prosthetic valve dysfunction

Transcatheter valve-in-valve implantation is a feasible and safe option for patients in whom re-operation would be at high risk. In a propensity-score matched analysis using the US National Readmission Database providing 2181 pairs of high-risk patients with degenerated bioprosthetic aortic valves, patients undergoing transcatheter procedures had significantly lower 30-day morbidity and mortality as well as less bleeding complications than those undergoing surgery (57). Long-term outcomes of valve-in-valve procedures were analysed in the VIVID registry (58). Long-term survival after the procedure was directly related to the size of the original failed valve, ranging from 40.5% to 33.2% at 8 years for internal diameters larger and smaller than 20 mm, respectively. Predictors for the need of re-intervention were pre-existing severe patient-prosthesis mismatch, valve malposition during the procedure, and use of the Edwards balloon-expandable valve (58). When the native valve is a previous percutaneous prosthesis, results of the Redo-TAVR Registry show that the valve-in-valve procedure is a safe and effective option, with the 1-year survival rates of 84% and 88% depending on whether the re-TAVI procedure is before or after the first year since the original implant (59). Thus, currently available data demonstrate that valve-in-valve procedures can be performed safely with high success rate. However, good long-term results can only be achieved with reasonable hemodynamics, which may frequently not be achieved when the original valve is small. When performing valve-in-valve procedures in small failed bioprostheses all efforts must therefore be made to achieve good hemodynamics (choice of valve type and size, implantation techniques including valve fracture); when achievement of reasonable hemodynamics is unlikely, the potentially resulting negative impact on outcome must be carefully weighed against the risk of surgery before deciding about the treatment modality (60).

Medical therapies pre- and post-correction

Subclinical leaflet thrombosis (SLT) has been recognized as an important late complication of transcatheter aortic bioprostheses, but its clinical implications remain unclear. SLT is typically diagnosed using CT as characteristic signs of hypo-attenuated leaflet thickening and reduced leaflet motion. Prospective CT substudies of the Evolut Low-Risk and the PARTNER 3 trials show that the one-year incidence of leaflet thickening and reduced leaflet motion is roughly 25–30% each, similarly frequent in self-expanding and balloon-expandable prostheses, and has a small impact on valve hemodynamics (61, 62). In addition, both studies demonstrated dynamic incidences of SLT including spontaneous resolution and late development in serial CT scans at 30 days and 1 year. Importantly, at 1 year, the incidence of SLT among TAVI and surgical prostheses was similar.

For preventing thrombosis, current guidelines recommend dual antiplatelet therapy for 3–6 months after TAVI followed by life-long single antiplatelet therapy, with no supporting evidence. The cohort A of the POPular (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation) trial compared aspirin alone with aspirin plus clopidogrel in patients undergoing TAVI without indication of oral anticoagulation. A total of 665 patients were 1:1 randomized to receive either aspirin or aspirin plus clopidogrel (for 3 months), and after 1 year of follow-up, the composite endpoint of bleeding or thromboembolic events were significantly less frequent with aspirin than with aspirin plus clopidogrel (63). The Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) clinical trial explored whether rivaroxaban 10 mg daily (combined with low-dose aspirin for the first 3 months) would be a suitable alternative to double antiplatelet therapy (64). The trial was prematurely interrupted because, after a median of 17 months, rivaroxaban was associated with a higher incidence of death (HR: 1.69, 95% CI: 1.13–2.53), of bleeding, and of the composite primary endpoint of death or thromboembolic complications than the antiplatelet-based group (64). However, in the subset of 231 patients studied by CT, rivaroxaban showed a lower incidence of reduced leaflet motion at 90 days. This observation emphasizes the need for better understanding the clinical implications of subclinical leaflet thrombosis findings.

A different group of patients are those with a formal indication for oral anticoagulation after the TAVI procedure. The cohort B of the POPular TAVI Trial randomized patients taking anticoagulants before the procedure to receive or not receive additional clopidogrel for 3 months. Patients on oral anticoagulation alone presented with a lower incidence of serious bleeding both at 1 month and 1 year (risk ratio 0.63), with a significant reduction in the composite endpoint of cardiovascular death, non-procedure-related bleeding, stroke, or myocardial infarction at 12 months (risk ratio, 0.69; 95% CI for superiority, 0.51–0.92) (65). Whether direct anticoagulants are a suitable alternative to vitamin-K antagonists in TAVI subjects is being explored in ongoing large-scale clinical trials, but registry data suggest a similar bleeding risk but higher ischaemic event rates with these drugs (66). Thus, either single antiplatelet treatment with aspirin or oral anticoagulants alone (for patients with a formal indication for anticoagulation) is the most suitable antithrombotic strategy for most patients after TAVI *(Figure 4)*.

Beyond antithrombotic treatment, no co-adjuvant medical treatment is currently indicated in patients after TAVI and patients receive conventional medications for treating concomitant risk factors and/or heart failure whenever present. A recent sub-analysis of the PART-

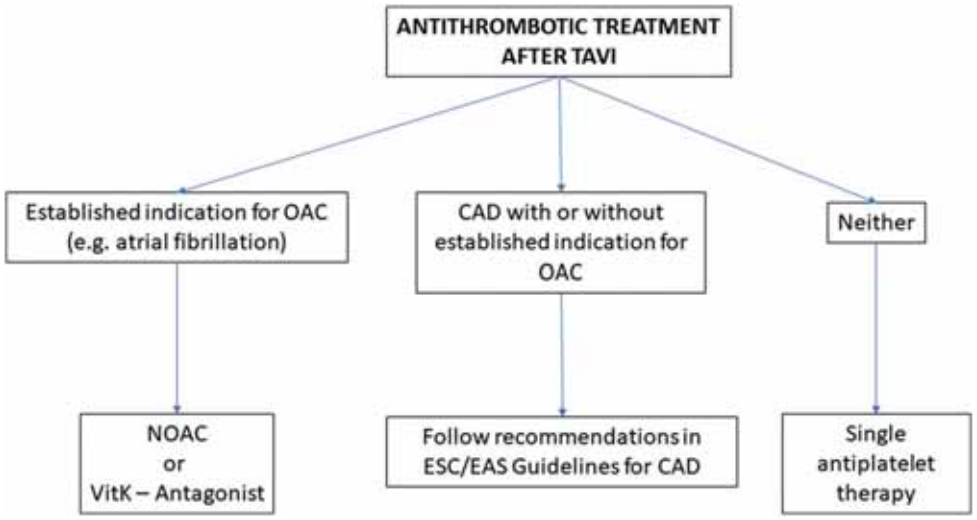

FIGURE 4. Algorithm for antithrombotic treatment after TAVI based on the POPULAR A and B and the GALILEO clinical trials. CAD, coronary ar- tery disease; NOAC, non-vitamin K antagonist oral anticoagulant; VitK, vitamin K.

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NER trial shows that in high- or intermediate-risk patients, TAVI pre-intervention with ACEIs is associated with better survival (67). In hypertensive patients, blood pressure needs to be monitored keeping in mind that target values carriers of prosthetic aortic valves are higher than in the general population (68).

Regarding other medical therapies for patients with valvular heart disease, the Pharmacological Reduction of Functional, Ischaemic Mitral Regurgitation (PRIME) study has demonstrated that sacubitril/valsartan is more effective than valsartan in reducing the severity of functional MR at 12 months (69).

Conclusions

In this difficult year, positive trends in epidemiological data of rheumatic heart disease anticipate a potential reduction of the burden of VHD. Basic and clinical research is providing new understanding of the basis of calcific-degenerative VHD, opening the door to future new pharmacological interventions in early phases. The role of percutaneous aortic valve interventions is expanding worldwide as long-term results and data for low-risk patients become available. Unfortunately, large worldwide registries show important income inequalities in the access to catheter procedures. Despite COVID-19 pandemic has radically changed health priorities worldwide, the global aims of the Agenda 2030 for Sustainable Development must be encouraged, keeping in mind that VHD is a major cause of mortality and disability in moderate and low-income countries.

Conflict of interest

Dr Baumagartner has received speaker fees and congress travel support from Actelion and Edwards Lifesciences. Dr Bermejo and Dr Postigo have no potential conflicts of interest to disclose.

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