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Valvular heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology

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Introduction

With an ageing population and improved diagnostic modalities, the number of patients with valvular heart disease is dramatically increasing. Considering projected changes in the age distribution, a further accentuation of this trend can be expected and this may indeed be considered "the next cardiac epidemic".¹ Obviously, we are faced with more complex decisions in patients with advanced age and increasing comorbidities. Advances in percutaneous valve interventional techniques have entered into routine practice. At the same time, new data on the natural history of disease and the identification of predictors of outcome permit improvement in the decision-making process and management of patients with valvular heart disease.

Aortic stenosis

Disease progression

In a population based study which followed up 953 subjects for 10 years, a high prevalence of calcific aortic valve disease (28%) associated with long-term exposure to raised cholesterol levels and active smoking was described.² Intraleaflet haemorrhage (detected by immunohistochemistry at the moment of aortic valve replacement

surgery) was frequently present in the valve leaflets of degenerative aortic stenosis (AS) and was associated with rapid progression of AS.³ In a small study of 164 patients with rheumatic AS (of whom 30 were treated with a statin), progression of AS was slower in patients receiving statins than in untreated patients (annual change of peak aortic velocity: 0.0560.07 m/s/year vs 0.1260.11 m/s/year, $p=0.001$).⁴ On the other hand in the ASTRON-OMER trial, a randomised double-blind study, that allocated 269 patients to rosuvastatin 40 mg daily or to placebo, statin treatment did not reduce progression of the disease in patients with AS.⁵

Predictors of outcome

Based on the aortic jet velocity and the B-type natriuretic peptide (BNP) level, a risk score predicting outcome in patients with moderate to severe asymptomatic AS was derived and validated in an independent cohort: score = (peak velocity (m/s) x 2) + (ln of BNP x 1.5) + 1.5 (if female sex). Event free survival after 20 months was particularly poor (7%) for patients in the fourth quartile.⁶ In a separate study of patients with severe asymptomatic AS, event-free survival rates at 3-years were 49%, 33% and 11% for patients with peak aortic jet velocities between 4.0 and 5.0 m/s, 5.0 and 5.5 m/s or >5.5 m/s, respectively. In

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addition to the important implications for risk stratification, these data introduce us to the entity of "very severe aortic stenosis" based on a peak aortic jet velocity ≤ 5.0 m/s.⁷ In another study, receiver-operator curve analysis identified a peak aortic jet velocity ≥ 4.4 m/s, a left ventricular (LV) longitudinal myocardial deformation $\leq 5.9\%$, a valvular arterial impedance ≥ 4.9 mmHg/mL/m² and an indexed left atrial area ≥ 12.2 cm²/m² as factors associated with adverse outcomes in 163 patients with moderate to severe AS.⁸ Early elective surgery was performed on 102 patients with severe AS (valve area ≤ 0.75 cm², AV-velocity ≥ 4.5 m/s), and conventional treatment was used for 95 patients. Compared with conventional treatment, early surgery in patients with very severe AS was associated with improved long-term survival by decreasing cardiac mortality.⁹ However, this was not a randomised study and selection bias might have affected the results.

In asymptomatic patients with AS (n=135) and a normal exercise response, an exercise induced increase in mean transvalvular gradient >20 mmHg was described as an independent risk predictor. These results thus suggest that exercise stress echocardiography may provide prognostic information additional to that obtained by standard exercise testing and resting echocardiography.¹⁰ Symptoms on treadmill exercise testing in 38 apparently asymptomatic patients with at least moderate AS were associated with a lower peak aortic VO_2 , a lower peak stroke index during exercise and BNP levels.¹¹ Increased valvuloarterial impedance (Z(va)) (which is calculated by dividing the estimated LV systolic pressure (systolic arterial pressure + mean transvalvular gradient) by the stroke volume indexed for the body surface area) is a marker of excessive LV haemodynamic load, and a value >3.5 successfully identifies patients with AS with a poor outcome.¹² However, the clinical value of this measure remains to be fully determined.

The prognostic significance of mid-wall fibrosis and infarct patterns detected by late gadolinium enhancement was evaluated in 143 patients with aortic stenosis. Mid-wall fibrosis (HR=5.35; $p=0.03$) and ejection fraction (HR=0.96; $p=0.01$) were independent predictors of all cause mortality and may provide a useful method of risk stratification.¹³ There is evidence of subclinical myocardial dysfunction early in the disease process despite normal left ventricular ejection fraction (LVEF). The myocardial dysfunction appears to start in the subendocardium and to progress to transmural dysfunction with increasing AS severity. Symptomatic patients with AS have more impaired multidirectional myocardial functions than asymptomatic patients.¹⁴ In patients with severe AS, impaired multidirectional LV strain and strain rate are present even with preserved LVEF, but a significant improvement occurs after aortic valve replacement (AVR).¹⁵ Lower average longitudinal strain is related to higher LV mass, concentric geometry and more severe AS.¹⁶ Inappropriately high LV mass was found in 58% of asymptomatic patients with severe AS and was related to cardiovascular events. Event free survival for patients with appropriate and inappropriate LV mass, respectively, was 78% vs 56% at 1-year, 68% vs 29% at 3-years and 56% vs 10% at 5-years (all $p<0.01$).¹⁷ However, in patients with calcific AS and a normal LVEF the severity of stenosis was the most important correlate of symptomatic deterioration. Tissue doppler measures

of LV systolic and diastolic function and LV mass provide limited predictive information after accounting for the severity of stenosis.¹⁸

Outcome of symptomatic patients with aortic stenosis

Severe aortic valve stenosis is a medical condition with limited short-term survival for patients over the age of 75-years, particularly those at high surgical risk. Patients with the highest surgical risk have the worst prognosis if AS is not treated.¹⁹ It has been confirmed, that patients screened but without the inclusion/exclusion criteria necessary to participate in a transcatheter aortic valve implantation trial do poorly and have extremely high mortality rates, especially in non-surgical groups: 274 such patients were treated medically or with balloon aortic valvuloplasty and had a mortality of 37.2% as compared with a mortality of 21.5% for 88 patients who underwent AVR (these latter patients were less symptomatic and had a lower EURO-score) during a median follow-up of about 1-year.²⁰ In an observational study of 25 patients with severe AS presenting in cardiogenic shock, the use of an intraaortic balloon pump improved the cardiac index from 1.77 to 2.18 and 2.36 L/min/m² at six and 24 hour, respectively ($p<0.001$) and should thus be considered in this critically ill population while being evaluated for further interventions.²¹

Low gradient aortic stenosis

Five year survival in patients with low-flow/low-gradient aortic stenosis without contractile reserve was higher in patients undergoing AVR than in medically managed patients ($54\pm 7\%$ vs $13\pm 7\%$, $p=0.001$) despite a high operative mortality of 22%. Surgery should thus not be withheld in this subset of patients solely on the basis of lack of contractile reserve on dobutamine stress echocardiography.²²

Measuring the degree of aortic valve calcification by multislice CT in patients with mild to moderate AS and an EF $\geq 40\%$, showed that a threshold of 1651 arbitrary units provided 82% sensitivity, 80% specificity, 88% negative predictive value and 70% positive predictive value to diagnose severe AS. Performance was best in a subset of patients with low EF when the threshold correctly differentiated between patients with severe AS (the diagnosis was confirmed by mean gradient, natural history or dobutamine stress echocardiography) and those with non-severe AS in 46 of 49 cases. This method may be particularly useful for the evaluation of AS severity in difficult cases, such as patients with reduced EF and low or absent contractile reserve.²³

On echocardiography approximately one-third of patients with severe aortic valve stenosis, based on aortic valve area <1.0 cm², have a non-severe mean pressure gradient (≤ 40 mmHg) despite apparently normal left ventricular function. Three hundred and thirty-three consecutive patients underwent cardiac catheterisation within 30 days after their index echocardiography. On invasive testing, 85 patients (26%) demonstrated inconsistent grading, with a significantly lower stroke volume and stroke volume index. However, 48% of inconsistently graded patients had a normal stroke volume index >35 mL/m². In the framework of current guidelines inconsistent grading of aortic valve stenosis is common, extends to cardiac

catheterisation and is only partially explained by low stroke volume despite apparently normal left ventricular systolic function.²⁴ In this SEAS substudy, aortic valve related events, major cardiovascular events and cardiovascular death in patients with low-gradient "severe" aortic stenosis (aortic valve area $<1.0 \text{ cm}^2$ and mean gradient $\leq 40 \text{ mmHg}$) were comparable to those of patients with moderate stenosis (aortic valve area $1.0\text{--}1.5 \text{ cm}^2$; mean gradient $25\text{--}40 \text{ mmHg}$).²⁵ These results fuel the debate on the management of such patients. In severe AS, a low gradient is associated with a higher degree of interstitial fibrosis in biopsy samples and more late enhancement MRI segments, decreased longitudinal function assessed by echocardiography and poorer clinical outcome despite preserved EF.²⁶

Experimental studies in aortic stenosis

Higher serum phosphate levels within the normal range were associated with aortic valve sclerosis and mitral and aortic annular calcification in a community based cohort of older adults. In contrast, serum calcium, parathyroid hormone and 25-hydroxyvitamin D concentrations were not associated with aortic or mitral calcification. Phosphate may be a new risk factor for calcific aortic valve disease and warrants further study.²⁷ The upregulation of the leukotriene pathway in human aortic valve stenosis and its correlation with clinical stenosis severity, taken together with the potentially detrimental leukotriene induced effects on valvular myofibroblasts, suggests one possible role of inflammation in the development of AS.²⁸ Mechanical properties of porcine aortic valve leaflets were evaluated: serotonin induced a decrease in the area stiffness of the cusp, which was reversed by N-nitro-L-arginine-methyl ester or endothelial denudation. Endothelin-1 caused an increase in stiffness, but not in the presence of cytochalasin B. Changes in cusp stiffness were accompanied by aortic cusp relaxations to 5-hydroxytryptamine, which were reversed by endothelial denudation and by N-nitro-L-arginine-methyl ester. These data highlight the role of the endothelium in regulating the mechanical properties of aortic valve cusps and underline the importance of valve cellular integrity for optimal valve function.²⁹ A reduced regenerative capacity of valvular endothelial cells due to senescence and decreased levels of endothelial progenitor cells might be, at least in part, a pathological link for the destruction of valvular endothelial cells, resulting in progression of degenerative AS.³⁰ Direct in vivo evidence was provided that cathepsin S-induced elastolysis accelerates arterial and aortic valve calcification in chronic renal disease, providing new insight into the pathophysiology of cardiovascular calcification.³¹ In the low-density lipoprotein receptor deficient mouse, regular exercise training prevents aortic valve sclerosis by several mechanisms, including the preservation of endothelial integrity, a reduction in inflammation and oxidative stress, and inhibition of the osteogenic pathway.³² Recombinant apolipoprotein A-I Milano treatment reverses AS in an experimental rabbit model. The beneficial effects seem to be mediated by enhanced cholesterol removal and by reduced inflammation and calcification.³³ Additional data indicate that reducing plasma lipid levels by genetic inactivation of the MTP gene in hypercholesterolaemic mice

with early aortic valve disease normalises oxidative stress, reduces proosteogenic signalling and halts the progression of aortic valve stenosis.³⁴ Patients with AS and diabetes have worse diastolic LV dysfunction, predisposing to heart failure. It appears to result from greater myocardial fibrosis (documented with perioperative LV biopsies), more intramyocardial vascular advanced glycation end product deposition and higher cardiomyocyte F_{passive} , which is related to hypophosphorylation of the N2B titin isoform.³⁵

Aortic regurgitation

In an observational study of 756 patients with severe aortic regurgitation (AR), those taking a β blocker ($n=355$) had significantly better survival rates of 90% and 70% at 1-year and 5-years than patients not receiving treatment (75% and 55%, respectively; $p=0.0009$), suggesting that β -blocker treatment may confer a survival benefit in patients with severe AR.³⁶ About one-quarter (191 of 756) of patients with severe AR have at least moderate mitral regurgitation (MR), and in a retrospective cohort study MR was an independent predictor of reduced survival. Moreover, performing AVR plus concomitant mitral valve repair was associated with improved survival. These data suggest that the development of MR might provide useful information about the timing of surgery in patients with AR.³⁷ Doctors are often reluctant to offer AVR to patients with severe AR and associated severe LV dysfunction ($\text{EF} \leq 35\%$), yet a recent study has shown that it results in significantly improved 5-year survival rates of 70% as compared with 37% for patients not receiving surgery. Significantly, however, surgery was only performed in 53 of 166 patients.³⁸ In patients with AR macroscopic LV hypertrophy normalises late after AVR, although fibre hypertrophy persists. These changes in LV myocardial structure late after AVR are accompanied by a change in passive elastic properties with persistent diastolic dysfunction.³⁹

There is increasing interest in surgical reconstruction procedures and in experienced hands, good early results have been reported. Thus, in 316 patients who underwent reconstruction of regurgitant bicuspid aortic valves hospital mortality was 0.63% and survival was 92% at 10-years. Freedom from reoperation at five and 10-years was 88% and 81%, respectively. Predictors of reoperation were age, aortoventricular diameter, effective height, commissural orientation and the use of a pericardial patch.⁴⁰ In another study, an acceptable mid-term outcome was reported for aortic valve sparing surgery. Root repair was performed with either a reimplantation (74%) or a remodelling (26%) technique. Cusp repair was required more often in bicuspid valves than in tricuspid valves (91% vs 38%, $p<0.001$). At 8-years, freedom from reoperation was $90 \pm 7\%$ and overall survival was $88 \pm 8\%$. Predictors of recurrent moderate or severe AR were preoperative left ventricular end diastolic diameter and more than mild AR on discharge echocardiography.⁴¹

Bicuspid aortic valve disease

Cardiovascular magnetic resonance allows characterisation of valve phenotype in patients with bicuspid aortic valves (BAVs). A raphe was identified in the majority of patients ($n=90$; 86%). Among patients with raphe, 76 patients had fusion between the right and left cusps and

14 patients had fusion between the right and the non-coronary cusps.⁴² The fused right and non-coronary leaflet BAVs are the product of a morphogenetic defect that occurs before cardiac outflow tract septation and probably relies on an exacerbated nitric oxide dependent epithelial to mesenchymal transformation. Fused right and left leaflet BAVs result from anomalous septation of the proximal portion of the cardiac outflow tract, probably caused by the distorted behaviour of neural crest cells. The two phenotypes are different aetiological entities and may rely on different genotypes.⁴³ The prevalence of aortic root dilation in BAV patients is 32% and 53% in their first degree relatives (even with tricuspid aortic valves). Like patients with BAV, their first degree relatives have a significantly lower aortic distensibility and greater aortic stiffness index than control subjects. Screening of first degree relatives of patients with a bicuspid aortic valve by echocardiography should be considered for detection of aortic valve malformation and dilated ascending aorta.⁴⁴ Careful clinical follow-up of patients after successful resection of subaortic stenosis is required. Of 121 adults with subaortic stenosis, 23% had bicuspid valves and 21% had coarctation of the aorta. Seventy-nine per cent of the patients had a surgical resection of subaortic tissue. Valve surgery for AS was required in 26% and was more common in patients with concomitant BAV disease, coarctation of the aorta and supraaortic stenosis. Moderate to severe AR was present in 16% of patients.⁴⁵

Aortic disease

Diastolic tenting of aortic leaflets is strongly related to the severity of functional AR in patients with ascending thoracic aortic aneurysms. A sinotubular junction/annulus mismatch is significantly associated with diastolic leaflet tenting and valve regurgitation, independently of the aneurysm dimension.⁴⁶ Aortic root dilatation and reduced aortic elasticity are common in patients with tetralogy of Fallot, in addition to minor degrees of AR and reduced left ventricular systolic function. Aortic wall pathology in patients with repaired tetralogy of Fallot may therefore represent an independent contributor to left ventricular dysfunction, as part of a multifactorial process.⁴⁷ In patients with ascending aortic aneurysm (unassociated with aortitis or acute dissection), the aortic valve is congenitally malformed (unicuspid or bicuspid) in 98% of patients with AS, and in 60% of patients with AR. Among the patients with congenitally malformed valves, those with AR have a significantly greater likelihood of significant aortic medial elastic fibre loss than those with AS. Distinction between AS and AR is helpful in predicting loss of aortic medial elastic fibres in patients with ascending aortic aneurysms and aortic valve disease.⁴⁸ Ninety-three patients with severe isolated calcific AS with a tricuspid aortic valve who also had moderate dilatation of the ascending aorta (diameter 50-59 mm) underwent AVR only. During a follow-up of 15-years, no acute aortic events (rupture, dissection, pseudoaneurysm), or need for reoperation occurred. Furthermore, there was no substantial increase in aortic dimensions, suggesting that indications for concomitant aortic surgery in patients with moderate post-stenotic dilatation of the ascending aorta and a tricuspid aortic valve, may be viewed more leniently, particularly

in the absence of connective tissue disorders.⁴⁹ In a community cohort that included 416 consecutive patients with definite BAV diagnosed by echocardiography, followed up for 16±7 years, the incidence of aortic dissection was low (two out of 41 patients) but higher than in the general population. Of 384 patients without baseline aneurysms, 49 developed aneurysms at follow-up and the 25-year rate of aortic surgery was 25%.⁵⁰

Prompt diagnosis of acute aortic dissection saves lives. Echocardiography has a time honoured role, and recent work suggests that contrast enhanced as compared with conventional transthoracic imaging improves diagnostic sensitivity and specificity for aortic dissection from 73.7% to 86.8% ($p<0.005$) and from 71.2% to 90.4% ($p<0.05$), respectively. Indeed, the diagnostic sensitivity and specificity of contrast enhanced transthoracic imaging was similar to that of conventional transoesophageal echocardiography in the ascending aorta (93.3% vs 95.6% and 97.6% vs 96.4%, respectively) and in the arch (88.4% vs 93.0% and 95.% vs 98.82%, respectively) and should be considered as an initial imaging modality in an emergency.⁵¹

Mitral regurgitation

Degenerative mitral regurgitation (MR) is often dynamic, and exercise induced increases of MR severity are seen in one-third of patients, associated with changes in systolic pulmonary artery pressure and reduced symptom free survival.⁵² When MR is severe it may be associated with unilateral pulmonary oedema.⁵³

Improving the timing of surgery for degenerative MR based on predictors of outcome is an important topic. The left atrial index was shown to predict outcome in 492 patients in sinus rhythm with organic MR and should thus be incorporated into routine clinical practice for risk stratification and clinical decision making.⁵⁴ A recent study showed that in MR, owing to flail leaflets, a left ventricular end systolic diameter ≥ 40 mm is independently associated with increased mortality for medically and surgically managed patients. Nevertheless, the left ventricular end systolic dimension may provide a useful guide for the timing of surgery in these patients but because both asymptomatic and symptomatic patients were included, the findings need confirmation in symptomatically homogeneous cohorts.⁵⁵ In another study of 256 patients with organic MR referred for mitral valve surgery, baseline pulmonary artery systolic pressure predicted long-term postoperative survival with 8-year survival rates of 58.6% and 86.6% for patients whose PA pressures were greater or less than 50 mmHg, respectively ($p<0.0001$).⁵⁶

As with other valvular pathologies, oxidative stress may be aetiologically important in MR. Thus, LV biopsy specimens taken during mitral valve repair surgery for isolated MR demonstrated that increased oxidative stress could cause lipofuscin deposition and cardiomyocyte myofibrillar degeneration.⁵⁷

The severity of MR seems to be an important determinant of left ventricular reverse remodelling after cardiac resynchronisation therapy when gains in LVEF and forward stroke volume are greatest for patients with improvement in total MR, intermediate for those with mild or no MR at baseline and least in those who's MR shows no improvement.⁵⁸

Guideline indications for surgical intervention in patients with MR are often ignored by cardiologists and in a recent assessment of current practice, surgery was performed in only about 50% of cases despite the fact that guideline indications for intervention were present in many of the patients not receiving surgery.⁵⁹ Among patients with guideline indications any delay in carrying out surgery may have important adverse consequences as reflected in a recent report where surgery at a median time of 0.42 months after listing was associated a lower hazard for death than for those who underwent later surgery at a median time of 8.75 months (HR=0.54, $p=0.039$).⁶⁰

In the study of Samad et al, mitral valve repair was independently associated with improved survival (HR=0.45, $p=0.01$).⁶⁰ This has been shown in many other recent studies but an assessment of 'real-world' clinical practice based on 12255 mitral valve operations performed in the UK between 2004 and 2008 showed a national rate of only 51%, and variability of 20% to 90% among different hospitals, which the authors likened to a "lottery of mitral valve repair surgery."⁶¹

This was emphasised further in a more recent analysis of the STS Adult Cardiac Surgery Database, which showed substantial variability in rates of mitral valve repair among individual surgeons, ranging from 0% to 100% (mean 41%). The greatest variability in repair rates was seen among surgeons carrying out a low volume of procedures, with increased surgeon level mitral volume being independently associated with an increased probability of mitral repair.⁶²

Experimental studies on the mechanism of mitral regurgitation

Understanding the mechanism of valve adaptation provides a potential means of identifying new biological and surgical therapeutic targets. Anteroapical myocardial infarction (MI) with inferoapical extension can mechanically displace papillary muscles, causing MR despite the absence of basal and mid inferior wall motion abnormalities.⁶³ In a sheep model of inferior MI an epicardial patch to limit ventricular dilatation and MR resulted in a leaflet area at three months that was not significantly different from baseline values. In untreated sheep, mitral valve area increased over time as the left ventricular remodelled after inferior MI, independently of systolic stretch but failed to compensate adequately for tethering to prevent MR.⁶⁴ Management of severe ischaemic MR remains difficult with disappointing early and intermediate term surgical results of valve repair. Posterior leaflet extension with annuloplasty of the mitral valve for severe type IIIb ischaemic regurgitation has been suggested to provide good early and intermediate term competence of the mitral valve and functional status.⁶⁵ In an experimental model, the papillary muscle tips in six adult sheep were retracted apically, short of producing MR thus replicating the effects of tethering without confounding MI or turbulence. At 60 days, total diastolic mitral leaflet area increased by 17% and stretched mitral valves were 2.8 times thicker than normal with an increased spongiosa layer. Cellular changes suggest a reactivation of embryonic developmental pathways.⁶⁶ It has been shown that mitral tenting leading to functional MR is mainly determined by tethering

(displacement of papillary muscles) and pushing forces (increased left atrial pressure), independently of ventricular function, findings that emphasise the central role of left ventricular preload as a key determinant of functional MR.⁶⁷ In patients with idiopathic dilated cardiomyopathy who underwent annuloplasty for functional MR, the postoperative distal mitral anterior leaflet angle was the major determinant of recurrent functional MR. The preoperative distal mitral anterior leaflet angle was the best predictor of MR recurrence. Since posterior leaflet tethering is invariable after mitral annuloplasty, postoperative mitral competence is highly dependent on distal anterior leaflet mobility.⁶⁸ A strong association between pre-existing hypertension and idiopathic mitral chordae tendineae rupture was described. However, it remains unclear whether prevention by hypertension control is feasible.⁶⁹

Tricuspid regurgitation

The tricuspid valve is often called the forgotten valve, partly because data concerning the optimal timing of surgery in tricuspid regurgitation (TR) are limited.

During inspiration, a large increase in effective regurgitant orifice causes a notable increase in tricuspid regurgitant volume, despite a decline in regurgitant gradient. Effective regurgitant orifice changes are independently linked to inspiratory annular enlargement (decreased valvular coverage) and to inspiratory right ventricular (RV) shape widening with increased valvular tenting. These physiological insights are important for clinical evaluation of the severity of TR.⁷⁰ Severe TR, constrictive pericarditis and restrictive cardiomyopathy can all present with signs and symptoms of right heart failure and similar haemodynamic findings of elevation and equalisation of diastolic pressures at catheterisation. The haemodynamic findings at cardiac catheterisation in patients with severe, symptomatic TR are similar to those of constrictive pericarditis. Careful analysis of the relationship of the LV and RV diastolic pressures during respiration can help differentiate between the two entities. During inspiration, the difference between the LV and RV diastolic pressures widens in patients with TR but narrows in those with constrictive pericarditis.⁷¹ Of 69 consecutive patients undergoing surgery for isolated severe TR, seven (10.1%) died before discharge. Of the remaining 62 patients, three died during follow-up and eight were readmitted owing to cardiovascular problems. RV end systolic area ($p=0.006$) and haemoglobin level ($p<0.001$) were independent predictors of event free survival. When early postoperative echocardiography variables were included, early postoperative RV fractional area change provided additional information for predicting long-term clinical events following corrective TR surgery.⁷² The overall incidence of late significant TR after successful left sided valve surgery was 7.7% (49/638). Age, female gender, rheumatic aetiology, atrial fibrillation and peak pressure gradient of TR at follow-up were independent factors associated with development of late significant TR. Patients who developed late significant TR showed a significantly lower 8-year clinical event-free survival rate (76% vs 91%, $p<0.001$).⁷³ After tricuspid annuloplasty, tenting angles of the three leaflets increase, whereas the annulus diameter decreases. Presurgical

tenting volume and anteroposterior tricuspid annulus diameter are independent predictors of residual TR severity, and may help to identify patients at high risk for severe residual TR for whom tricuspid valve replacement may be considered.⁷⁴ Tricuspid valve replacement for severe TR can be performed with an acceptable operative mortality if patients undergo surgery before the onset of advanced heart failure symptoms. Late mortality is associated with a high preoperative Charlson index, short right index of myocardial performance ratio and advanced New York Heart Association class.⁷⁵

Risk of non-cardiac surgery

In a prospective cohort of 2054 patients undergoing elective major non-cardiac surgery, high preoperative NT-proBNP or C reactive protein were strong, independent predictors of perioperative major cardiovascular events (MI, pulmonary oedema or cardiovascular death) in non-cardiac surgery. The relative event risk of highest versus lowest quartile was 5.2 for NT-proBNP ($p<0.001$) and 3.7 for C reactive protein ($p<0.001$). The predictive power of the current clinical risk evaluation system might be strengthened by application of this biomarkers.⁷⁶

Endocarditis

The high mortality of patients with endocarditis makes it an important focus of continuing clinical research. Blood culture negative early prosthetic valve endocarditis exhibits specific aetiologies, and fungi are the most common pathogens identified. They should be investigated by molecular methods on surgical specimens and an antifungal drug might be added to the empirical treatment.⁷⁷ Almost 50% of cases of coagulase negative staphylococcal prosthetic valve endocarditis occur between 60 and 365 days after prosthetic valve implantation and area associated with a high rate of methicillin resistance and significant valvular complications.⁷⁸ Increasing age is associated with less valvular impairment (insufficiency and perforation) and a more favourable microbiological profile in patients with left sided infective endocarditis. However, the therapeutic approach differs depending on patient age because of the growing proportion of older patients who receive only medical treatment. Clinical course and hospital prognosis are worse in older patients because of an increased surgical mortality.⁷⁹ Three independent risk factors obtained within 72 hours of admission for left sided infective endocarditis (*Staphylococcus aureus*, heart failure and periannular complications) predict in hospital mortality or the need for urgent surgery.⁸⁰ Bicuspid aortic valve infective endocarditis accounts for 16% of cases of definite native aortic valve endocarditis and is associated with a perivalvular aortic abscess in half of the cases. The presence of a bicuspid aortic valve ($HR=3.79$, $p<0.001$) is independently predictive of abscess formation, and early surgery is often required.⁸¹ There is now evidence that preoperative coronary angiography can be performed with low risk in selected patients with aortic valve endocarditis. A recent study reported no embolic events, no increase in in hospital mortality ($p=0.80$) and no worsening of renal function ($p=0.93$).⁸² By performing preoperative coronary angiography in patients with cardiovascular risk factors, those with significant coronary disease can

be considered for bypass at the time of valve surgery. In a multinational cohort of 1552 patients with native valve endocarditis, early surgery was associated with a significant reduction in mortality compared with medical treatment (12.1% vs 20.7%).⁸³ Strategies of early surgery within seven days, at the discretion of the attending doctor, and of conventional management in patients with left sided native valve were compared in another study. During the initial hospitalisation, there were no embolic events and two in hospital deaths in the surgical group ($n=64$) and 14 embolic events and two in hospital deaths in the conventional group ($n=68$). The 5-year event free survival rate was significantly better in the surgical group ($93\pm3\%$) than in the conventional group ($73\pm5\%$, $p=0.0016$).⁸⁴ Although the timing of surgery was not randomly allocated, the data suggest that early surgery, when feasible, may offer important advantages to the patient.

Valve surgery

Ross procedure

The controversy surrounding the Ross procedure is highlighted by four studies. In a randomised study 216 patients received either an auto-graft or a homograft aortic root replacement. At 10-years, four patients in the auto-graft group and 15 in the homograft group died. Actuarial survival at 10-years was 97% in the auto-graft group versus 83% in the homograft group.⁸⁵ MRI of 45 patients at a median interval of 8-years postoperatively demonstrated minor auto-graft and homograft dysfunction in the majority of cases, associated with good ventricular function and exercise capacity.⁸⁶ Another study compared the outcome of the Ross procedure (918 patients) with that of 406 mechanical valve recipients under optimal self management anticoagulation treatment; there was no late survival difference in the first postoperative decade between the two groups. Survival in these selected young adult patients closely resembles that of the general population, possibly as a result of optimised anticoagulation self management, timing of surgery and patient selection.⁸⁷ A less optimistic picture was depicted by a study emphasising the broad spectrum of complex reoperations that may be required relatively often after the Ross procedure. The four most common indications for reoperation ($n=56$) were isolated auto-graft (neo-aortic) regurgitation in 20%, isolated pulmonary conduit regurgitation/stenosis in 16%, combined auto-graft regurgitation/dilatation in 14%, and combined auto-graft regurgitation and pulmonary conduit regurgitation/ stenosis in 11%. Patients and family members considering the procedure should be informed of the potential for associated morbidity should reoperation be necessary.⁸⁸

Predictors of postoperative outcome after aortic valve replacement

A six minute walk test was found to be safe and feasible to carry out in patients with severe AS before AVR, and provides potentially important functional and prognostic information for clinical assessment and the Euroscore risk score. At 12 months, the rate of death, MI or stroke was 13% in patients walking <300 m as compared with 4% in those who walked ≥ 300 m ($p=0.017$).⁸⁹ Physical quality of

life 1-year after valve surgery was predicted by baseline physical quality of life and walk performance. Postoperative mental quality of life was predicted by depression, baseline mental quality of life and age, with age having a positive effect, suggesting that treating depression and modifying negative illness beliefs preoperatively, may improve outcome.⁹⁰ Women referred for AVR were found to be older and more symptomatic. Although operative and long-term mortality were not increased, women remained in a more symptomatic stage.⁹¹ Patients undergoing renal transplantation requiring valve replacement have high mortality rates (approximately 20%/year). Two-year survival estimates were comparable for patients receiving a tissue valve (61.5%) or a non-tissue valve (59.5%, $p=0.30$).⁹²

Impact of age on valve surgery

Patients aged 55-70 years undergoing AVR either with mechanical or bioprosthetic valves had similar 13-year rates of survival, thromboembolism, bleeding, endocarditis and major adverse prosthesis-related events. However, patients with bioprosthetic valves had a significantly higher risk of valve failure and reoperation.⁹³ Using microsimulation of survival and valve related outcomes from 5470 AVR procedures, it was found that bioprostheses may be implanted selectively in patients as young as 56 without significant adverse effects on life expectancy, although event free survival remains significantly lower with bioprostheses for patients up to age of 63.⁹⁴ Increasing numbers of the very elderly are undergoing AVR procedures. Late survival of 2890 consecutive elderly patients (≥ 70 -years) who underwent AVR was influenced by age and preoperative comorbidities; the 33% in the lowest risk tertile had an overall survival similar to that of the age and sex matched general population. Structural deterioration of aortic bioprostheses was rare and there was no conclusive evidence that valve type affected survival in these patients.⁹⁵ Also in octogenarians, survival after AVR is favourable even with concomitant bypass surgery and more than half of the patients survive for more than 6-years after their surgery. Median survival for patients undergoing isolated AVR was 6.8 years for those aged 80-84 years ($n=419$) and 6.2 years for those aged ≥ 85 years ($n=156$), similar to the life expectancy of the general population.⁹⁶

Patient prosthesis mismatch

Patient prosthesis mismatch (PPM) was identified in 40% of 645 patients after AVR in a study in which indexed effective orifice area was obtained by postoperative echocardiography and modelled as a continuous variable. After a median follow-up of 2.35 years, 92.1% of the patients were alive. Cardiac death among patients with a smaller indexed effective orifice area was significantly increased ($HR=0.32$, $p=0.022$).⁹⁷ Among 2576 patients who survived AVR and after adjustment for other risk factors, severe PPM was associated with increased late overall mortality ($HR=1.38$; $p=0.03$) and cardiovascular mortality ($HR=1.63$; $p=0.0006$). Moderate PPM was a predictor of mortality in patients with LV ejection fraction $<50\%$ ($HR=1.21$; $p=0.01$), but not in patients with preserved LV function.⁹⁸ The presence of PPM after AVR attenuates postoperative mitral regurgitation changes, mainly in patients with

organic mitral regurgitation.⁹⁹ In 564 patients receiving an aortic valve bioprosthesis, structural valve deterioration was diagnosed in 40 patients (7%). Stenosis type structural valve deterioration ($n=24$) was found to be an early, PPM-related, and thus preventable, phenomenon. Regurgitation type structural valve deterioration ($n=16$) is a time dependent, non-specific wear of bioprosthetic valves, which is not related to PPM.¹⁰⁰ In a multicentre series of 1006 mechanical and bioprosthetic mitral valves, PPM was not associated with worse early outcomes or worse mid-term survival.¹⁰¹

Mitral valve surgery

Elective mitral valve (MV) repair can be performed with a low operative mortality and good long-term outcomes in selected octogenarians with degenerative mitral disease, and is associated with better long-term survival than mitral replacement. Overall 90-day mortality of consecutive octogenarians who underwent MV repair was significantly lower (18.9%) than for MV replacement (31.6%). Adjusted one, three and 5-year survival for patients undergoing MV repair was 7163, 6164 and 5964%, respectively, compared with 5665, 5066 and 4566% for patients undergoing MV replacement ($p=0.046$). The survival benefit associated with surgery for non-degenerative disease is more questionable.¹⁰²

Of 402 patients with atrial fibrillation-associated MV disease who underwent MV replacement with a mechanical prosthesis, 159 underwent a concomitant Maze procedure. At a median follow-up of 63.1 months, patients who had undergone the Maze procedure were at significantly lower risk of thromboembolic events ($HR=0.26$; $p=0.041$) and were at comparable risk of death and cardiac death as patients who underwent MV replacement alone.¹⁰³

In 370 patients with ischaemic MR after adjusting for other risk factors and propensity score, the type of procedure (MV repair versus MV replacement) was not an independent predictor of either operative or overall mortality.¹⁰⁴ One hundred and thirty-five patients with ischaemic heart disease and moderate ischaemic MR underwent isolated coronary artery bypass graft surgery. At 1-year, 57 patients had no or mild ischaemic MR, whereas 64 patients had failed to improve. Large extent (≥ 5 segments) of viable myocardium ($OR=1.45$; $p<0.001$) and absence (<60 ms) of dyssynchrony ($OR=1.49$; $p<0.001$) were independently associated with improvement in ischaemic MR.¹⁰⁵

Combined mitral and tricuspid valve repair in rheumatic disease showed satisfactory early results in 153 consecutive patients (mean age 46-years) who underwent combined mitral and tricuspid valve repair for rheumatic disease. However, long-term results were poor because of high mortality and a high number of valve related reoperations. Survival rate was 74.4% at 10-years and 57.0% at 15-years. At 20-years, the rate of freedom from reoperation was 48.5%.¹⁰⁶

Anticoagulation

Despite the use of intravenous unfractionated heparin, the rate of early thromboembolism in a series of 300 consecutive mechanical valve replacements remained significant. Early thromboembolism within 30 days of surgery

occurred in 22 patients (14.8%) after a mitral or double mechanical valve replacement and in two patients (1.3%) after an aortic mechanical valve replacement ($p=0.005$). Inappropriate anticoagulation on day three was significantly associated with early thromboembolism, suggesting that early effective anticoagulation is required after mitral mechanical valve replacement.¹⁰⁷

Prosthetic valve thrombosis

A randomised controlled trial comparing an accelerated infusion with the conventional infusion of streptokinase was performed in 120 patients with a first episode of left sided prosthetic valve thrombosis, recruited over a 2.5 year period at a single centre in India. The large patient number underlines the massive burden of prosthetic valve thrombosis in developing countries. Fibrinolytic therapy with streptokinase is less efficacious than previously believed, with a complete clinical response in 70 of 120 patients. The accelerated streptokinase infusion is no better than standard infusion for left sided prosthetic valve thrombosis.¹⁰⁸

Transcatheter aortic valve implantation

Patient selection

Objective parameters to assess interventional risk and thus to identify patients at high risk who would benefit from percutaneous procedures are needed. For this, reliable risk scores that predict surgical mortality would be helpful. While the Euro-SCORE still successfully discriminates high risk patients undergoing surgical aortic valve replacement, it has become increasingly uncalibrated with absolute risk, resulting in over estimation of 30-days mortality.¹⁰⁹ The limitations of risk scores are also commented upon in a recent ESC position paper on risk assessment before interventions in patients with valvular disease.¹¹⁰

Imaging of the aortic annulus and of transcatheter aortic valve deployment

Adequate sizing of the aortic annulus is essential in order to assess the suitability of a patient for a transcatheter aortic valve implantation (TAVI) procedure and the choice of the prosthesis size. By CT an ellipsoid shape of the aortic valve annulus with a larger coronal than sagittal diameter (25.162.4 vs 22.962.0 mm, $p<0.001$) was measured.¹¹¹ 2D imaging techniques underestimate aortic annulus diameters and 3D imaging techniques are now recommended for this purpose. 3D trans-oesophageal echocardiography (TOE) provides measurements of aortic annulus diameters similar to those obtained by CT.¹¹² While measurements using transthoracic echocardiography, TOE and CT are close but not identical, a strategy based on TOE measurements provides good clinical results.¹¹³ The presence of LV dysfunction, male gender and larger body surface area are independent determinants of a larger aortic annular diameter.¹¹⁴ By CT, incomplete and non-uniform expansion of the Core Valve frame can be identified: undersizing and incomplete apposition is commonly present.¹¹⁵ Non-circular deployment of the prosthesis is found in 14% of patients. Moderate postprocedural aortic regurgitation is seen in 11% patients and is associated

with larger aortic valve annulus, more calcified native valves and less favourable prosthesis deployment.¹¹¹

Establishing a transcatheter aortic valve implantation programme

To provide consistency across studies that can facilitate the evaluation of this new catheter based treatment, and improve the quality of clinical research, the Valve Academic Research Consortium proposed standardised consensus definitions for important clinical end points in TAVI investigations.¹¹⁶ Retrospective examination of adherence to patient selection criteria identified an "off label" use of TAVI beyond premarket label indications in 42 of 63 patients.¹¹⁷ This study highlights the challenges encountered in the rollout phase of a new technology. The ability to offer either transfemoral or transapical aortic valve implantation, using a standardised approach, with the transfemoral approach as the first option, may expand the scope of the treatment of AS in high risk patients and provide satisfactory 1-year results.¹¹⁸ Introduction of a TAVI service does not appear to have a negative effect on conventional surgical activity. One study reported a 37% increase in surgical AVR in the 2-years after introduction of TAVI in a dedicated centre, compared with an 8% increase nationally ($p<0.001$).¹¹⁹

Feasibility of transcatheter aortic valve implantation

An early single centre experience established the feasibility of TAVI, both by the transfemoral approach ($n=168$), with a success rate of 94.1% and 1-year survival of 74%,¹²⁰ and by the transapical approach ($n=100$), with a success rate of 97% and 1-year survival of 73%.¹²¹ Data for an extended follow-up period of 3-years have been reported, and no cases of structural valvular deterioration, stent fracture, deformation, or valve migration occurred.¹²²

Procedural outcome of transcatheter aortic valve implantation: registries and randomised trials

Patients with severe AS, considered unsuitable candidates for surgery ($n=358$), were randomly assigned to standard treatment (including balloon aortic valvuloplasty) or transfemoral TAVI using the Edwards SAPIEN valve in the PARTNER B trial. TAVI, as compared with standard treatment, significantly reduced the rates of death from any cause (30.7% vs 50.7%), the composite end point of death from any cause or repeat hospitalisation (42.5% vs 71.6%) and cardiac symptoms, despite a higher incidence of major strokes (5.0% vs 1.1%) and major vascular events (16.2% vs 1.1%).¹²³ This study also nicely depicts the contemporary natural history of severe symptomatic AS.

The PARTNER A trial randomised 699 high risk patients with severe AS to undergo TAVI or surgical AVR. Transcatheter and surgical procedures for AVR were associated with similar rates of survival at 1-year (24.2% vs 26.8%, respectively), although there were important differences in periprocedural risks, with vascular complications more common in the TAVI group (11.0% vs 3.2%, $p<0.001$) and more frequent major bleeding and new onset atrial fibrillation with surgery.¹²⁴ One-year survival in the SOURCE registry ($n=1038$) was 76.1% (72.1% for transapical and 81.1% for transfemoral TAVI). Interestingly, causes of death were mainly non-cardiac in 49.2% (cardiac in 25.1%, and unknown in 25.7%) with pulmonary complications (23.9%),

renal failure (12.5%), cancer (11.4%) and stroke (10.2%) as the most common non-cardiac causes of death.¹²⁵ These data reflect the importance of associated comorbidities. Several other multicentre registries (including the PARTNER EU registry, the German TAVI registry, the French FRANCE registry, an Italian and a Canadian registry) have confirmed the feasibility of the procedure in high risk or unoperable patients with AS with good procedural success, haemodynamic results and mid-term outcomes.¹²⁶⁻¹³¹

Specific predictors of outcome for transcatheter aortic valve implantation

Mean transprosthetic gradients were lower for TAVI (1064 mmHg) than for stented (1365 mmHg) and stentless (1466 mmHg) bioprostheses ($p < 0.001$). Severe PPM was significantly lower with TAVI (6%) than with a bioprosthesis (24%; $p = 0.007$).¹³² TAVI can be successfully carried out in most patients (34/35) with a small aortic annulus diameter < 20 mm, with severe PPM occurring in two patients only, and gradients remaining low in the other patients.¹³³ It may also provide an interesting alternative to AVR in patients with depressed LV systolic function, where it is found to be associated with better LVEF recovery than conventional AVR (change in LVEF $14 \pm 15\%$ vs $7 \pm 11\%$; $p = 0.005$), although these patients were older and had more significant comorbidities. At 1-year, 58% of TAVI patients had a normalisation of LVEF ($> 50\%$) as opposed to 20% in the AVR group.¹³⁴ Pre-procedural functional performance status (assessed by the Karnofsky index) predicts the in hospital procedural success rates and MI and stroke rates after TAVI.¹³⁵ Thirty days after TAVI quality of life and 6 min walk distance improved significantly while BNP levels declined.¹³⁶ Acute kidney injury occurring in 11.7% of patients after TAVI, is associated with a greater than fourfold increase in the risk of postoperative mortality. Hypertension, chronic obstructive pulmonary disease and blood transfusion are predictive factors of acute kidney injury.¹³⁷ TAVI was systematically associated with some degree of myocardial injury in the majority of patients. The greater degree of myocardial injury seen with the transapical approach and baseline renal dysfunction is associated with less improvement in LVEF and a greater cardiac mortality at follow-up.¹³⁸ Significant AR was reported to occur in 17.2% of patients and is associated with significantly higher in-hospital death rates (15.1% vs 6.7%), rates of low cardiac output and respiratory failure.¹³⁹ For the CoreValve a greater likelihood of significant AR was found with a greater angle of LV outflow tract to ascending aorta ($OR = 1.24$, $p = 0.001$).¹⁴⁰ New cerebral ischaemic lesions can be detected by diffusion weighted MRI in between 68% and 84% of patients after TAVI.¹⁴¹⁻¹⁴³ These lesions were usually multiple (one to 19 per patient) and dispersed in both hemispheres in a pattern suggesting cerebral embolisation. These foci were not associated with apparent neurological events or measurable deterioration of neurocognitive function.

The rate of major stroke was in the range of 3.3% to 3.8%.^{124,141,143}

Transcatheter valve in a valve implantation

The concept of a valve in valve implantation in a degenerated aortic bioprosthesis was successful in 24 patients,

with a decline of mean transaortic gradient from 45.4 ± 14.8 to 10.1 ± 4.2 mmHg. Major adverse cerebrovascular and cardiac event rates were 0% and 14.1%, at 30 days and 12 months, respectively.¹⁴⁴ Valve in valve implantations was also performed in 24 high risk patients with bioprostheses in different positions (aortic, $n = 10$; mitral, $n = 7$; pulmonary, $n = 6$; or tricuspid, $n = 1$). Implantation was successful, with immediate restoration of satisfactory valve function in all but one patient. Thirty-day mortality was 4.2%. Mortality was related primarily to inexperience of the surgeon in this high risk procedure.¹⁴⁵

Transcatheter pulmonary valve implantation

Transcatheter pulmonary valve implantation of the Melody valve was shown to be feasible in three series including 14, 102 and 136 patients with dysfunctional right ventricular outflow tract conduits, respectively.¹⁴⁶⁻¹⁴⁸ One death due to compression of the left coronary artery¹⁴⁷ and one death from intracranial haemorrhage after coronary artery dissection occurred.¹⁴⁸ The studies consistently showed a significant reduction of the right ventricular outflow tract gradient, a reduction of right ventricular volume and of pulmonary regurgitation. Freedom from Melody valve dysfunction or reintervention was 93.562.4% at 1-year. A higher right ventricular outflow tract gradient at discharge ($p = 0.003$) and younger age ($p = 0.01$) were associated with shorter freedom from dysfunction.¹⁴⁸ The incidence of stent fractures was 5%.¹⁴⁷ Pre-stenting with a bare metal stent is associated with a lower risk of developing percutaneous pulmonary valve implantation stent fractures ($HR = 0.35$, $p = 0.024$).¹⁴⁹ While short-term follow-up data are encouraging, longer-term information is required to determine if this form of palliation has a significant impact on management strategies.

Transcatheter tricuspid valve implantation

The first human experience of successful percutaneous tricuspid valve implantation (Melody valve) in 15 patients with significant stenosis and/or regurgitation of a bioprosthetic tricuspid valve or a right atrium to right ventricle conduit was reported with a reduction of the mean tricuspid gradient from 12.9 to 3.9 mmHg ($p < 0.01$) and only mild or no residual regurgitation.¹⁵⁰

Percutaneous mitral valve therapies

The challenges when implementing new techniques include patient selection, an adequate setting, and continuous evaluation, and are well summarised by the NICE guidelines for percutaneous mitral valve repair.¹⁵¹ After the initial EVEREST Trial, which was a feasibility study performed in 23 patients,¹⁵² the randomised EVEREST II Trial compared the outcome of percutaneous implantation of a clip (the MitraClip) that grasps and approximates the edges of the mitral leaflets to conventional mitral valve surgery in 279 patients with moderate or severe MR. At 12 months, the following end points were seen for patients in the percutaneous repair group and in the surgery group, respectively: death, 6% in each group; surgery for mitral valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% vs 20%. At 12 months, both groups had improved LV size, New York Heart Association functional class and quality of life measures, as compared with baseline.¹⁵³ From a

haemodynamic perspective, successful MitraClip implantation in 107 patients resulted in an immediate and significant improvement in forward stroke volume, cardiac output and LV loading conditions. There was no evidence of a low cardiac output state after MitraClip treatment for MR.¹⁵⁴ Histological evaluation of 67 explanted MitraClip devices showed that mechanical integrity of the device was maintained. Four phases of physiological healing include platelet and fibrin deposition, inflammation, granulation tissue and, finally, fibrous encapsulation. At long-term, device fibrous encapsulation with extension over adjacent mitral leaflets and tissue bridge formation adds structural stability.¹⁵⁵ The feasibility of percutaneous mitral annuloplasty through the coronary sinus with the CARILLON Mitral Contour System was shown in 30 of 48 patients, with functional improvement and a major adverse event rate of 13% at 30 days.¹⁵⁶

Percutaneous balloon mitral valvuloplasty

An increasing preprocedural MR severity was associated with reduced percutaneous balloon mitral valvuloplasty (PMV) success in a large study that included 876 patients (no MR, 75%; 1+ MR, 65%; 2+ MR, 44%; $p < 0.0001$), increased in hospital mortality (0.6% vs 2.8% vs 4.9%, respectively; $p = 0.007$). Patients with moderate preprocedural MR, in particular, appear to have suboptimal short and long-term outcomes, requiring careful monitoring and early referral for mitral valve surgery, when appropriate.¹⁵⁷ After successful PMV, left atrial volume and percentage change of the left atrial volume immediately after PMV emerged as independent predictors of event free survival together with age, pre-PMV tricuspid regurgitation and post-PMV mitral valve area. Ten year survival was 93% in patients with smaller left atria before PMV (≤ 72 mL/m²), whereas it was only 60% in those with larger left atria (> 72 mL/m²).¹⁵⁸ After successful PMV ($n = 329$) an immediate post-PMV mitral valve area ≥ 1.8 cm² predicted both restenosis and clinical eventfree survival.¹⁵⁹

Competing interests

None.

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