Survival and functional recovery following valve replacement in patients with severe aortic stenosis

Wenhong, Ding
我走得很慢，但我从不后退。

_I am a slow walker, but I never walk backwards._

-Abraham Lincoln
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## Objectives

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Abstract

Background: Aortic stenosis (AS) is the most common heart valve disease in Europe and North America. Age-related calcification of the valve is the commonest cause of acquired AS, especially in patients older than 70 years. Conventional surgical aortic valve replacement (SAVR) and the novel, minimally invasive transcatheter aortic valve implantation (TAVI), effectively preserve left ventricular (LV) function, relieve symptoms and improve survival in patients with severe symptomatic AS. However, patients with impaired LV function may carry significant operative risk, and long recovery time. In addition, such patients might have other comorbidities, and hence adding another challenge. Thus evaluation of ventricular function before and after AVR, as well as critical evaluation of TAVI patients should contribute to better clinical outcome.

Methods: We studied LV function by conventional echocardiography before and after SAVR in the following groups; (I) 86 patients (aged 71±10 years) with severe AS and LV dysfunction; (II) 112 consecutive elderly AS patients (aged 77±2 years) and compared them with 72 younger patients (aged 60±1 years); (III) 66 patients (age 70±2 years, 53 male) who underwent AVR for severe AS with concurrent LV dysfunction; (IV) 89 consecutive patients with symptomatic severe AS who underwent successful TAVI, 45 of whom received trans-apical TAVI (TA) (age 80.8±4.9 year, 26 male) and 44 trans-femoral TAVI (TF) (age 82.9±5.8 year, 22 male).

The conventional echocardiographic measurements were made according to the guidelines. Severe AS was identified by aortic valve mean pressure gradient >40 mmHg or valve area <1.0 cm². LV systolic dysfunction was identified as ejection fraction (EF) <50%. LV long-axis function was presented by mitral annular plane systolic excursion (MAPSE) at lateral wall and septal wall, which were measured from apical four-chamber view. Also from the same view, LV septal and lateral wall deformation using STE as well as global longitudinal systolic strain. The LV systolic twist as the net difference between apical rotation and basal rotation was measured from the parasternal apical and basal short-axis views in the TAVI patients.

Results: Study I: In the low flow and high gradient group, operative (30-day) mortality was 10%, and peri-operative mortality was associated with lower mean LVEF, higher mitral E:A ratio, peak systolic pulmonary artery pressure (PSPAP), and higher serum creatinine (all p<0.001), NYHA class III–IV, concomitant
coronary artery bypass graft (CABG), urgent surgery, and longer bypass-time (all p<0.05). Mortality at 4 years was 17%. Univariate predictors of 4-year mortality were: lower EF (p<0.001), presence of restrictive LV filling (p<0.001), raised PSPAP (p<0.001) and CABG (p=0.037). However, only EF<40 % (p=0.03), the presence of restrictive LV filling (p=0.033) and raised PSPAP (p<0.01) independently predicted mortality in this group.

**Study II:** Elderly patients had higher NYHA class, more frequent atrial fibrillation (AF), coronary artery disease (CAD), emergency operation and use of bioprosthetic valves. They also had shorter E-wave deceleration time (DT) and larger left atria (LA) (p<0.05 for all). 30-day mortality was 12% vs 4 % (Log Rank x²=3.02, p=0.08) and long term mortality was 18% vs 7% (Log Rank x²=4.38, p=0.04) in the two groups, respectively. Age was not related to mortality after adjustment for other variables. Among all variables, anemia (OR 4.20, CI: 1.02–6.86, p=0.04), cardiopulmonary bypass (CPB) time (OR 1.02, CI 1.01–1.04, p<0.01), significant patient prosthesis mismatch (PPM) (OR 5.43, CI 1.04–18.40, p<0.05) were associated with 30-day mortality in elderly patients. Their long-term mortality was related to CBP time (OR 1.02, CI 1.00–1.05, p=0.04), PPM (OR 4.64, CI 1.33–16.11, p=0.02) and raised LA pressure: DT (OR 0.94, CI 0.84–0.99, p=0.03) and pulmonary artery systolic pressure (PASP) (OR 1.12, CI 1.03–1.19, p<0.001).

**STUDY III:** Following SAVR peak aortic pressure gradient (AOPG) decreased and indexed valve area increased (64±3 to 19±1 mmHg and 0.30±0.01 to 0.89±0.03 cm²/m², p<0.001 for both). LVEF increased (from 45±1 to 54±2%; p<0.001), LV end diastolic and end-systolic dimensions fell (LVEDD index: from 33±1 to 30±1 mm/m²; and LVESD index: from 27±1 to 20±1 mm/m²; (p<0.01 for both). LV diastolic dysfunction improved as evidenced by the fall in E/A ratio (from 2.6±0.2 to 1.9±0.4) and prolongation of total filling time; (from 29.2±0.6 to 31.4±0.5 s/min, p=0.01 for both). Among all echocardiographic variables, LV dimensions (LVEDD index, OR 0.70, CI 0.52–0.97, p<0.05; LVESD index, OR 0.57, CI 0.40–0.85, p=0.005) were the two independent predictors of post-operative LV functional recovery on multivariate analysis. A cut-off value of pre-operative LVESD index<=27.5 mm/m² was 85% sensitive and 72% specific in predicting intermediate-term recovery of LV function after AVR (AUC, 0.72, p=0.002).

**STUDY IV:** Before TAVI, there was no difference between the two patient groups in gender, age, body surface area (BSA) and baseline LV function. However, left
ventricular mass index (LVMi), left atrial volume index (LAVi) and tricuspid regurgitation pressure drop (TRPdrop) were increased in the TA group (p<0.05). One week after TAVI, aortic pressure gradient (AOPG) markedly dropped in the two groups (both p<0.001), LVEDD index and LVESD index fell but EF and myocardial strain remained unchanged. Overall cavity twist reduced (p<0.048). Significant LVESD index reduction was only seen in TF group (p=0.02) with a slight increase in LVEF (p=0.04). Lateral MAPSE increased only in the TF group (p=0.02). LV longitudinal systolic strain remained unchanged in TA patients while apical lateral strain increased in TF group. LV apical rotation fell in the two groups but basal rotation increased only in the TA patients (p=0.02). LAVi reduced in both groups and to a greater extent in TF TAVI (p=0.006), as did TRPdrop (p<0.001).

**Conclusion:** SAVR and TAVI are two effective treatments for severe AS patients. The severity of pre-operative systolic and diastolic LV dysfunction is the major predictor of mortality following SAVR for low-flow and high gradient AS. Peri-operative AVR survival is encouraging in the elderly. Long term mortality in the elderly is related to PPM, LV diastolic dysfunction and secondary pulmonary hypertension. LV functional recovery was evident in most patients with LV dysfunction after SAVR. A lower prevalence of LV functional recovery in patients with large pre-operative LVESD index might signify the loss of contractile reserve and thus predict post-operative functional recovery. TAVI results in significant early improvement of segmental and overall ventricular function, particularly in patients receiving the trans-femoral approach. The delayed recovery of the trans-apical TAVI group, we studied, might reflect worse pre-procedural diastolic cavity function.

**Keywords:** Aortic stenosis, surgical aortic valve replacement, transcatheter aortic valve implantation, survival, predictor, echocardiography, speckle tracking, ventricular function, twist, strain
List of Papers


IV Early effect of TAVI on left ventricular function in severe aortic stenosis: trans-apical vs. trans-femoral approach. Wenhong Ding, Ying Zhao, Astrid Watt, Per Lindqvist, JohanNilsson, Reidar Weintar, Anders Holmgren, Andreas Ruck, Michael Y Henein
## Abbreviations & Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>peak atrial filling velocity</td>
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<tr>
<td>ACE-inhibitor</td>
<td>Angiotensin-converting enzyme inhibitor</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
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<tr>
<td>AS</td>
<td>Aortic stenosis</td>
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<tr>
<td>AVA</td>
<td>Aortic valve area</td>
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<td>AVC</td>
<td>Aortic valve closure time</td>
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<td>AVR</td>
<td>Aortic valve replacement</td>
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<tr>
<td>BAV</td>
<td>Balloon aortic valvuloplasty</td>
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<tr>
<td>BNP</td>
<td>Brain natriuretic peptide</td>
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<tr>
<td>BSA</td>
<td>Body surface area</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CAS</td>
<td>Calcific aortic stenosis</td>
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<tr>
<td>CO</td>
<td>Cardiac output</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DT</td>
<td>Deceleration time</td>
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<tr>
<td>DVI</td>
<td>Doppler velocity index</td>
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<tr>
<td>E</td>
<td>Peak velocity in early diastole</td>
</tr>
<tr>
<td>E/A</td>
<td>Ratio of E and A velocity</td>
</tr>
<tr>
<td>E/Em</td>
<td>Ratio of E and Em velocity</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EDT</td>
<td>E-wave deceleration time</td>
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<tr>
<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>Em</td>
<td>Myocardial peak early diastolic velocity</td>
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<tr>
<td>EOA</td>
<td>Effective orifice area</td>
</tr>
<tr>
<td>ET</td>
<td>Ejection time</td>
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<tr>
<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
</tr>
<tr>
<td>FS</td>
<td>Fractional shortening</td>
</tr>
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<td>FT</td>
<td>Filling time</td>
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<tr>
<td>GLS</td>
<td>Global longitudinal strain</td>
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<tr>
<td>HP</td>
<td>Hypertension</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>IVRT</td>
<td>Isovolumic relaxation time</td>
</tr>
<tr>
<td>IVST</td>
<td>Interventricular septal thickness</td>
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<tr>
<td>LA</td>
<td>Left atrium</td>
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<tr>
<td>LAVI</td>
<td>Left atrial volume index</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
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<tr>
<td>LVEDD</td>
<td>Left ventricular end-diastolic dimension</td>
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<tr>
<td>LVEDDI</td>
<td>Left ventricular end-diastolic dimension index</td>
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<tr>
<td>LVEDV</td>
<td>Left ventricular end-diastolic volume</td>
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<tr>
<td>LVEDVI</td>
<td>Left ventricular end-diastolic volume index</td>
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<tr>
<td>LVESD</td>
<td>Left ventricular end-systolic dimension</td>
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<tr>
<td>LVESDI</td>
<td>Left ventricular end-systolic dimension index</td>
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<td>LVESV</td>
<td>Left ventricular end-systolic volume</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>LVESVI</td>
<td>Left ventricular end-systolic volume index</td>
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<td>LVH</td>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>LVMI</td>
<td>Left ventricular mass index</td>
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<tr>
<td>LVOT</td>
<td>Left ventricular outflow tract</td>
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<tr>
<td>LVOTO</td>
<td>Left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>MAPSE</td>
<td>Mitral annulus plane systolic excursion</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association class</td>
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<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>PHT</td>
<td>Pulmonary hypertension</td>
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<tr>
<td>PPM</td>
<td>Patient prosthesis mismatch</td>
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<tr>
<td>PSPAP</td>
<td>peak systolic pulmonary artery pressure</td>
</tr>
<tr>
<td>PWT</td>
<td>Posterior wall thickness</td>
</tr>
<tr>
<td>RA</td>
<td>Right atrium</td>
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<tr>
<td>RIMP</td>
<td>RV index of myocardial performance</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>RV</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>RVP</td>
<td>Rapid ventricular pacing</td>
</tr>
<tr>
<td>SAVR</td>
<td>Surgical aortic valve replacement</td>
</tr>
<tr>
<td>Sm</td>
<td>Myocardial peak systolic velocity</td>
</tr>
<tr>
<td>SR</td>
<td>Strain rate</td>
</tr>
<tr>
<td>STE</td>
<td>Speckle tracking echocardiography</td>
</tr>
<tr>
<td>STS PROM</td>
<td>Society of Thoracic Surgeons Predicted Risk of Mortality</td>
</tr>
<tr>
<td>STS score</td>
<td>Society of Thoracic Surgeons scoring system</td>
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</tbody>
</table>
Septal radial motion: Measurement of the extent of systolic anterior septal motion with respect to its position in end-diastole using the M-mode technique from the parasternal long axis view. Positive (+) motion towards the LV cavity and negative (-) motion towards the RV cavity.

Strain: The deformation of the myocardium relative to its original length. Strain is expressed in percent (%).

Twist: The myocardium rotates around the long axis of the left ventricle during the cardiac cycle “rotation”. Normally, the LV base (clockwise, negative value) and apex (counter clockwise, positive value) rotate in opposite directions. The absolute LV apex-to-base rotation difference is referred to as twist (degree).
Introduction

Epidemiology

Aortic stenosis (AS) is the most common valvular disease in the West, with a significant increasing prevalence with age (1,2). In the Euro Heart Survey on Valvular Heart Disease, AS was the most common valve abnormality (33.9% and 46.6% in the overall group and surgical subgroup, respectively) (3). The etiology of AS is degenerative-calcific in the majority of patients however a number of other potential pathophysologies have been invoked including atherosclerosis, calcific and genetic (4-6). Symptoms of AS usually develop gradually after an asymptomatic latent period of approximately 10-20 years. Degenerative AS is recognized as a valve disease characterized by years to decades of slow progression of leaflet fibrosis and calcification followed by rapid clinical deterioration and high mortality after symptoms development (7) if not attended to optimally. With the development of symptoms, patients may carry a mortality of 36-52%, 52-80% and 80-90% at 3, 5 and 10 years, respectively if left untreated, even carrying a high risk of sudden death (8). Symptoms in AS are mainly caused by left ventricular disease, with ejection fraction remaining initially maintained but later drops (9,10). Aortic valve replacement (AVR), surgically or interventionally by transcatheter approach is the only effective treatment for severe AS.

Pathophysiology

Etiology

Age-related calcification of the valve is the commonest cause of acquired AS, especially in patients older than 70 years. The old theory suggested gradual calcium deposition on the aortic leaflets but recent evidence supports a dynamic valve leaflet pathology, with progressive leaflet fibrosis and hardening ‘sclerosis’ causing limited movement and eventually stenosis of various severities. About 1 in 20 people aged over 65 have some degree of aortic sclerosis which may mature into valve stenosis. Such pathology is traditionally described as "senile calcific AS" for commonly affecting senile patients. Pathological investigations have shown that with age, collagen of the valve leaflets is destroyed, and calcium is deposited on the leaflets. With this, blood turbulence across the valve also increases causing scarring, thickening, and eventually stenosis once valve leaflet mobility is reduced...
by calcification. Histological studies also demonstrated inflammation, lipid accumulation and fibrosis of the stenotic aortic valve, which takes similar morphology to those seen in atherosclerotic disease. Less common causes of acquired AS is rheumatic valve disease which presents with typical pathological leaflets, thickened and calcified with fused commissures resulting in additional regurgitation. Most patients with rheumatic aortic valve disease have some evidence for concomitant mitral valve disease too. Isolated congenital AS is a rare pathology, with bileaflet aortic valve being the commonest and sub or supra aortic valve stenosis the less common presentation. Bileaflet aortic valve may remain silent for years and may become stenotic early in life. Itself, bileaflet aortic valve is seen as a substrate for future development of calcific AS. Although can result in similar hemodynamic effects on the left heart, subaortic membrane may cause severe narrowing of the left ventricular outflow tract (LVOT) early in life and constitute a serious need for surgical removal.

**Aortic stenosis and cardiac function**

When the aortic valve becomes stenotic, resistance to left ventricular (LV) ejection occurs and a systolic pressure drop develops between the LV and the aorta causing increase in pressure afterload and ventricular wall stress that stimulates hypertrophy of the LV myocardium (11,12). As a compensatory mechanism to normalize LV wall stress, LV wall thickness increases by parallel replication of sarcomeres, producing LV concentric hypertrophy. The progressive increase in LV wall stress as the valve stenosis worsens results in subendocardial ischaemia, which is worsened in the presence of additional epicardial coronary artery disease, a frequent finding in almost 50% of AS patients. Myocardial perfusion is thus compromised by the relative decline in myocardial capillary density and by a reduced diastolic transmural coronary (coronary) perfusion gradient due to elevated LV diastolic pressure. Therefore, the subendocardium is susceptible to underperfusion, which results in myocardial ischemia. At this stage, the chamber is not dilated and ventricular systolic function is preserved, however, diastolic compliance is reduced. Eventually, LV end-diastolic pressure (LVEDP) rises and causes a corresponding increase in left atrial pressure and pulmonary capillary pressure. The contractile function of the myocardium may later reduce resulting in a fall in cardiac output due to systolic dysfunction. Ultimately, heart failure develops.

In most patients with AS, LV systolic function is preserved and cardiac output is maintained for many years despite an elevated LV systolic pressure. In these
patients, although cardiac output is normal at rest, it often fails to increase during exercise, which may result in exercise-induced symptoms. As LV disease gets worse and systolic function deteriorates the cavity power generation and the pressure drop across the aortic valve fall. Careful assessment of newly presenting patients with such condition should be undertaken since isolated consideration of the transvalvar pressure drop would underestimate severity of valve stenosis. Following aortic valve replacement and removal of LV afterload myocardial hypertrophy often regresses and LV performance improves. However, some individuals develop extensive myocardial fibrosis, which may not resolve despite regression of hypertrophy.

The hypertrophy of cardiac muscle is considered as a useful physiologic adaptation to keep systolic function normalized. However, this kind of adaptation may become incapable of meeting the increased work load after a long time before heart failure occurs. Thus myocardial hypertrophy is considered the interface between the normal and failing heart (11). LV hypertrophy can be interpreted as being a synonymous with a maladaptive response to aortic valve disease rather than a compensatory reaction (13).

In patients with severe AS, atrial contraction plays a particularly important role in diastolic filling of the left ventricle, due to the slow relaxation related to the LV hypertrophy and subendocardial ischaemia. The left atrium of these patients has been found to increase, particularly in those with additional systemic hypertension. As the pathology progresses and severe stenosis occurs mitral regurgitation develops which results in increased left atrial pressure, atrial enlargement and unstable function, then atrial fibrillation. Development of atrial fibrillation further compromises cardiac output and results in worsening symptoms.

**Mechanism of Aortic valve Calcification**

Calcific AS is the most frequent heart valve disease and the main cause of valve replacement in patients over the age of 60. Despite the high prevalence and mortality associated with aortic valve calcification and AS, little is known about its pathogenesis. Osteopontin, a multifunctional protein implicated in the regulation of physiological calcification and biomineralization, has generated significant interest for its potential role in the pathogenesis of calcific valvular disease. Although osteopontin inhibits calcification, elevated levels of osteopontin are present in the heart valves of patients with calcified valvular disease. Recent
studies have shown a correlation between increased plasma osteopontin levels and valvular calcification(14). However, all studies have been limited to the quantitative assessment of osteopontin. In addition, CAS and atherosclerosis share common features regarding histopathology of lesions, raising a new perspective on potential prevention and treatment of disease.(4,5,15)

Assessment of AS and ventricular function

Clinical evaluation

Unlike congenital bicuspid AS and rheumatic AS which usually occur before the age of 65, calcific AS occurs in the elderly because of senile calcification. Progress of senile calcific AS is usually slow. Due to the extraordinary compensatory ability of left ventricle, patients may remain asymptomatic for several years until they develop severe obstruction. This fact makes diagnosing asymptomatic severe AS a real challenge. The main indicators of the severity of AS are patient’s symptoms and the clinical signs elicited on physical examination. Thus, careful interrogation for the presence of symptoms is critical for correct diagnosis and optimum management. The classical clinical symptoms of AS include angina, syncope and dyspnoea. Clinicians should also pay attention to even slight deterioration in daily activities, as the above commonly seen symptoms may frequently be attributed to other comorbidities in the elderly (1,16). New York Heart Association (NYHA) classification has been commonly used for functional assessment and categorization of patients with heart failure for many years, but has been questioned by some studies which suggested that NYHA classification is poorly reproducible (17). AS causes systolic murmur which results from turbulent blood flowing through a narrowed valve. The loudness of the murmur does not, however, correlate with the severity of stenosis. Patients with mild AS may have loud murmurs, whereas those with severe stenosis and LV dysfunction may have a low pitched murmur because of poor contractile ability to build enough pressure and hence blood flow across the narrowed valve.

Biomarkers

There are no biomarkers specific for AS but those used for diagnosing ventricular dysfunction and managing heart failure are used in AS. In patients with AS, the higher the BNP the more impaired LV function and increased wall stress. B-type natriuretic peptide (BNP) may also provide incremental prognostic information in predicting symptom onset in asymptomatic patients with severe AS (18). A high or
steadily rising BNP may predict the short-term need for valve replacement in asymptomatic, severe AS. Furthermore, preoperative BNP provides prognostic information on post-operative clinical outcome (18,19).

Despite such wealth of clinical and biochemical markers for diagnosing and managing AS accurate diagnosis of AS requires the use of methods which allow direct imaging of the valve and the study of leaflets anatomy, extent of calcification and overall valve function. Conventionally used methods include echocardiography, chest X-ray, electrocardiography, MRI, and in some cases cardiac catheterization.

**Imaging investigations**

**Doppler echocardiography**

Doppler Echocardiography is now recommended as the key diagnostic tool for assessing the presence and severity of AS as well as other related cardiac structure and function.

**Aortic valve structure and function estimation**

2D echocardiographic study assesses AV anatomy, number of leaflets and the relationship of the valve to other neighboring structures e.g. LV outflow tract and mitral valve. 2D images also evaluate qualitatively the extent of leaflet calcification, leaflet motion and overall valve opening. Continuous wave Doppler is the cornerstone ultrasound modality for quantifying AS severity. It enables accurate recording of peak transvalvular velocities, from which peak pressure drop can be calculated using the modified Bernoulli equation $4V^2$. Likewise, continuous wave Doppler displays clear recordings of aortic regurgitation velocities, from which severity can be estimated using pressure half time, particularly in patients with normal LV end-diastolic pressure. In patients with combined AS and subvalvar narrowing of LV outflow tract by basal septal hypertrophy, M-mode technique can confirm the extent of valve leaflet mobility as a rough guide to the level where maximum narrowing is. Colour Doppler can also assist in demonstrating the level of maximum obstruction, in addition to its valuable use in confirming the presence and severity of aortic regurgitation.
Left ventricular structure and function

2D and M-mode echocardiographic techniques allow detailed assessment of LV structure and function, including cavity dimensions, systolic function i.e ejection fraction, wall thickness and LV mass. They also assess left atrial dimensions, area and volume, which provide an indirect evidence for raised LV filling pressures. 2D echocardiography also assesses the presence and extent of calcification that involves other cardiac structures e.g mitral valve annulus. Pulsed wave Doppler has essential role in the management of AS patients. It provides accurate and reproducible recording of LV filling velocities, from which a number of measurements can be made to evaluate filling pressures including, E/A ratio, E wave deceleration time, isovolumic relaxation time as well as E/e’. An isolated A wave in a patient with AS suggests severe degree of LV dyssynchrony, which could be the cause of patient’s symptoms rather than AS, particularly in those with maintained LV systolic function and modest degree of AS. Colour Doppler confirms the presence of mitral regurgitation and its severity, a common finding in most patients with AS, detect the presence of other associated valve disease or aortic pathology, and provides prognostic information (1,20). Compared with other imaging modalities, echocardiography provides bedside diagnosis, accurate estimation of the degree of AS, even in patients with poor LV function and masked signs of AS. It is also an ideal tool for assessment of the valve and ventricular function before and after operation, even in patients with pacemakers.

Right ventricular and pulmonary circulation

Right ventricular (RV) hemodynamic function is physiologically different from that of the LV. RV is difficult to assess both structurally and functionally because of its complex 3-dimensional anatomy and limited echocardiographic windows. RV dysfunction starts with impairment of its function, and then structure, the combination of the two is bound to affect cavity filling and ejection later. Mild and moderate degree of RV dysfunction is well tolerated, severe dysfunction results in inability of the RV to pump optimally in order to cope with the body demand for blood and oxygen. This results in fluid retention in the form of lower limb edema then later on ascites, and anasarca, decreased systolic reserve or low cardiac output, which may lead to exercise intolerance and fatigue; or atrial or ventricular arrhythmias (21).

Isolated (primary) RV failure is very rare. The most common cause of RV
dysfunction is chronic left-sided heart failure. In severe senile AS, affected by a worsening diastolic and systolic function, an elevated left atrial pressure and pulmonary artery hypertension (PH) results in a pressure overload on the right heart and may lead to progressive RV functional impairment. It is generally accepted that RV adapts better to volume overload than to pressure overload. So a moderate to severe PH often leads to RV dilatation, myocardial hypertrophy and impairment of systolic function (22). These secondary changes in RV function may appear slowly and insidiously, but can be detected by clinically accepted standard tests (eg, right heart catheterization and echocardiography) and evolving technologies (eg, magnetic resonance imaging [MRI] and positron emission tomography [PET]) (23). However, Echocardiography is widely used as a non-invasive tool for clinical estimation of RV function.

**Echocardiographic evaluation of RV function in AVR**

Doppler echocardiography is the most commonly used screening modality for the assessment of RV structure and function. RV systolic function is evaluated using several recommended parameters; RV index of myocardial performance (RIMP), 2D RV Fractional area change (FAC), TAPSE, tissue Doppler–derived tricuspid lateral annular systolic velocity (s’), 2D longitudinal strain and strain rate, three-dimensional (3D). However, 3D RV EF seems to be more reliable with fewer reproducibility errors by recent studies, but sufficient supporting data demonstrating its clinical value remain lacking (24). RV diastolic function is assessed by pulsed Doppler of the tricuspid inflow (E, A and E/A ratio), tissue Doppler of the lateral tricuspid annulus (s’, e’, a’ and e’/a’), E/e’, pulsed Doppler of the hepatic vein and measurements of IVC size and collapsibility showing the RA pressure. Previous studies have demonstrated the clinical utility and value of TAPSE and s’ in evaluating RV function recovery before and after TAVI or SAVR (25-27).

**Valve function estimation**

Echocardiographic examination is applied in diagnosing and following-up of AS patients before and after intervention. The severity of AS can be measured accurately and reliably on the basis of antegrade velocity, mean pressure gradient, and continuity equation valve area (28). 2D echocardiographic examination includes assessing the LV outflow tract (LVOT) diameter, valve leaflet pathology, mobility and severity of stenosis and regurgitation. The valve calcification can be qualitatively evaluated by 2D imaging but not quantitative evaluation of the extent
of the valve calcification. Doppler interrogation is therefore the standard technique to assess severity of AS. Parameters include jet peak velocity (measured using continuous-wave (CW) Doppler (CWD) ultrasound (severe AS peak jet velocity ≥ 4 m/s), mean transaortic gradient, and effective AVA were calculated using the continuity equation: \( \text{AVA} = \frac{\text{CSA}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{AV}}} \) (29) and mean transaortic pressure gradient > 40 mmHg and AVA < 1.0 cm\(^2\) is defined as severe AS. AVA by continuity equation requires three measurements: AS jet velocity time integral (VTI) by CW Doppler, LVOT diameter for calculation of a cross sectional area, which is assumed to be circular, and LVOT velocity time integral recorded with PW Doppler. The reproducibility of continuity equation is limited because of the variability of its three components. This becomes the greatest potential source of error (30). Gutierrez’s study showed AVA calculated by real-time 3-D echocardiography (3 DE) stroke volume in continuity equation was more accurate and reproducible than the conventional continuity equation based on measurement of LVOT diameter and than two-dimensional volumetric methods to calculate area and to grade the severity of the AS (31).

After AVR, echocardiography is unique in assessing prosthetic valve function by determination of gradients across prosthetic Valves, calculating the effective orifice area (EOA), pressure recovery and patient-prosthesis mismatch (PPM). The EOA of prosthesis by the continuity equation is a better index of valve function than gradient alone. This is calculated as EOA = stroke volume/ VTIPrV; where VTIPrV is the velocity-time integral through the prosthesis determined by CW Doppler (32).

PPM is defined as a smaller than expected EOA in relation to the patient’s body surface area (BSA) which results in higher transvalvar gradients. The parameter used to characterise PPM is the indexed EOA (EOA / BSA). PPM is considered to be hemodynamically insignificant if the indexed EOA is >0.85 cm\(^2\)/m\(^2\), moderate if between 0.65 and 0.85 cm\(^2\)/m\(^2\), and severe if <0.65 cm\(^2\)/m\(^2\). The indexed EOA is in fact the only parameter that has been found to consistently correlate with postoperative gradients (33) DVI is calculated a ratio of the proximal velocity in the LVOT to that of flow velocity through the prosthesis, that is expressed by DVI = \( \frac{V_{\text{LVO}}}{V_{\text{PrAV}}} \). A DVI < 0.25 is highly suggestive of significant valve obstruction (32).

Other technique

Three-dimensional (3D) volume quantification of aortic valve calcification using
multi-slice computed tomography (CT) scanning demonstrates a close, nonlinear relationship to echocardiographic parameters for the severity of AS (34). This method is not yet clinically validated. In a study by Shah et al that compared multidetector CT scanning with transesophageal echocardiography (TEE), multidetector CT scanning was found to be an accurate modality for determining aortic valve measurements in patients with AS (35).

Cardiac magnetic resonance imaging (MRI) has also been investigated for assessment of AS. AVA measurements made with cardiac MRI have shown excellent correlation with those made with Doppler echocardiography. This method is not yet clinically validated (36,37).

**Treatment of AS**

There is no medical treatment that proved to benefit AS patients, neither in slowing disease progression nor in controlling symptoms, since the main problem is organic obstruction of the outflow tract of the left ventricle with its consequences. On the other hand, symptomatic patients, according to current American and European guidelines, benefit symptomatically and prognostically by valve replacement (38).

**Medical treatment**

Patients with mild AS can lead a normal life without any symptoms, unless they have poorly controlled systemic hypertension, in addition, which could cause symptoms and which requires aggressive medical treatment. Conventional treatment of heart failure might be used in small doses to control patients’ symptoms, particularly those who are not candidates for surgical intervention. However, all these medications are known to worsen the pressure gradient across the valve and consequently its effect on left ventricular wall stress and myocardial perfusion. Patients with AS who develop poorly controlled atrial fibrillation might benefit from a small dose of digoxin, only if other commonly used medications for this purpose e.g. amiodarone or beta blockers are contra-indicated (1). Patients with fluid retention may respond to optimum dosage of diuretics, although this would not affect the original problem of AS.

**ACE-inhibitors:** Being vasodilators, ACE inhibitors are traditionally contraindicated in AS, however there is no contemporary evidence, based on randomized trials is available to support that. Furthermore, the potential benefit
of ACE-inhibitors in mild AS has not been studied. Although they might be conceptually of benefit to AS patients presenting with heart failure, they still carry a significant risk for hypotension.

**Angiotensin receptor blockers**: These drugs have the same limitations and potential benefits as ACE-Inhibitors.

**Statins**: Statins are another controversial medication for AS. Studies have shown that progression of AS calcification is an active process, and it shares similar risk factors to those of coronary atherosclerosis (20). But randomized, double-blind, placebo controlled trials have already shown that intensive lipid-lowering therapy does not halt the progression of calcific AS or induce its regression (39-41). Therefore, statins are considered of no benefit in AS unless they are given to better control dyslipidemia in patients with known atherosclerosis in order to lower low-density lipoprotein (LDL) cholesterol. In fact, these findings mirror the results of using statins in calcific coronary artery disease shown by a number of randomized trials and a recent meta-analysis which showed no structural benefit (42).

**Beta blockers**: Beta-blockers might be used in severe AS if the predominant symptom is angina. It is well known that Beta-blockers relieve dynamic left ventricular outflow tract obstruction and decrease aortic jet velocity and heart rate, thus could decrease hemodynamic stress with its potential benefit on the degenerative process in patients whose disease is not too advanced. A resting gradient of 60 mmHg in an asymptomatic patient is likely to double with increase in heart rate. Therefore, beta blockers have traditionally been used for heart rate control in AS patients. In asymptomatic AS patients, it may be useful since it can potentially reduce sudden death, ischemic events or atrial fibrillation, but are poorly tolerated by severe AS patients (43). Despite that there are no clear evidence for their unique benefit in AS, apart from rate control and its good effect on the cardiac function.

**Intervention**

**Surgical Aortic valve replacement (SAVR)**

In adults with severe symptomatic calcific AS aortic valve replacement AVR is the only recommended treatment and receives a class I recommendation according to the current ACC/AHA 2006 guidelines (20). Although patients
with severe AS may remain without symptoms for a while, once symptoms develop the prognosis of severe AS becomes dismal, with survival rates of only 15–50% at 5 years. Therefore, timely performed SAVR is recommended in order to preserve left ventricle (LV) function, relieve symptoms and improve function. Even in octogenarians SAVR has been shown to carry very good clinical outcome and better survival than medical therapy (38), with satisfactory long-term results (44-47).

Operative mortality of isolated AVR for AS is 1–3% in patients younger than 70 years and 4–8% in selected older adults (38). Patients with AS might have concomitant coronary artery disease in approximately half of those above the age of 75 years (48). Such patients usually require simultaneous coronary artery bypass grafting (CABG) and SAVR which increases operative mortality as has been shown in most series (47). According to the ESC/EACTS guidelines, a number of risk factors may increase the operative mortality including old age, associated comorbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, co-existing CAD, and previous bypass or valve surgery. Risk factors for late death include age, comorbidities, severe symptoms, LV dysfunction, ventricular arrhythmias, and untreated co-existing CAD. In addition, poor postoperative outcome may result from prosthesis-related complications and suboptimal prosthetic valve haemodynamic performance (38).

**SAVR in high-risk patients**

The effects of SAVR on operative mortality in patients carrying high risk, irrespective of symptoms, have been assessed by many groups. Most studies reported old age, severe co morbidities, co-existing CAD, higher functional class and LV dysfunction before and after procedure to be related to peri-operative mortality and long term survival. In single-center-based studies published between 2004 and 2010, the mortality of AVR in octogenarians was 3.0-10.6% for isolated AVR and 8.4-13.0% for AVR with concomitant CABG (45,46,49-52). One single-center- based study in elderly patients who underwent SAVR showed the overall operative mortality rate to be 3.9%, with no age influence on the results (75.1±2.8 vs. 83.5.1±2 year) or postoperative complication rate (53). A multi-institutional study analyzed 159 very high-risk patients (Median age: 80 years) who underwent isolated SAVR with mean STS-PROM (Society of Thoracic Surgeons Predicted Risk of Mortality) of 16.3%±7.3% from 2002-2007 (54). The in-hospital mortality was 16.4%, in-hospital mortality was equivalent to that
predicted by the STS-PROM with an observed-to-expected ratio of 1.00. The median follow-up at 1, 3, and 5-year survival was 70.9%, 56.8%, and 47.4%, respectively. In-hospital mortality in this cohort increased with the combination of high-risk pre-operative variables (low ejection fraction, congestive heart failure, high NYHA functional class, and renal dysfunction) but there was no significant predictor for in-hospital or midterm survival. Although AVR in the elderly can be performed with acceptable mortality and excellent long-term survival and functional recovery, the European Heart Survey on valvular heart disease demonstrates that surgery was denied in 33% of patients over 75 years of age with severe, symptomatic AS. Old age and LV dysfunction were the two most striking characteristics of patients who were denied surgery, whereas comorbidities e.g. kidney impairment, chronic obstructive pulmonary disease (COPD) and neurological dysfunction played a less important role (55). NYHA class IV functional class, a higher Charlson comorbidity index predicted the 1 year mortality.

Patients with severe AS and poor LV function before AVR carry a significantly higher surgical risk (amounting for up to 10%) compared to those with maintained LVEF, with an estimated higher in-hospital mortality of 8-9%. However, AVR in these patients has significantly better outcome confirmed by some studies if compared to those unoperated patients (38,56,57). Tarantini et al. evaluated 85 consecutive patients with severe AS and LVEF<35% before surgery, 32/33 of the 85 did not undergo aortic valve replacement died within 3 years. Fifty-two patients underwent AVR including 16 concomitant CABG had an in-hospital mortality of 8%. Significant post-operative improvement was seen in functional class and in LVEF. LVESVI remained as the only independent predictor of cardiac death during a mean 53 months follow-up. LV dysfunction has a prognostic value in patients undergoing AVR for AS (56). In spite of high risk of pre-operative impaired LV function, compared with those untreated deaths, the gain benefit in terms of clinical outcome is worthy of recognition. In fact, SAVR in patients with low flow, low gradient and lack of flow reserve before procedure has been shown to improve LVEF and clinical status. This has been supported by recent guidelines (38)

**Left Ventricular function after SAVR**

**LV mass regression**

It is generally recognized that chronic left ventricular (LV) pressure overload
results in increased wall thickness and concentric hypertrophy. As a result, concentric LV geometry changes occur, not only to normalize wall stress but also to optimize subendocardial systolic function as part of the overall cavity pump function even though mid-wall and longitudinal shortening remain impaired (58). LV hypertrophy is known to be associated with increased cardiac mortality and morbidity not only in AS patients even after aortic valve replacement (59-61). Increased LV mass has also been shown to predict the development of systolic dysfunction and heart failure regardless of the severity of the valvular obstruction (13,62). In contrast, aortic valve replacement, for AS, and removal of afterload results in regression of myocardial hypertrophy which completed by the 6 months after surgery (63). Late regression of myocardial hypertrophy usually takes a slower course over the mid and long term follow up. Despite that, the magnitude of LV mass regression may vary in different cases. Recently, Ali et al has suggested that the magnitude of LV mass regression independently predicts long-term survival with preoperative LV mass higher in patients who demonstrated the greatest postoperative reduction in LV mass, which is in accordance with previous reports (64,65). LV regression of myocardial hypertrophy after AVR is also influenced by a number of other factors including age, gender, hemodynamic factors, prosthetic valve types, myocyte alterations, interstitial structures, blood pressure control, ethnicity, myocardial metabolism and coronary artery circulation. Previous studies reported controversial results regarding the effect of age and gender on LV hypertrophy regression (66-68), but a systematic review has shown no statistical association between age and sex with the rate of LV mass regression and change in EF. The reasons why LV mass regression occurs in some individuals and is incomplete in others, despite similar preoperative LV mass and postoperative hemodynamic and clinical profiles, remain to be explored (69).

Hypertension (HT) is a common co-morbidity which is found in 33-72% of patients with AS (70-72). Hypertension and AS represent two different models of chronic pressure overload and both can lead to the development of LV hypertrophy, with different patterns of ventricular geometrical disturbances as shown by echocardiography, i.e. concentric remodeling, concentric hypertrophy and eccentric hypertrophy (72-74), of which eccentric hypertrophy is commonest presentation seen with that combination.

In patients with AS, hypertension has a significant impact on LV function pre-operatively and after AVR. Hypertensive patients have slower regression of LV mass resulting in higher LVMi than normotensive patients even after years of follow-up (75). Gaudino et al reported LV hypertrophy reduction over 28 months
only in AS patients without HT (76). However, how the HT influences the LV mass regression after AVR remain controversial. It must be recognized, however, that AS affects the LV myocardium through almost entirely load-dependent mechanisms, whereas HT extensively invokes additional neurohumoral mechanisms as well as being labile. On the other hand, interaction between the 2 mechanisms has not been completely clarified to date in the literature.

**LV function after AVR**

LVEF is recognized as the most popular measure of LV global systolic function, particularly using the available non-invasive imaging techniques e.g echocardiography and magnetic resonance imaging (MRI). The attraction behind using EF is that it simply reflects the changes in the LV cavity volume and does not take into consideration the complex architecture of the cavity (77,78). In early hypertrophy, the subendocardial layer may be affected by ischaemia and later fibrosis but mid-myocardial and subepicardial layers may continue to function normally. Subendocardial function can be studied by assessing longitudinal LV systolic and diastolic function. Impaired longitudinal LV function can be compensated for by the efficient behaviors of the circumferential and rotational function of the two respective myocardial components (79). The long-axis systolic function has already been noticed to be significantly decreased in AS patients with normal EF (80,81). This integrated myocardial function continues to preserve overall LV systolic function and EF until the transmural myocardial fibers function become affected too. At that stage overall cavity function reduces as shown by low EF. Current echocardiographic techniques allow more precise study on evaluation of LV global and segmental myocardial motion as well as deformation by tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE). STE permits accurate and noninvasive evaluation of the LV spiral muscle configuration and quantification of LV shortening, thickening, and twisting deformations, particularly, accurate assessment of multidirectional LV strain (longitudinal, circumferential, and radial)(82). The radial and circumferential strain and strain rate changes present later than the longitudinal function, which may remain normal in mild AS patients, but decrease in moderate and severe AS leading to a decreased LVEF (83).

With the relief of LV outflow tract obstruction (LVOTO) following a successful SAVR, LV pressure overload decreases immediately, resulting in rapid increase of LV myocardial velocities, strain and strain rate occur in the three directions. LV lateral long-axis amplitude normalized early after surgical AVR but strain lagged
behind for several months after surgery. These changes happen earlier than those in global systolic function and LV mass regression (84-88). During mid-term and long-term follow-up, the strain and strain rate in all directions increase gradually and eventually normalize (88,89) but with a respective late recovery in the longitudinal direction if compared with strain and strain rate changes in radial and circumferential direction. STE can reliably detect early regional changes of myocardial function before benefits in LVEF are detectable.

LV diastolic function could remain unchanged early after AVR (88) but improves significantly over the early postoperative period as myocardial hypertrophy regresses and the ventricle become more synchronous in function. Diastolic stiffness increases in aortic stenosis early after AVR parallel to the increase in interstitial fibrosis, whereas relaxation rate decreases with a reduction in LV muscle mass. Late after AVR, both diastolic stiffness and relaxation are normalized due to the regression of both muscular and non-muscular tissue. Thus, reversal of diastolic dysfunction in AS takes years and is accompanied by a slow regression of interstitial fibrosis (90). E/E’ and E/A ratio are markers of diastolic function and ventricular preload, which sensitively indicate the reduction of pressure overload after AVR, and may indicate a positive effect on myocardial relaxation (86). A population-based study by Pritchett (91) showed LAVi also serves as a sensitive marker for the magnitude and duration of LV diastolic dysfunction. Other studies too supported that LAVi sensitively predicts LV diastolic dysfunction (92-94). Yoshifumi Naito reported that in patients with severe AS, a preoperative LAVi of >/=52 ml/m² may be a useful predictor of atrial fibrillation post SAVR. Dalsgaard and colleagues demonstrated that LV hypertrophy and diastolic dysfunction also are closely associated with LA volume changes.

During diastole, the LA is directly exposed to LV pressure through the open mitral valve; thus, with increased filling pressure the LA dilates and can be considered a morphologic indicator of chronic LA pressure overload. Dahl and colleagues found that preoperative severe LA dilatation remained associated with increased postoperative filling pressures and severity of LV hypertrophy at 1 year follow-up (93). These are in accordance with a previous study showing that severity of LV hypertrophy and of elevated filling pressures before surgery were predictive of elevated filling pressures after AVR (95).

LA dilatation may also be secondary to volume overload, most commonly associated with moderate to severe mitral regurgitation (MR) in AS. After SAVR,
severity of MR significantly reduced along with LV systolic and diastolic functional recovery. The reduction of MR is due not only to decreased intraventricular pressure, but also to changes in ventricular morphology.

**Other alternative (nonsurgical) interventions**

**Percutaneous balloon valvuloplasty**

Percutaneous balloon aortic valvuloplasty (BAV) was developed as a nonsurgical option in the 1980s. It through a retrograde transfemoral approach can be used as a bridge to AVR or transcatheter aortic valve implantation in unstable patients with high surgical risk to allow for improvement in LVEF, severe MR, pulmonary hypertension, and clinical status (96,97).

BAV can be considered to apply in patients with other comorbidities with a very short life expectancy, who refuse surgery, who have severe heart failure and need an urgent procedure, and also pregnancy with critical AS. Procedural process includes lower-profile balloon catheters, avoidance of double balloon inflations, balloon sizing based on aortic annular diameter determined by echocardiography, rapid ventricular pacing for more precise balloon positioning, and percutaneous suture arterial closure. In critically ill patients, the mortality rate associated with the procedure is 3-7% (98).

Another 6-11% develop serious complications, including perforation, myocardial infarction, and severe aortic regurgitation (97,99). Restenosis is common, particularly in patients with valves affected by severe dysplasia (>60% at 6 mo, virtually 100% at 2 y). However, repeat procedures have been shown to provide a median survival rate of approximately 3 years and to maintain clinical improvement (100).

However, percutaneous balloon aortic valvuloplasty provides only modest hemodynamic improvement and is done for achieving temporary improvement in quality of life or buying time before more definitive treatment. Again the long-term survival after this procedure is not significantly different from the natural history of AS and the small hemodynamic benefit only lasts months because of early recoil restenosis (101,102), all preclude its use as a definitive treatment method. The current focus of scientific interest has shifted from balloon aortic valvuloplasty to percutaneous transcatheter aortic valve replacement (TAVI).
**Transcatheter aortic valve implantation (TAVI)**

Conventional SAVR operation was the only recommended management of severe symptomatic AS 10 years ago. It preserves left ventricular (LV) function, relieves symptoms and improves survival in patients with severe symptomatic AS (103). Despite that, a considerable number of patients are not referred for SAVR because of advanced age and other significant comorbidities, which could raise the peri-operative surgical risk (2,104,105). On the other hand, if ignored, severe AS carries a mortality of 50% in the first 2 years after symptom development (20). However, the situation changed in 2002, the first human percutaneous transcatheter aortic valve implantation was successfully performed by Alain Cribier in a patient with severe calcific AS and very poor LV function (106). Since that early experience, multiple alterations and new designs developed. TAVI has now become a novel, minimally invasive alternative treatment for patients who are at high risk from SAVR (107,108). Recent studies have shown TAVI results in satisfactory clinical outcome, with a success rate exceeding 90% (109). Indeed, early and mid-term functional improvement after TAVI has already been reported (110-112), showing reduced mortality, improved symptoms, as well as overall cardiac function (113).

**TAVI procedure**

**Patient Selection**

TAVI is appropriate only for a highly select population. Patients should be carefully evaluated before TAVI by the clinical multidisciplinary team (consists of cardiothoracic surgeons, cardiologists, anesthesiologists, nurse practitioner, echocardiographer, and imaging specialists—CT or CMR). Inclusion and exclusion criteria in clinical practice should follow 2012 ACCF/AATS/SCAI/STS expert consensus on TAVI. (109) Factors may have an impact on the decision-making should be taken into account by this multidisciplinary team to define the population with most benefit and acceptable risk.

**Artificial aortic valve**

In replacing diseased aortic valves by TAVI, an artificial aortic valve is implanted by means of a sophisticated catheterization procedure. Current mostly used two types of devices from different companies - The balloon-expandable Edwards Sapien (Edwards Lifesciences, Irvine, California) and the self-expandable
CoreValve (Medtronic, Irvine, California).

The Sapien valve is a trileaflet bovine pericardial valve mounted with a tubular slotted balloon-expandable stent composed of a cobalt chromium alloy. The Sapien valve suites an annulus size range of 18 mm to 27 mm. It is available in 23-mm and 26-mm sizes in the United States and 23-mm, 26-mm, and 29-mm sizes in Europe. The first and second generations of Sapien valves have been tested in randomized controlled trials for both transfemoral and transapical implantation. The Core Valve is comprised of 3 porcine pericardial tissue leaflets mounted in a self-expanding nitinol frame. It is available in 3 sizes—26 mm, 29 mm, and 31 mm. Core Valve has only been used by a retrograde approach—either via transfemoral, subclavian, or direct aortic access. Both valves work similarly. The artificial valve is attached to a collapsed wire frame, which in turn is attached to the catheter. The catheter is inserted into a blood vessel or through the LV apex, and is advanced to the area of the aortic valve. When in position, the wire frame is expanded, allowing the artificial valve to open and to begin functioning.

**Insertion technique**

Although TAVI can be performed through different insertion techniques, there are specific advantages and disadvantages to each vascular access approach. Selection of the optimal route requires consideration of specific patient anatomy and the specific device to be used. Now TAVI is mainly performed through the retrograde trans-femoral or by the antegrade trans-apical approach. The retrograde approach (trans-femoral) by which it is delivered via an arterial route; and the trans-apical route requiring a mini thoracotomy for delivery of the device via the apex of the left ventricle. While trans-femoral approach is usually favored for most patients, the trans-apical approach is recommended for those in whom the trans-femoral access is difficult.

**Trans-femoral approach**

The trans-femoral approach requires an adequate peripheral vascular access (more than 6 mm in diameter, no more than mildly diseased and tortuous vessels, no presence of mural thrombus, no significant aortic disease or previous aortic surgery) and can be performed fully percutaneously under general or local anesthesia. A femoral approach is used in the vast majority of retrograde deployments, starting with either a standard percutaneous femoral arterial access or a surgical exposure of the artery. A series of dilators is employed, under
fluoroscopic vision, to reach the size of the deployment sheath. The sheath is passed into the body of the thoracoabdominal aorta. Aortic valve is crossed using standard interventional techniques, and a stiff wire exchange is performed, with redundancy in the LV cavity to prevent loss of position. Care must be taken to avoid damage to the LV, resulting in perforation.

*Trans-apical approach*

The transapical approach is the only currently available antegrade approach, and equipment is only available for this approach for the Sapien valve. Access is obtained via a left anterior thoracotomy, which is made after localization of the apex by fluoroscopy or TTE. Patients receive general anaesthesia and a left sided anterolateral mini-thoracotomy, opening the anterolateral segment of the pericardium near the apex. TEE is of great value in helping to localize the apex of the LV. Puncture is made and a 0.035-inch guide wire is passed through the native valve. External temporary pacing wires are attached to the LV apex. An arterial needle puncture allow placement of a 6F sheath through the apex into the LV cavity using a standard over-the-wire technique. A stiff support wire is then positioned across the arch and placed into the descending aorta. Under a rapid ventricular pacing, balloon aortic valvuloplasty is performed and the valve is delivered under fluoroscopy and TEE for optimum positioning.

TAVI procedure is performed under X-ray monitoring, and transoesophageal echocardiography is also recommended for accurate monitoring of valve positioning, evaluating the LV function before and immediately after valve implantation as well as detecting any early procedure related complications e.g. para-valvular regurgitation (114).

**Clinical outcome**

Following the first successful case in the human, TAVI has been rapidly developed as a valid alternative treatment to SAVR in inoperable and high-risk patients along with the improvement of procedural technique and equipments. A number of clinical trials have been designed to assess the safety and efficacy of this novel technique during the past decade. The procedure’s efficacy has been proved with overall procedural success rates ranging between 74% and 100%. The short-term (30 days) overall mortality is 0-25% (115), 1, 2 and 3 years survival rates are 76.1%, 61.9% and 57.0%, respectively (116-118). Survival after TAVI is not different between trans-apical and trans-femoral approach at short and mid-term
In a multi-center PARTNER (Placement of AoRtic TraNscathetER Valves) clinical trial, a total of 358 AS patients who were not considered suitable candidates for surgery were studied. At 1 year, the rate of death from any cause was 30.7% with TAVI compared with 50.7% with standard therapy. The rate of the composite end point of death from any cause or repeat hospitalization was 42.5% with TAVI compared with 71.6% with standard therapy. Among survivors at 1 year, the rate of cardiac symptoms (NYHA class III or IV) was lower among patients who had undergone TAVI than those who had received standard therapy, and there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation. However, high incidence of perioperative complications, including stroke and vascular events, was seen in TAVI patients but not in the surgery group (113). Another randomised trial (121) reported mortality rate around one year was 46.6% in medical and balloon aortic valvuloplasty group, 26.7% in SAVR and 30.8% in TAVI showing equal improvements in SAVR and TAVI group. Therefore TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause. Patients with severe AS who did not undergo TAVI or AVR had high mortality. Tamburino (122) compared complications and outcomes in one year follow up between 218 TAVI and 400 SAVR patients. No significant differences between TAVI and SAVR group in procedural death and in-hospital mortality rate. TAVI was not associated with a higher risk of 1-year major adverse cerebrovascular and cardiac events compared to SAVR.

LV function after TAVI

In patients undergoing TAVI, previous studies have shown immediate almost complete normalization in afterload and a significant decrease in pressure gradient, between the aorta and the LV, as well as clinical improvement shown by improved NYHA class. In addition to the favorable clinical outcome, TAVI results in significant improvement in LV function and survival benefit in high-risk patients during medium-term follow-up. Forsberg reported after 8 weeks of procedure, TAVI results in similar increase of LV lateral wall longitudinal amplitude and myocardial velocity compared to AVR (123). Significant LV remodeling, decreased LAVi and also increasing in tissue Doppler velocities during the mid-term follow up were reported, which clearly reflected a diastolic functional recovery (124). There has been a number of data showing LV systolic function recovery in most of TAVI during mid-term and long-term follow-up.
Significant improvement of EF and posterior wall myocardial velocity, strain and strain rate had already been observed 24 hours or within 72 hours after procedure (125,126). But Dworakowski (127) reported that successful transfemoral (TF) TAVI results in a transient depression of both systolic and diastolic LV function within the first 24 postoperative hours. Other study showed myocardial injury during transapical TAVI access resulted in transient apical dysfunction and was associated with a decrease in left ventricular function but did not affect mortality (128). Meanwhile, similar to surgical AVR, the decreased longitudinal systolic strain and strain rate in severe AS patients increased after 1 month of TAVI with unchanged EF. The unchanged radial and circumferential strain and strain rate after procedure may be due to the near-normal values before TAVI (129). It seems that the changes of LV myocardial motion and deformation after TAVI or surgical AVR are more dependent on the baseline patients’ characteristics than the procedure per se. Currently, fewer studies on the twist function after TAVI, since TAVI and surgical AVR both relieve the LVOT obstruction. The twist function changes after TAVI are expected to be the same as with AVR. And also, very rare studies compared effect of TAVI approaches on ventricular function. These remain to be proved.
Based on the foregoing knowledge of AS and the effect of surgical AVR and TAVI on the left ventricle, several questions are to be explained through my four studies in this thesis:

I  Little is known about surgical risk and outcome after surgical AVR (SAVR) in patients in low flow high gradient AS.

II  SAVR in the elderly over 70 years old is challenging given the associated comorbidities. The predictors of mortality in the elderly receiving AVR need to be revisited to better select patients for potential benefits from surgical procedure.

III  Little has been published to address the pre-operative echocardiographic predictors of LV functional recovery in AS patients with low EF.

IV  Transapical and transfemoral TAVI have been shown to result in satisfactory clinical outcome in early and mid-term follow up. However, the preferential effect of individual procedure on cardiac function remains not fully determined.
Objectives

The objective of this study was to evaluate survival and functional recovery following surgical and transcatheter valve replacement in patients with severe aortic stenosis

Study I

To identify predictors of survival following SAVR in patients with low-flow and high-gradient AS.

Study II

To identify predictors for mortality following SAVR in elderly patients with severe AS.

Study III

To identify the most sensitive echocardiographic measurements that predict recovery of LV function following SAVR in patients with severe AS and LV dysfunction.

Study IV

To compare transapical (TA) and transfemoral (TF) TAVI effects on LV function
Material and Methods

Study population

We studied surgical AVR patients in study I ~III and TAVI patients (including transapical TAVI and transfemoral TAVI) in study IV.

**SAVR patients:** All SAVR patients were from a group of 221 patients with severe AS who underwent conventional AVR at The Royal Brompton Hospital between 1998~2003. Operations were performed by two experienced surgeons. Clinical and echocardiographic data were collected with informed consent according to a strict clinical protocol, approved by The local Research Ethics Committee.

The conventional echocardiographic measurements were made before and after AVR in the following groups according to the guidelines.

1. 86 patients (aged 71±10 years) with severe AS and LV systolic dysfunction
2. 112 elderly AS patients (aged 77±2 years) and compared them with 72 younger patients (aged 60±1 years);
3. 66 patients (mean age 70±2 years, 53 male) who underwent AVR for severe AS and had preoperative and post-operative complete echocardiographic examination.

Patients with sub-optimal echocardiographic windows, pacemakers, prosthetic valves, prior aortic valve surgery, concomitant significant aortic regurgitation and other hemodynamically significant cardiac diseases were excluded from the study. Conventional echocardiographic techniques were used to assess LV function before and after AVR according to the guideline. Severe AS was defined by at least five-fold increase in trans-valvular aortic velocity with respect to sub-valvular velocity, aortic valve area<1.0 cm² and a mean trans-valvular gradient >40 mmHg. LV systolic dysfunction were defined as LV ejection function (EF) <50%. Pulmonary hypertension was recorded as a RV-RA peak pressure drop >40 mmHg. Clinical data were collected including demographics, symptoms, comorbidities.
(diabetes, hypertension, coronary artery disease, renal dysfunction, anemia et al), surgical data (urgent operation, valve used and bypass time), NYHA functional class and survival status. Patients underwent clinical and echocardiographic follow-up within 1 week of surgery and then every 3–6 months thereafter. Peri-operative mortality and med-term follow up mortality were measured for outcome evaluation. Post-operative LV functional recovery was defined as improvement of LVEF >10%.

**TAVI patients:** In study IV, I studied 89 consecutive patients with symptomatic severe AS who underwent transapical (TA) or transfemoral (TF) TAVI procedures between 2008 to early 2012. These patients were deemed unsuitable for surgical AVR because of either technical reasons or serious comorbidities as judged by EuroSCORE or the Society of Thoracic Surgeons (STS) scoring system. They were carefully studied by the Heart Centre multidisciplinary team and recruited for TAVI procedure, having fulfilled the published suggestions for inclusion (130)

45/89 patients received TA (age 80.8±4.9 year, 26 male) at Umeå Heart Center and 44 underwent TF (age 82.9±5.8 year, 22 male) at the Karolinska Institute, Stockholm. TAVI procedures were performed according to the methods described in the literatures (109,130). Patients’ general clinical data including demograheics, comorbidities, TAVI procedure information and peri-operative survival were compared between two groups. Conventional 2–D Doppler and 2-D strain echocardiographic examination were performed prior to and within 7 days after TAVI procedures. Severe AS was identified by aortic valve mean pressure gradient >40 mmHg or valve area <1.0 cm². LV systolic dysfunction was identified as ejection fraction (EF) <50%. LV function was compared before and after TAVI in each group and between groups. The study design and protocol were approved by the General Ethics Committee of Umeå and Karolinska Institute.

**SAVR and TAVI procedure**

**Surgical AVR**

Conventional surgical AVR were performed by 2 experienced surgeons at The Royal Brompton Hospital. The aorta was cannulated just proximal to the innominate artery and the right atrium was cannulated in the area of the appendage using a two-staged venous cannula. Extracorporeal circulation was then established with mild to moderate hypothermia and a standard AVR was performed during cardioplegic arrest. Cold crystalloid or cold blood cardioplegia
was delivered antegrade and/or retrograde. Both mechanical and bioprostheses (stent or stentless) were used according to the surgeon’s own assessment and preference.

**TAVI procedure in two approaches**

**Trans-femoral approach**

The trans-femoral approach was performed fully percutaneously under general or local anesthesia. It started with either a standard percutaneous femoral arterial access or a surgical exposure of the artery. After the percutaneous access was established the aortic valve was crossed and a stiff exchange guide wire was placed in the LV and a balloon valvuloplasty pre-dilated the native valve. Accurate assessment of the aortic root and dimension measurements were made from CT angiography and transesophageal echocardiography (TEE) images before valve implantation.

**Trans-apical approach**

Patients received general anaesthesia and a left sided anterolateral mini-thoracotomy, opening the anterolateral segment of the pericardium near the apex. TEE is of great value in helping to localize the LV apex. Puncture is made and a 0.035-inch guide wire is passed through the aortic native valve. External temporary pacing wires were attached to the LV apex. An arterial needle puncture allowed placement of a 6F sheath through the apex into the LV cavity using a standard over-the-wire technique. A stiff support wire was then positioned across the arch and placed into the descending aorta. Under a rapid ventricular pacing, balloon aortic valvuloplasty was performed and the valve was delivered under fluoroscopy and TEE for optimum positioning.

**Echocardiographic Assessment**

**Application of echocardiographic technique**

Conventional echocardiographic techniques were used both in SAVR patients and TAVI patients, while in addition, the 2-D strain or 2-D speckle tracking imaging (STI) was only applied in the TAVI group to evaluate LV longitudinal strain and twist function. The reason for this is because SAVR patients were examined before 2003 and some new techniques had not been available.
In the SAVR patients, echo measurements used either a Hewlett-Packard 2500 echocardiograph interfaced to a 2.5 MHz phased-array transducer (prior to 1999) or a Phillips Agilent Sonos 5500 system and a multifrequency transducer (Andover, MA, USA). A Vivid 7 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a phased array transducer (1.5–4 MHz) or an IE33 ultrasound system (Philips, Bothell, WA USA) equipped with a broadband (1–5 MHz) S5-1 transducer were used in TAVI patients.

Conventional echocardiographic measurements

Echocardiographic images were taken before and after AVR according to the guidelines of the American Society of Echocardiography (131,132). The LV end diastolic and end-systolic dimensions (LVEDD and LVESD) were taken at end diastole (the onset of the QRS complex) and at end systole A2 (the first high frequency vibration of the aortic component of the second heart sound on the phonocardiogram), respectively, using leading edge methodology from M-mode recordings of the parasternal long axis view. A2 was identified as the sound synchronous with the onset of the closure artifact on the aortic pulsed Doppler trace. LV dimensions were indexed to the body surface area. LV ejection fraction (EF) was estimated by 2D Simpson’s method. LV outflow tract diameter (LVOT), septal and posterior wall thickness were measured from the parasternal long-axis view using the 2D or M-mode techniques. The LV mass was calculated using the Penn conversion equation (133,134), and corrected for body mass index:

\[
\text{LV mass (gm)} = 1.04 \times (\text{LVEDD} + \text{IVST} + \text{LVPWTd})^3 - \text{LVEDD}^3 - 13.6 \quad (\text{study I})
\]

\[
\text{LV mass (gm)} = 0.8 \times (1.04(\text{LVEDD} + \text{IVST} + \text{LVPWTd})^3 - \text{LVEDD}^3) + 0.6 \quad (\text{study II})
\]

Where EDD=end-diastolic dimension, IVSTd=interventricular septal thickness at end-diastole, PWTd=posterior wall thickness at end-diastole. LA and septal and posterior wall thickness were taken from the parasternal long-axis view using the M-mode technique, according to the conventionally published criteria by the American Society of Echocardiography (132). Left atrial volume (LAV) was measured from LV apical 4-chamber view, and was calculated using an ellipsoid model (132). LAV index (LAVi) was obtained by normalizing absolute measurements to BSA. Continuous wave Doppler recordings were obtained from the apical five-chamber view to measure the maximum velocity (V) across the aortic valve and velocity-time integral (VTI). Peak aortic systolic pressure gradient (peak aortic SPG) was calculated from the Doppler velocities using the modified Bernoulli equation (peak SPG=4V²). Aortic valve area was calculated from LVOT
diameter and VTI was calculated by the continuity equation (135). \(AVA = CSA_{LVOT} \times VTI_{LOVT}/VTI_{AV}\). CSA_{LVOT} (cross sectional area) is calculated by \(\pi (d/2)^2\) with \(d\) is LVOT diameter. VTI_{LOVT} and VTI_{AV} are flow velocity-time integral derived from Doppler LVOT and trans-aortic valve velocities. Sub-aortic peak velocity was measured from the same view by pulsed wave Doppler with the sample volume positioned 5-10 mm beneath the aortic valve leaflet level. The indexed effective orifice area (EOA) for each prosthesis was calculated from the normal reference value of EOA divided by the patient’s body surface area [14]. Severity of prosthesis-patient mismatch (PPM) was defined as mild, moderate or severe if the indexed EOA was >0.85 cm\(^2\)/m\(^2\), 0.65 cm\(^2\)/m\(^2\) to 0.85 cm\(^2\)/m\(^2\) and<0.65 cm\(^2\)/m\(^2\), respectively as previously reported (136). Trans-mitral flow velocities were measured by placing a 2 mm size sample volume of pulsed wave Doppler at the tip of mitral valve leaflets from the apical 4-chamber view. Peak early diastolic velocity (E), peak atrial filling velocity (A), E/A ratio, E wave deceleration time (DT) and isovolumic relaxation time (IVRT) were measured from the LV filling recordings. Total ejection time (ET), total filling time (FT), LV myocardial performance index (Tei index) and total isovolumic time (tIVT) were obtained as previously described (137). Tricuspid regurgitation (TR) was assessed by color flow and continuous wave Doppler from the apical 4-chamber view. Pulmonary artery systolic pressure was estimated from right ventricular systolic pressure (peak retrograde) as TR pressure drop + right atrial (RA) pressure.

Systolic septal radial motion (study IV) was measured as the extent of anterior septal motion with respect to its position in end-diastole using the M-mode technique from the parasternal long-axis view. Positive (+) motion was towards the LV cavity and negative (-) motion was towards the RV cavity.

LV and RV free wall M-mode long axis systolic amplitudes were recorded as previously reported (138). Mitral annular plane systolic excursion (MAPSE) was obtained from the apical four-chamber view with the M-mode cursor placed at the LV lateral and septal angles of the mitral annulus. MAPSE was measured as the distance between the innermost point and outermost point of the motion displacement (139,140). Tricuspid annulus plane systolic excursion (TAPSE) was measured by M-mode from apical four-chamber view at the RV free wall. TAPSE was measured as the distance between the innermost point and outermost point of the motion displacement.

All M-mode and Doppler velocity recordings were made using a sweep speed of 100 mm/s, with ECG (lead II) and phonocardiogram superimposed.
2- D Speckle tracking echocardiography (study IV)

Gray scale digital cine loops triggered to the QRS complex were acquired from the LV apical 4-chamber view and from the two LV short-axis planes at the basal and apical levels. Care was taken to ensure that the basal short-axis plane contained the mitral valve. The apical plane was acquired as previously described (141). Segmental systolic strain, peak displacement and time from the onset of QRS to peak displacement were analyzed from the LV apical 4-chamber view. Rotation and twist were measured from the short-axis views. At each plane, three consecutive cardiac cycles were acquired during quiet breath-hold at a frame rate of 60-70 f/s, without using dual focus, and were stored on a hard disk for off-line analysis.

Left ventricular longitudinal strain (study IV)

LV longitudinal strain measurements were obtained using 2-D speckle tracking of the apical 4-chamber images, and an average frame rate of 60 frames per second. The LV longitudinal function was analyzed using a 2-D cardiac performance analysis (2-D CPA) software (TomTec imaging system, Germany). 2-D CPA is a speckle tracking based analysis tool that can analyze 2D data from various ultrasound machines that has been previously validated with sonomicrometry (142,143). 2D strain was measured as previously described. From the 4-chamber view the endocardial border was traced at end-systole. The software automatically tracked the contour on subsequent frames. Adequate tracking was also verified in real-time and corrected by adjusting the ROI or manually correcting the contour to ensure optimal tracking. Average longitudinal strain was calculated from six segments from basal, middle and apical regions of the septal and lateral wall.

Twist function (study IV)

It has been known for years that the heart rotates along its long-axis with a wringing (twisting) motion. Echocardiographic measurement of rotation and twist function is an optimal tool for studies of cardiac mechanics of diseased and healthy hearts. Looking from the apex, the LV base rotates clockwise (negative value) and the apex rotates counter-clockwise (positive value), producing a wringing motion. The net rotation difference between apex and base is called cavity twist.

The twist function before and within 7 days after AVR were measured in this study.
Short-axis recordings were acquired from the basal and apical segments to study cavity rotation function. The basal plane was identified as that including the tips of the mitral leaflets, and the apical plane distal to the papillary muscles. Particular attention was paid to have the LV cross section as circular as possible. Regional rotation was measured by tracing the endocardial border of the basal and apical sections, and the software provided different angles of six equidistant regions around the short axis circumference. Adequate tracking was also verified in real-time and corrected by adjusting the ROI or manually correcting the contour to ensure optimal tracking. LV apical or basal rotation was calculated as the average angular displacement of the 6 myocardial segments along the central axis. Counterclockwise LV rotation was expressed as a positive value and clockwise LV rotation as a negative value. The net difference in peak rotation angles at the two short-axis levels was used to calculate LV twist (145).

**Statistical analysis**

All statistics were processed using standard statistical software package of Social Science (SPSS, Inc., Chicago, IL, USA) version 13 for study I-III and 19 for study IV respectively. Normally distributed continuous variables are presented as mean ± standard deviation or mean±standard error. Categorical variables are expressed as numbers (n) and percentages (%). Comparisons between groups were made using the unpaired t-test (continuous variables). Paired t-test was used to compare pre and post-operative (SAVR or TAVI) data (continuous variables). Chi-square test was used to assess gender, comorbidities and survival rate difference between groups before and after SAVR or TAVI. A p-value <0.05 was considered statistically significant.

**Study I-II:**

Life table estimated actuarial survival was calculated by Kaplan–Meier curve in the first two studies, wherein the log-rank x² values was presented (Study II). Correlation analysis was made to compare the relationship between various pre-operative variables and mortality after AVR in a univariate model, followed by multivariate analysis in a Cox proportional hazards regression model. A p-value <0.05 was considered statistically significant.

**Study II-III:**

Receiver-operating-characteristic (ROC) curves were analyzed to assess the best
cut-off value that predicts mortality (Study II) and post-op LV systolic function recovery (Study III). A $p$ value $< 0.05$ and $p \leq 0.01$ were considered statistically significant and highly significant respectively.

**Reproducibility**

Intra-observer and inter-observer variability were assessed in 20-25 randomly selected patients. Variability was calculated as the mean percent error, derived as the absolute difference between 2 sets of measurements, divided by the mean of the observations (146).
Results

Clinical characteristics of the studied population

Both patients in SAVR studies and TAVI studies had degenerative aortic valve stenosis needing AVR procedure.

SAVR studies

A total of 221 severe AS patients underwent AVR between 1998 to 2003, conforming the first three studies: 86 patients in study I and 66 in study III had LV systolic dysfunction with LVEF<50%, 112 elderly and 72 younger patients included in study II. Patient’s clinical characteristics, echocardiographic measurements, early and median-term survival and cavity function recovery predictors are listed in tables.

TAVI study

Between 2008 and early 2012, 89 patients with symptomatic severe AS who successfully underwent TAVI procedure were retrospectively studied, 45 of whom received transapical (TA) TAVI at Umeå Heart Center, and 44 transfemoral (TF) TAVI at the Karolinska Institute, Stockholm. Patients had similar demographics and comorbidities pre-operatively, except the echo measurements showing higher LAVi, LVMi and tricuspid regurgitation pressure drop (TRPdrop) in TA group.
Study I: Predictors of survival after aortic valve replacement in patients with low-flow and high-gradient aortic stenosis

Proposal

To identify predictors of survival following aortic valve replacement (AVR) in patients with low-flow and high-gradient aortic stenosis (AS).

All 86 patients (mean age 71±10 years, range 32–87 years, 69 male) were symptomatic severe AS preoperatively. There was no difference in age, gender, QRS duration, haemoglobin level, prevalence of myocardial infarction, hypertension, or diabetes, cross-clamp time, valve size or type (stented or stentless). Clinical and echocardiographic parameters between survival and died patients are listed in (Table 1).

Table 1 showed 9 patients died within 30 days of AVR (six from cardiac failure, two from refractory post-operative haemorrhage, one from septicaemia), resulting in a peri-operative mortality of 10%. Compared with survived, died patients had significantly reduced LVEF, higher E/A ratio, peak systolic pulmonary artery pressure and serum creatinine (all p<0.001). Died patients were also clinically worse than the survived with higher NYHA function, more CABG and longer bypass time.

Overall mortality

Median duration of follow-up was 46 months (interquartile range 19–73 months). In addition to the nine deaths which occurred during the peri-operative period, four further patients died between 1 and 3 months after AVR (two from respiratory infection and two from cardiac failure), and two more patients died during follow-up (both from cardiac failure). Survival at 1, 3, and 4 years was therefore 85, 84, and 83%, respectively (Figure 1).

Predictors of mortality

Univariate predictors of mortality were: lower LVEF (HR: 0.68 per percentage increase, CI: 0.60–0.78, p< 0.001), PSPAP (HR: 1.07, CI: 1.05–1.09, p<0.001), the presence of restrictive LV filling (HR: 3.52, CI: 2.06–6.01, p< 0.001), higher serum creatinine (HR: 1.01, CI: 1.00–1.01, p< 0.001), concomitant CABG (HR: 4.93, CI: 1.10–22.1, p=0.037), the presence of AF (HR: 2.01, CI: 1.01–10.5, p= 0.039), longer cardiopulmonary bypass time (HR: 1.01, CI: 1.00–1.02, p= 0.041),
and the need for emergency surgery (HR: 3.10, CI: 1.04–9.25, p = 0.043, Table 2).
Although patients were not matched, 15 of 64 patients who received a stented valve died, while none of the 22 patients with a stentless valve died ($x^2$ 6.25, p = 0.025).

Independent predictors of mortality were pre-operative LVEF<40% (HR: 0.74, CI: 0.63–0.89, p = 0.030), the presence of restrictive LV filling (HR: 1.77, CI: 1.04–2.98, p = 0.033), and PSPAP >45 mmHg (HR: 2.71, 1.49–3.99, p = 0.01, Table 2).

Table 1. Peri-operative mortality: patient demographics, surgical data and echocardiographic measurements

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All patients (n = 86)</th>
<th>Peri-operative mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survived (n=77)</td>
<td>Died (n = 9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 10</td>
<td>71 ± 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74 ± 7</td>
</tr>
<tr>
<td>Male:female, n</td>
<td>69:17:00</td>
<td>61:16:00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8:01</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>108 ± 24</td>
<td>108 ± 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>112 ± 15</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>119 ± 54</td>
<td>111 ± 29</td>
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<tr>
<td></td>
<td></td>
<td>185 ± 130***</td>
</tr>
<tr>
<td>NYHA class III-IV, n (%)</td>
<td>59 (69)</td>
<td>50 (65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 (100)*</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>50 (58)</td>
<td>42 (55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 (89)*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>38 (44)</td>
<td>33 (43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (56)</td>
</tr>
<tr>
<td>Type II diabetes, n (%)</td>
<td>32 (37)</td>
<td>28 (37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (45)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>14 (16)</td>
<td>9 (12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (56)*</td>
</tr>
<tr>
<td>Surgical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency surgery, n (%)</td>
<td>34 (40)</td>
<td>27 (35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (78)*</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>119 ± 39</td>
<td>116 ± 37</td>
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<tr>
<td></td>
<td></td>
<td>144 ± 49***</td>
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<tr>
<td>Cross-clamp time (min)</td>
<td>82 ± 28</td>
<td>82 ± 29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76 ± 23</td>
</tr>
<tr>
<td>Prosthesis diameter (mm)</td>
<td>23 ± 2</td>
<td>23 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 ± 2</td>
</tr>
<tr>
<td>Stented valve, n (%)</td>
<td>64 (74)</td>
<td>55 (71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 (100)</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>50 (58)</td>
<td>42 (55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 (89)*</td>
</tr>
<tr>
<td>Echocardiographic data</td>
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</tr>
<tr>
<td>LVEDD (mm)</td>
<td>58 ± 8</td>
<td>58 ± 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 ± 8</td>
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<td>LVESD (mm)</td>
<td>47 ± 7</td>
<td>46 ± 7</td>
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<td></td>
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<td>51 ± 7</td>
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<td>LVEF (%)</td>
<td>40 ± 9</td>
<td>42 ± 87</td>
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<tr>
<td></td>
<td></td>
<td>31 ± 5***</td>
</tr>
<tr>
<td>SV/BSA (mL/m²)</td>
<td>39 ± 10</td>
<td>39 ± 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37 ± 9</td>
</tr>
<tr>
<td>LVMI (gm/m²)</td>
<td>255 ± 87</td>
<td>253 ± 88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>274 ± 81</td>
</tr>
<tr>
<td>AVMG (mmHg)</td>
<td>48 ± 6</td>
<td>50 ± 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47 ± 7</td>
</tr>
<tr>
<td>E:A ratio</td>
<td>2.7 ± 1.7</td>
<td>2.5 ± 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.8 ± 1.1***</td>
</tr>
<tr>
<td>PSPAP (mmHg)</td>
<td>27 ± 17</td>
<td>24 ± 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52 ± 9***</td>
</tr>
</tbody>
</table>

A, peak late diastolic velocity; AVPG, aortic valve pressure gradient; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery disease; CPB, cardiopulmonary bypass; E, peak early diastolic velocity; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NYHA, New York Heart Association; PSPAP, peak systolic pulmonary artery pressure; SV, stroke volume. *P, 0.05. **P, 0.01. ***P, 0.001 non-survivors vs. survivors.
Figure 1. Overall Kaplan–Meier survival plot (including 95% confidence limits).

Table 2  Predictors of mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>0.68 (0.60–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSPAP &gt;45 mmHg</td>
<td>1.07 (1.05–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Restrictive LV filling</td>
<td>3.52 (2.06–6.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>1.01 (1.00–1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>4.93 (1.10–22.1)</td>
<td>0.037</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.01 (1.01–10.5)</td>
<td>0.039</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>1.01 (1.00–1.02)</td>
<td>0.041</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>3.10 (1.04–9.25)</td>
<td>0.043</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>6.52 (0.85–49.9)</td>
<td>0.071</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.00 (0.95–1.05)</td>
<td>0.919</td>
</tr>
<tr>
<td>Gender</td>
<td>3.37 (0.44–25.7)</td>
<td>0.242</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>1.00 (0.98–1.02)</td>
<td>0.567</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1.35 (0.47–3.83)</td>
<td>0.578</td>
</tr>
<tr>
<td>Prosthesis diameter (mm)</td>
<td>1.02 (0.80–1.29)</td>
<td>0.895</td>
</tr>
<tr>
<td>AVMG (mmHg)</td>
<td>0.97 (0.94–1.02)</td>
<td>0.205</td>
</tr>
<tr>
<td>SV/BSA (mL/m²)</td>
<td>1.01 (0.77–1.34)</td>
<td>0.612</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>1.19 (0.85–2.91)</td>
<td>0.77</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>1.21 (0.90–2.61)</td>
<td>0.27</td>
</tr>
<tr>
<td>LVMI (gm/m²)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.675</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>1.26 (0.81–2.57)</td>
<td>0.128</td>
</tr>
<tr>
<td><strong>Multivariate predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSPAP &gt;45 mmHg</td>
<td>2.71 (1.49–3.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>0.74 (0.63–0.89)</td>
<td>0.03</td>
</tr>
<tr>
<td>Restrictive LV filling</td>
<td>1.77 (1.04–2.98)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

AVMG=aortic valve mean pressure gradient; BSA= body surface area; CABG=coronary artery bypass graft; CI=confidence interval; CPB cardiopulmonary bypass; LVEDD= left ventricular end-diastolic dimension; LVESD= left ventricular end-systolic dimension; LVEF=left ventricular ejection fraction; LVMI= left ventricular mass index; NYHA=New York Heart Association; PSPAP= peak systolic pulmonary artery pressure; SV=stroke volume.
Study II: Early and long-term survival after aortic valve replacement in septuagenarians and octogenarians with severe aortic stenosis

Proposal

To identify predictors of mortality following AVR in elderly patients with severe AS.

112 consecutive elderly AS patients (aged 77±2 years) were compared with 72 younger patients (aged 60±1 years). Clinical and echocardiographic data of LV function were recorded before and 46 months after AVR. Elderly AS patients had a higher NYHA class before AVR (2.9±0 vs 2.7±0, p<0.05), were more anaemic (Hb 12.8±0.2 g/dl vs. 13.5±0.2 g/dl, p<0.01), and had a significantly higher prevalence of coronary artery disease (59% vs. 44%, p<0.05), atrial fibrillation (36 vs. 19%, p<0.01) and emergency operation (40% vs. 28%, p<0.05) than younger AS patients. Elderly patients also had higher LV mass index (242±6 g/m² vs. 221±9 g/m², p<0.05), shorter E wave DT (158±4 ms vs. 200±4 ms, p<0.001) and larger left atrial diameter (44±1 mm vs. 40±1 mm, p<0.001)(Table 3).

30 day and long-term mortality between elderly and younger patients

The Kaplan Meier survival curves for all cause 30-day and long-term mortality in the two patient groups is shown in Fig. 2 and 3 respectively.

At 30 days after surgery, the mortality rate among elderly patients was 12% as compared with 4% in younger patients, but this difference was not significant (Log rank x² 3.02, p=0.08). The long term mortality rate after 46-month follow up was significantly higher in elderly patients than younger counterparts (18% vs. 7%, Log rank x² 4.38, p=0.04).

The risks of death both at 30-day and long-term follow-up, however, were not significantly higher in elderly patients than younger patients after adjustment of other significant predictors by multivariate Cox regression models as illustrated in Table 4.
Fig. 2 Kaplan–Meier curves for 30-day all-cause mortality in 2 patient groups.

Log Rank $x^2 = 3.02$ (p = 0.08)

Fig. 3. Kaplan–Meier curves for long term all-cause mortality in 2 patient groups.

Log Rank $x^2 = 4.38$ (p = 0.04)
Table 3. Pre-operative characteristics: elderly vs. younger patients.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Elderly group (n = 112)</th>
<th>Younger group (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>77 ± 2</td>
<td>60 ± 1***</td>
</tr>
<tr>
<td>Male:female</td>
<td>76:36</td>
<td>56:16</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 2</td>
<td>71 ± 1*</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.9 ± 0</td>
<td>2.7 ± 0*</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12.8 ± 0.2</td>
<td>13.5 ± 0.2**</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>115 ± 3</td>
<td>109 ± 7</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>66 (59)</td>
<td>32 (44)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>15 (13)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>48 (43)</td>
<td>33 (46)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>22 (20)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>40 (36)</td>
<td>15 (19)**</td>
</tr>
<tr>
<td>Surgical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent operation, n (%)</td>
<td>45 (40)</td>
<td>20 (28)%</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>116 ± 4</td>
<td>122 ± 5</td>
</tr>
<tr>
<td>Stented valve, n (%)</td>
<td>80 (71)</td>
<td>47 (65)</td>
</tr>
<tr>
<td>Homograft</td>
<td>4 (4)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Stentless bioprosthesis</td>
<td>28 (25)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Stented bioprosthesis</td>
<td>73 (65)</td>
<td>28 (39)%</td>
</tr>
<tr>
<td>Mechanical</td>
<td>7 (6)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Effective orifice area index (cm²/m²)</td>
<td>9 (8)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>&lt; 0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.65–0.85</td>
<td>36 (32)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>&gt; 0.85</td>
<td>63 (56)</td>
<td>35 (49)</td>
</tr>
<tr>
<td>Not applicable (homograft)</td>
<td>4 (4)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>242 ± 6</td>
<td>221 ± 9*</td>
</tr>
<tr>
<td>Peak AV gradient (mmHg)</td>
<td>74 ± 2</td>
<td>74 ± 3</td>
</tr>
<tr>
<td>Mean AV gradient (mmHg)</td>
<td>48 ± 1</td>
<td>49 ± 2</td>
</tr>
<tr>
<td>Aortic valvular area index (cm²/m²)</td>
<td>0.3 ± 0.0</td>
<td>0.3 ± 0.0</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>54 ± 2</td>
<td>57 ± 2</td>
</tr>
<tr>
<td>LV ejection fraction &lt; 50% (n, %)</td>
<td>17/112 (15%)</td>
<td>10/72 (14%)</td>
</tr>
<tr>
<td>Mitral E (cm/s)</td>
<td>96 ± 3</td>
<td>88 ± 3</td>
</tr>
<tr>
<td>Mitral A (cm/s)</td>
<td>65 ± 3</td>
<td>67 ± 4</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>158 ± 4</td>
<td>200 ± 4***</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>44 ± 1</td>
<td>40 ± 1***</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>33 ± 1</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Effective orifice area index (cm²/m²)</td>
<td>0.94 ± 0.02</td>
<td>0.93 ± 0.03</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day all cause mortality</td>
<td>13 (12)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Long-term all cause mortality</td>
<td>20 (18)</td>
<td>5 (7)*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard error. AV: aortic valve; LA: left atrial; LV: left ventricle; E: peak early diastolic velocity; A: peak late diastolic velocity; PASP: pulmonary artery systolic pressure

*p<0.05, **p<0.01, ***p<0.001 for comparisons between patient groups.
Table 4  Multivariate Models of 30-day and long term mortality in the entire cohort of AS patients.

<table>
<thead>
<tr>
<th>Multivariate models</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30-day mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 70 vs. Age &lt; 70</td>
<td>0.82 (0.11–6.32)</td>
<td>0.85</td>
</tr>
<tr>
<td>Anemia (Hb &lt; 10 g/dl)</td>
<td>1.63 (0.47–5.58)</td>
<td>0.43</td>
</tr>
<tr>
<td>Renal dysfunction (Cr &gt; 120 mmol/dl)</td>
<td>2.82 (0.78–10.18)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>1.02 (1.01–1.05)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.85 (1.06–3.22)</td>
<td>0.03</td>
</tr>
<tr>
<td>DT</td>
<td>0.98 (0.95–1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>PASP</td>
<td>1.02 (0.87–1.25)</td>
<td>0.72</td>
</tr>
<tr>
<td>Significant PPM (EOA index &lt; 0.85 cm²/m²)</td>
<td>2.96 (1.02–10.41)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Long-term mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 70 vs. Age &lt; 70</td>
<td>0.84 (0.17–4.11)</td>
<td>0.83</td>
</tr>
<tr>
<td>Anemia (Hb &lt; 10 g/dl)</td>
<td>2.58 (0.98–6.67)</td>
<td>0.08</td>
</tr>
<tr>
<td>Renal dysfunction (Cr &gt; 120 mmol/dl)</td>
<td>2.48 (0.88–6.28)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>1.02 (1.01–1.04)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.09 (1.24–3.12)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>DT</td>
<td>0.89 (0.88–1.12)</td>
<td>0.21</td>
</tr>
<tr>
<td>PASP</td>
<td>4.11 (2.02–8.21)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

AV: aortic valve; LA: left atrial; LV: left ventricle; E: peak early diastolic velocity; A: peak late diastolic velocity; DT: deceleration time; PASP: pulmonary artery systolic pressure

Survivors vs. non-survivors in elderly

Mortality in the elderly group was associated with: higher NYHA functional class (3.3±0.1 vs 2.8±2.1, p<0.01), lower Hb level (11±0 g/dl vs 13±0 g/dl, p<0.01), worse renal dysfunction (serum Cr 135±7 mmol/l vs. 113±3 mmol/l), higher prevalence of atrial fibrillation (55% vs. 32%, p<0.05) and emergency operation (60% vs. 36%, p<0.05), longer CPB time (132±11 min vs. 113±4 min, p<0.05), smaller aortic valve effective orifice area index (0.81±0.04 cm²/m² vs. 0.95±0.02 cm²/m², p<0.01), worse LV diastolic dysfunction and raised left atrial pressure (higher E/A ratio; 3.1±0.2 vs. 1.7±0.1, shorter DT; 133±2 ms vs. 163±4 ms, p<0.01 for all) and higher PASP (50±3 mmHg vs. 30±1 mmHg, p<0.01) (Table 5). A higher prevalence of restrictive LV filling was observed in nonsurvivors (75% vs. 40%, p<0.05, )(Fig.4).
Table 5  Pre-operative characteristics: survivors vs non-survivors in elderly.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Survivors (n = 92)</th>
<th>Non-survivors (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77 ± 0</td>
<td>78 ± 1</td>
</tr>
<tr>
<td>Male:female, n</td>
<td>63:29</td>
<td>13:07</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 1</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.8 ± 0.1</td>
<td>3.3 ± 0.1**</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13 ± 0</td>
<td>11 ± 0**</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>112 ± 3</td>
<td>135 ± 7*</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>52 (57)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>40 (43)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>17 (20)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>29 (32)</td>
<td>11 (55)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical data</th>
<th>Survivors (n = 92)</th>
<th>Non-survivors (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent operation, n (%)</td>
<td>33 (36)</td>
<td>12 (60)*</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>113 ± 4</td>
<td>132 ± 11†</td>
</tr>
<tr>
<td>Stented valve, n (%)</td>
<td>65 (71)</td>
<td>15 (75)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiographic data</th>
<th>Survivors (n = 92)</th>
<th>Non-survivors (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOA index (cm²/m²)</td>
<td>0.95 ± 0.02</td>
<td>0.81 ± 0.04**</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>236 ± 6</td>
<td>266 ± 10</td>
</tr>
<tr>
<td>Peak AV gradient (mmHg)</td>
<td>76 ± 2</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>Mean AV gradient (mmHg)</td>
<td>49 ± 2</td>
<td>41 ± 4*</td>
</tr>
<tr>
<td>Aortic valvular area index (cm²/m²)</td>
<td>0.3 ± 0.0</td>
<td>0.3 ± 0.0</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>55 ± 2</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>Mitral E (cm/s)</td>
<td>93 ± 3</td>
<td>111 ± 6*</td>
</tr>
<tr>
<td>Mitral A (cm/s)</td>
<td>70 ± 3</td>
<td>41 ± 5**</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.7 ± 0.1</td>
<td>3.1 ± 0.2**</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>163 ± 4</td>
<td>133 ± 2**</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>44 ± 0</td>
<td>46 ± 1</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>30 ± 1</td>
<td>50 ± 3**</td>
</tr>
</tbody>
</table>

Data are presented as mean± standard error.

*p<0.05, **p<0.01  for comparisons between groups.

Predictors of early (30-day) and long-term mortality in the elderly

By multivariate analysis, anemia (OR 4.20, CI: 1.02–6.86, p=0.04), cardiopulmonary bypass time (OR 1.02, CI 1.01–1.04, p<0.01), prosthesis patient mismatch (OR 5.43, CI 1.04–18.40, p<0.05) predicted early mortality in the elderly patients. The long-term mortality of the same group was related to CBP time (OR 1.02, CI 1.00–1.05, p=0.04), patient prosthesis mismatch (OR 4.64, CI 1.33–16.11, p=0.02), raised left atrial pressure: DT (OR 0.94, CI 0.84–0.99, p=0.03) and peak systolic pulmonary artery pressure (OR 1.12, CI 1.03–1.19, p<0.001) (Table 6).
<table>
<thead>
<tr>
<th></th>
<th>Clinical &amp; Echocardiographic data</th>
<th>30-day all-cause mortality</th>
<th>Long term all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>(p), OR (95% CI)</td>
<td>(p), OR (95% CI)</td>
<td>ROC (AUC, (p))</td>
</tr>
<tr>
<td>Age</td>
<td>0.35, 1.05(0.94–1.20)</td>
<td>0.34, 1.05(0.95–1.15)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.90, 1.08(0.33–3.52)</td>
<td>0.81, 0.89(0.36–2.23)</td>
<td></td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>0.32, 0.47(0.10–2.10)</td>
<td>0.04, 1.27(1.06–1.98)</td>
<td>0.27, 1.22(0.88–2.72)</td>
</tr>
<tr>
<td>Anemia (Hb &lt; 10 g/dl)</td>
<td>&lt; 0.01, 5.45(1.80–9.47)</td>
<td>0.04, 4.20(1.02–6.86)</td>
<td>0.66, 0.03</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0.02, 6.49(1.44–20.31)</td>
<td>0.29, 2.10(0.54–8.18)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.41, 1.65(0.51–5.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.78, 0.85(0.28–2.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.30, 1.88(0.55–7.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.41, 1.60(0.53–4.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent operation</td>
<td>0.31, 1.77(0.59–5.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB time</td>
<td>&lt; 0.01, 1.02(1.01–1.04)</td>
<td>&lt; 0.01, 1.02(1.01–1.04)</td>
<td>0.71, 0.01</td>
</tr>
<tr>
<td>Stented valve</td>
<td>0.29, 0.44(0.10–2.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.10, 1.01(0.99–1.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AV gradient</td>
<td>0.14, 0.97(0.94–1.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valvular area index</td>
<td>0.94, 1.38(0.15–5.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.63, 0.98(0.96–1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>&lt; 0.01, 2.20(1.36–3.56)</td>
<td>0.20, 1.58(0.79–3.16)</td>
<td>&lt; 0.001, 2.77(1.82–4.22)</td>
</tr>
<tr>
<td>Deceleration time</td>
<td>0.02, 0.94(0.89–0.98)</td>
<td>0.10, 0.92(0.84–1.02)</td>
<td>&lt; 0.01, 1.94(0.90–0.98)</td>
</tr>
<tr>
<td>LA size</td>
<td>0.26, 1.04(0.97–1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASP</td>
<td>&lt; 0.01, 1.04(1.01–1.07)</td>
<td>0.55, 1.01(0.97–1.06)</td>
<td>&lt; 0.001, 1.06(1.03–1.09)</td>
</tr>
<tr>
<td>Significant PPM</td>
<td>0.04, 3.83(1.02–14.45)</td>
<td>&lt; 0.05, 5.43(1.04–18.40)</td>
<td>0.63, &lt; 0.05</td>
</tr>
</tbody>
</table>
E/A ratio and PASP consistently performed better in predicting long-term mortality in the elderly group after AVR (area under the curve [AUC], 0.83 and 0.87 respectively, p<0.001 for both, Fig. 5). With a cut off value of PASP>40 mmHg, a sensitivity and specificity of 85% and 64% respectively were obtained to predict long-term mortality.

Fig.4 Distribution of LV filling patterns in elderly patients. *p<0.05 for comparisons between survivors and non-survivors.

Fig.5 The ROC curves for predicting long term all cause mortality as reflected by pre-operative PASP (solid line, area under curve 0.87, p<0.001) and E/A ratio (dotted line, area under curve 0.87, p<0.001).
Study III: Echocardiographic predictors of left ventricular functional recovery following valve replacement surgery for severe aortic stenosis

Proposal

To identify the most sensitive echocardiographic measurements that predict recovery of left ventricular function following valve replacement surgery in patients with severe AS and LV dysfunction.

All 66 patients (mean 70±2, 53 male) were symptomatic pre-operatively: 42 (64%) patients were in Class III and IV. 24 (36%) patients had associated pulmonary hypertension. Significant coronary artery disease (CAD) was present in 56% patients. 24 patients (36%) underwent urgent surgery after medical stabilization of recent decompensated congestive heart failure. 39 patients (60%) demonstrated LV functional recovery after successful AVR during the median 48-months follow-up. There was no significant difference between patient groups with or without LV functional recovery with respect to age, gender, NYHA functional class, follow-up duration and comorbidities. Surgical characteristics were similar in the two patient groups except a significantly higher prevalence of stented valve implantation in patients without LV functional recovery (p<0.01).

LV function after valve replacement

Peak aortic pressure gradient dropped (64±3 to 19±1 mmHg); and aortic valve area index increased after operation (0.30±0.01 to 0.89±0.03 cm²/m² p<0.001 for all) (Table 7). Post-operatively, there was significant reduction in indexed LV end-diastolic (LVEDD index 33±1 to 30±1 mm/m², p<0.001) and systolic dimensions (LVESD index 27±1 to 20±1 mm/m², p<0.001). LV mass index regressed (255±10 to 228±9 g/m²; p<0.01), and consequently LV EF increased from45±1 to 54±2% (p<0.001) after surgery. Post-operative improvement in diastolic function was evident by longer total LV filling time (FT 29.2±0.6 to 31.4±0.6 s/min; p<0.05) and lower E/A ratio (2.6±0.2 to 1.9±0.1, p<0.05).

Predictors of LV recovery

After initial univariate and subsequent multivariate analysis, the only two independent echocardiographic predictors were indexed LV end-diastolic and
end-systolic dimension. Receiver Operating Characteristic (ROC) for pre-operative LVESD index $<=27.5 \text{ mm/m}^2$ to predict intermediate-term LV recovery (area under the curve [AUC], 0.72, p=0.002). The cut-off value of LVESD index $<=27.5 \text{ mm/m}^2$ demonstrated a sensitivity and specificity of 73% and 64%, in predicting LV recovery (Fig.6).

Table 7 Impact of AVR on LV structure and function

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-operation</th>
<th>Post-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of AS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak aortic SPG (mmHg)</td>
<td>64±3</td>
<td>19±1***</td>
</tr>
<tr>
<td>Mean AG (mm Hg)</td>
<td>42±2</td>
<td>13±1***</td>
</tr>
<tr>
<td>AVA index</td>
<td>0.30±0.00</td>
<td>0.89±0.03***</td>
</tr>
<tr>
<td><strong>LV structure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD index (mm/m$^2$)</td>
<td>33±1</td>
<td>30±1***</td>
</tr>
<tr>
<td>LVESD index (mm/m$^2$)</td>
<td>27±1</td>
<td>20±1***</td>
</tr>
<tr>
<td>IVSTd (mm)</td>
<td>15.0±0.5</td>
<td>14.7±0.4</td>
</tr>
<tr>
<td>PWTd (mm)</td>
<td>13.6±0.4</td>
<td>13.3±0.3</td>
</tr>
<tr>
<td>LVMI (g/m$^2$)</td>
<td>255±10</td>
<td>228±9**</td>
</tr>
<tr>
<td><strong>LV function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>45±1</td>
<td>54±2***</td>
</tr>
<tr>
<td>ET (s/min)</td>
<td>22.2±0.5</td>
<td>19.2±0.4***</td>
</tr>
<tr>
<td>LV MPI</td>
<td>0.44±0.05</td>
<td>0.50±0.02</td>
</tr>
<tr>
<td>LV tIVT (s/min)</td>
<td>8.9±0.5</td>
<td>9.4±0.3</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.6±0.2</td>
<td>1.9±0.1*</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>57±4</td>
<td>69±3**</td>
</tr>
<tr>
<td>FT (s/min)</td>
<td>29.2±0.6</td>
<td>31.4±0.6**</td>
</tr>
</tbody>
</table>

Data are presented as mean±standard error. *: p<0.05; **: p<0.01; ***: p<0.001, pre-op versus post-op (paired t test). A: peak late diastolic velocity; peak aortic SPG: peak trans-aortic systolic pressure gradient; Mean AG: Mean aortic gradient; AVA: aortic valve area; AVAi: aortic valve area index to body surface area; E: peak early diastolic velocity; EDD: end-diastolic dimension; ESD: end-systolic dimension; ET: total ejection time; EF: ejection fraction; FT: total filling time; IVRT: isovolumic relaxation time; IVSTd: interventricular septal thickness; LVMI: left ventricular mass index; PWTd: posterior wall thickness.

Fig.6 The ROC curves for predicting intermediate-term LV recovery as reflected by pre-operative LVESD index (solid line) and LVEDD index (dotted line).
The positive and negative predictive values, using such cut-off value, were 0.69 and 0.85 respectively. Furthermore, the pre-operative LVESD index was consistently more sensitive than LVEDD index in predicting post-operative LV recovery (Fig. 7).

![Graph showing Pre-operative LV end-systolic dimension index vs Improvement of LV ejection fraction]

Fig. 7 A pre-operative LV end-systolic dimension index \( \leq 27.5 \text{ mm/m}^2 \) was 85.2% sensitive and 71.8% specific in predicting intermediate-term LV functional recovery \((p<0.001)\).

**Table 8 Echocardiographic predictors of post-operative LV functional recovery**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic gradient (mmHg)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>AVA index (cm/m²)</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Pre-operative LV EF (%)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>LVEDD index (mm/m²)</td>
<td>0.018</td>
<td>0.017</td>
</tr>
<tr>
<td>LVESD index (mm/m²)</td>
<td>&lt; 0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>LVMI (gm/m²)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>PASP &gt; 40 mmHg</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe PPM</td>
<td>0.59</td>
<td></td>
</tr>
</tbody>
</table>

**Long-axis systolic amplitude after AVR**

Biventricular free wall long axis systolic amplitudes (LSA) were recorded before and after surgery in 49 (74%) patients (Table 5). LV long axis systolic function echoed the improvement in short axis fractional shortening, increasing from 7.8±0.5 to 9.4±0.6mm, \((p=0.004)\), while RV long axis amplitude fell after surgery, from 14.7±0.6 to 10.9±0.5 mm \((p<0.001)\). Sub-group analysis revealed that patients with pre-operative LV end-systolic dimension index \( > 27.5 \text{ mm/m}^2 \) were characterized by poorer baseline LV long axis function (LSA 6.8±0.5 mm vs 8.8±0.6 mm, \(p=0.022\)) and lack of statistically significant long axis functional improvement (LSA 6.8±0.5 to 7.2±0.9 mm, \(p=0.387\)).
Study IV: Early effect of TAVI on left ventricular function-trans-apical vs. trans-femoral approach

Proposal

To compare transapical (TA) and transfemoral (TF) transcatheter aortic valve implantation effect on LV function in patients with severe AS.

A total of 89 patients successfully underwent TAVI, of whom 45 TA TAVI (age 80.9 ± 4.9 year, 26 male) and 44 TF TAVI (age 82.6 ± 5.8y, 22 male). Clinical data is listed in table 9. Echocardiographic measurements before and after procedures are listed in table 10-11.

Before TAVI

Patients’ clinical data including demographic information, comorbidities and intervention are listed in table 7. There was no significant difference in age, gender or BSA between the two groups of patients. Comorbidities were also similar in the two groups (all \( p > 0.05 \)). However, more patients in the TA group had paroxysmal AF within the first week after TAVI (\( p=0.002 \)). The same group of patients tended to have slightly longer hospital stay compared to the TF patients (\( p=0.08 \)). Two male patients who underwent TA TAVI died peri-operatively, one of multiple organ failure within 1 week of procedure and the other from sudden death within 10 days after hospital discharge. All TF patients survived the peri-operative period.

Pre-procedure ventricular function

LV EF, was equally reduced in the two groups (\( p=0.41 \)). Likewise, sepal motion tended to be lower in TA patients before procedure (\( p=0.06 \)). MAPSE at the lateral and septal sites was similarly reduced in the two groups (\( p=0.89 \) and \( p=0.87 \), respectively), when compared with normal range previously reported. LV longitudinal strain, LV basal, apical rotation and cavity twist were not different between groups (all \( p > 0.05 \)). However, LVMi was larger in the TA group (\( p=0.04 \)) as was LAVi (\( p=0.02 \))(Table 11). TRPdrop was also higher in TA patients (39.5±8.4 vs. 35.8±7.7 mmHg, \( p=0.03 \)).

Post-procedural ventricular function

In the patients group as a whole, one week after TAVI, AOPG (aortic pressure gradient) had dropped (\( p<0.001 \)), mean LVEDD index and LVESD index fell but EF
remained unchanged ($p=0.08$). Septal motion increased ($p=0.01$) as did lateral MAPSE ($p=0.005$) (Fig.8) but myocardial strain remained unchanged. Basal LV rotation increased ($p<0.04$), apical rotation reduced ($p=0.001$) and overall cavity twist reduced ($p<0.048$). LVMi slightly decreased ($p=0.04$) as did LAVi ($p<0.01$) (table 10).

**TA vs. TF approach**

The two patient groups showed different degrees of decline in LV cavity dimensions with significant LVESD index reduction only seen in TF groups ($p=0.02$) and a slight increase in LVEF ($p=0.04$). LVMi remained unchanged in the two groups ($p=0.09$ and 0.11, respectively). Septal motion did not significantly change in either group ($p=0.08$) but lateral MAPSE increased only in the TF ($p=0.02$) (Fig.8).

LV longitudinal strain remained unchanged in TA patients but apical lateral strain increased in TF group (Fig.9). LV apical rotation fell in the two groups ($p=0.04$ and 0.002, respectively) but basal rotation increased only in the TA patients ($p=0.02$). This resulted in unchanged LV twist function in TA ($p=0.32$) and normalized twist in TF patients ($p=0.048$) (Fig.10).

TRPdrop dropped in both groups (36.3±8.4 vs. 28.3±5.2 mmHg), particularly in the TF group compared with TA ($p<0.001$ vs. $p=0.03$). LAVi reduced in both groups and to a greater extent in the TF group ($p=0.006$ vs. $p=0.04$). (table 11)
Figure 10. Twist function changes after TAVI. LV basal rotation (A), LV apical rotation (B), LV twist (C).

9 Lateral strain changes after TAVI in all groups

TA: trans-apical
TF: transfemoral
**Table 9. Clinical data between trans-apical (TA) and trans-femoral (TF) TAVI approaches**

<table>
<thead>
<tr>
<th></th>
<th>TA(n=45)</th>
<th>TF(n=44)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>80.9 ± 4.9</td>
<td>82.6 ± 5.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>26 / 19</td>
<td>22 / 22</td>
<td>0.42</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.84 ± 0.19</td>
<td>1.78 ± 0.22</td>
<td>0.15</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.70 ± 0.13</td>
<td>0.67 ± 0.10</td>
<td>0.17</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>7 (15.2 %)</td>
<td>7 (15.9 %)</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (19.6 %)</td>
<td>7 (15.9 %)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (65.2 %)</td>
<td>35 (76.0 %)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (15.2 %)</td>
<td>9 (20.4 %)</td>
<td>0.51</td>
</tr>
<tr>
<td>AF (paroxysmal)</td>
<td>9 (19.6 %)</td>
<td>14 (31.8 %)</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine</td>
<td>97.0 ± 30.9</td>
<td>107.0 ± 46.8</td>
<td>0.24</td>
</tr>
<tr>
<td>&gt;110mmol/l (n, %)</td>
<td>10(22.2 %)</td>
<td>15 (34.1 %)</td>
<td>0.19</td>
</tr>
<tr>
<td>Logistic Euroscore&gt; 15%</td>
<td>28 (62%)</td>
<td>24 (55%)</td>
<td>0.46</td>
</tr>
<tr>
<td>NYHA III-IV</td>
<td>44(95.7 %)</td>
<td>41 (93.2 %)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>TAVI procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>45 (100%)</td>
<td>25 (56.8%)</td>
<td></td>
</tr>
<tr>
<td>Prosthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve type</td>
<td>Edwards-Sapien (100%)</td>
<td>Core-Valve (100%)</td>
<td></td>
</tr>
<tr>
<td>Size(mm)</td>
<td>23 / 26 / 29</td>
<td>(3 / 35 / 7)</td>
<td></td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-op stroke</td>
<td>2 (4.3 %)</td>
<td>2 (4.5 %)</td>
<td>0.64</td>
</tr>
<tr>
<td>AF (paroxysmal)</td>
<td>15 (32.6 %)</td>
<td>2 (4.5 %)</td>
<td>0.002</td>
</tr>
<tr>
<td>Post-op Creatinine</td>
<td>105.3 ± 49.3</td>
<td>110.2 ± 53.9</td>
<td>0.65</td>
</tr>
<tr>
<td>&gt;110mmol/L</td>
<td>11 (24.4 %)</td>
<td>16 (36.4 %)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>8.7 ± 3.9</td>
<td>7.4 ± 3.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Survival 30 days</td>
<td>43 (95.5 %)</td>
<td>44 (100 %)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

All values are presented as mean±SD.

### Table 10. Early LV function changes in whole patients underwent TAVI

<table>
<thead>
<tr>
<th></th>
<th>Before TAVI</th>
<th>1 week After TAVI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AV gradient (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak PG</td>
<td>70 ± 22</td>
<td>21 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean PG</td>
<td>46 ± 10</td>
<td>12 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVi (ml/m²)</td>
<td>41.0 ± 14</td>
<td>38.4 ± 12</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEDD index (mm²/m³)</td>
<td>28.4 ± 4.0</td>
<td>27.6 ± 3.6</td>
<td>0.045</td>
</tr>
<tr>
<td>LVESD index (mm²/m³)</td>
<td>20.3 ± 4.5</td>
<td>19.3 ± 3.9</td>
<td>0.011</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50.4 ± 14.4</td>
<td>51.9 ± 12.2</td>
<td>0.08</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>153 ±38</td>
<td>149 ± 29</td>
<td>0.04</td>
</tr>
<tr>
<td>Septal motion (mm)</td>
<td>3.9 ± 1.3</td>
<td>4.3 ± 1.4</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MAPSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lateral (mm)</td>
<td>11.1±2.8</td>
<td>11.8±2.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Septal (mm)</td>
<td>10.1±2.8</td>
<td>10.5±2.3</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>LV strain (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-lateral</td>
<td>14.82 ± 5.88</td>
<td>15.89 ± 5.93</td>
<td>0.06</td>
</tr>
<tr>
<td>Mid-lateral</td>
<td>12.13 ± 5.26</td>
<td>12.54 ± 5.30</td>
<td>0.47</td>
</tr>
<tr>
<td>Api-lateral</td>
<td>15.74 ± 5.91</td>
<td>15.72 ± 6.56</td>
<td>0.98</td>
</tr>
<tr>
<td>Basal-septal</td>
<td>10.53 ± 4.90</td>
<td>11.13 ± 4.58</td>
<td>0.24</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>13.93 ± 5.84</td>
<td>14.69 ± 4.79</td>
<td>0.18</td>
</tr>
<tr>
<td>Api-septal</td>
<td>16.73 ± 5.42</td>
<td>17.32 ± 4.49</td>
<td>0.18</td>
</tr>
<tr>
<td>GS</td>
<td>14.17 ± 4.31</td>
<td>14.66 ± 4.03</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>LV twist function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal rotation (°)</td>
<td>-3.31 ± 1.07</td>
<td>-3.58 ± 1.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Apical rotation (°)</td>
<td>5.48 ± 2.25</td>
<td>4.69 ± 2.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Twist (°)</td>
<td>8.79 ± 2.80</td>
<td>8.28 ± 2.85</td>
<td>0.048</td>
</tr>
</tbody>
</table>

All values are presented as mean±SD.
AVI: transcatheter aortic valve implantation; AV: aortic valve; PG: pressure gradient; LAVi: left atrial volume index; LVEDD index: left ventricular end-diastolic dimension index; LVESD index, left ventricular end-systolic dimension index; LVEF: left ventricular ejection fraction; LVMi, left ventricular mass index; MAPSE: mitral annular plane systolic excursion; mid-lateral: middle lateral strain; api-lateral: apical lateral strain; GS:global strain. (These abbreviations are same with table11)
### Table 11  LV function between trans-apical and trans-femoral approaches

<table>
<thead>
<tr>
<th></th>
<th>Before TAVI</th>
<th>After TAVI</th>
<th>p₁</th>
<th>p₂</th>
<th>p₃</th>
<th>p₄</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TA (1) (n=45)</td>
<td>TF (2) (n=44)</td>
<td>TA (3) (n=45)</td>
<td>TF (4) (n=44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV gradient (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak PG</td>
<td>74 ± 26</td>
<td>68 ± 15</td>
<td>0.09</td>
<td>21 ± 7</td>
<td>21 ± 6</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean PG</td>
<td>47 ± 15</td>
<td>45 ± 6</td>
<td>0.28</td>
<td>13 ± 5</td>
<td>12 ± 7</td>
<td>0.29</td>
</tr>
<tr>
<td>LAVi (ml/m²)</td>
<td>44 ± 13</td>
<td>38 ± 14</td>
<td>0.02</td>
<td>42 ± 10</td>
<td>35 ± 12</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEDD index (mm²/m²)</td>
<td>28.4 ± 3.7</td>
<td>28.3 ± 4.3</td>
<td>0.98</td>
<td>27.9 ± 3.3</td>
<td>27.4 ± 3.9</td>
<td>0.048</td>
</tr>
<tr>
<td>LVESD index (mm²/m²)</td>
<td>20.6 ± 4.7</td>
<td>19.9 ± 4.4</td>
<td>0.46</td>
<td>20.1 ± 3.4</td>
<td>18.5 ± 4.2</td>
<td>0.05</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>49.2 ± 15.4</td>
<td>51.5 ± 13.4</td>
<td>0.41</td>
<td>49.9 ± 12.5</td>
<td>54.1 ± 11.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Septal motion (mm)</td>
<td>161 ± 38</td>
<td>145 ± 37</td>
<td>0.04</td>
<td>156 ± 34</td>
<td>139 ± 30</td>
<td>0.02</td>
</tr>
<tr>
<td>MAPSE (mm)</td>
<td>3.7 ± 1.5</td>
<td>4.2 ± 0.9</td>
<td>0.06</td>
<td>4.1 ± 1.5</td>
<td>4.6 ± 1.2</td>
<td>0.13</td>
</tr>
<tr>
<td>LV strain (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-lateral</td>
<td>15.17 ± 6.71</td>
<td>14.98 ± 4.99</td>
<td>0.60</td>
<td>15.78 ± 6.52</td>
<td>15.72 ± 4.78</td>
<td>0.87</td>
</tr>
<tr>
<td>Mid-lateral</td>
<td>12.58 ± 5.22</td>
<td>11.68 ± 5.24</td>
<td>0.42</td>
<td>12.67 ± 5.25</td>
<td>12.41 ± 5.23</td>
<td>0.82</td>
</tr>
<tr>
<td>Apical-lateral</td>
<td>15.49 ± 6.31</td>
<td>15.95 ± 5.26</td>
<td>0.69</td>
<td>14.43 ± 6.22</td>
<td>16.84 ± 6.43</td>
<td>0.06</td>
</tr>
<tr>
<td>Basal-septal</td>
<td>10.66 ± 5.08</td>
<td>10.40 ± 4.61</td>
<td>0.80</td>
<td>11.63 ± 5.26</td>
<td>10.62 ± 3.52</td>
<td>0.30</td>
</tr>
<tr>
<td>Mid-septal</td>
<td>12.94 ± 6.30</td>
<td>14.95 ± 5.17</td>
<td>0.11</td>
<td>13.73 ± 4.68</td>
<td>15.68 ± 4.72</td>
<td>0.05</td>
</tr>
<tr>
<td>Apical-septal</td>
<td>16.53 ± 6.20</td>
<td>16.93 ± 4.27</td>
<td>0.73</td>
<td>16.17 ± 7.26</td>
<td>17.95 ± 3.28</td>
<td>0.19</td>
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<tr>
<td>GS</td>
<td>14.09 ± 5.08</td>
<td>14.25 ± 3.25</td>
<td>0.86</td>
<td>14.25 ± 4.63</td>
<td>15.06 ± 3.31</td>
<td>0.34</td>
</tr>
<tr>
<td>LV twist function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Rotation (°)</td>
<td>-3.10 ± 0.94</td>
<td>-3.52 ± 1.15</td>
<td>0.07</td>
<td>-3.53 ± 1.07</td>
<td>-3.62 ± 1.14</td>
<td>0.96</td>
</tr>
<tr>
<td>Apical rotation (°)</td>
<td>5.89 ± 2.44</td>
<td>5.06 ± 1.97</td>
<td>0.08</td>
<td>5.02 ± 2.49</td>
<td>4.33 ± 1.41</td>
<td>0.13</td>
</tr>
<tr>
<td>Twist (°)</td>
<td>8.99 ± 2.75</td>
<td>8.58 ± 2.86</td>
<td>0.49</td>
<td>8.59 ± 3.18</td>
<td>7.95 ± 2.36</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Reproducibility

Intra-observer and inter-observer variability of conventional Doppler and M-mode derived variables ranged from 1% to 8%. Intra-observer and inter-observer variability for conventional Doppler and M-mode derived variables (peak aortic SPG, LVPWTd, LVEDD and LVESD) ranged from 1% to 7%. The reproducibility of cardiac rotation and twist measurements of our laboratory has been previously reported, being 5-19% (147).
Discussion

In this thesis, we focused on the survival and LV function recovery after both SAVR and transcatheter aortic valve implantation (TAVI) in a series of severe AS patients. We identified predictors of survival in low flow and high gradient AS (study I), predictors of mortality in elderly patients (study II), echocardiographic predictors of LV function recovery (study III) and compared the effect of transapical TAVI and transfemoral TAVI on LV function (study IV). The main findings are: 1) Early mortality and overall survival was determined by patients’ cardiac function, LV EF<40%, the presence of restrictive LV filling and a raised PSPAP. 2) in septuagenarians and octogenarians, age is not an independent predictor for mortality, but anaemia and CBP time predict early mortality and PPM, LV diastolic dysfunction predicted long term mortality. 3) pre-operative LV recovery is predicted by end-systolic dimension index (LVESD index). 4) despite similar patients demographics and severity of AS, trans-femoral TAVI results in earlier recovery of LV function compared with Trans-apical TAVI.

Survival in patients with low-flow and high-gradient AS

In severe AS, the LV compensates for chronic pressure overload by developing hypertrophy in an attempt to normalize wall stress. When wall stress exceeds the compensating mechanism, LV systolic function may decline, LV dilatation and adverse remodeling may follow, and the pressure drop generated by the LV may fall. Under these circumstances, end diastolic pressures and left atrial pressure rise, manifested in the form of restrictive LV filling and secondary increased pulmonary artery systolic pressure. Aortic valve replacement removes the pressure afterload, reduces LV wall stress, and improves overall ventricular function. However, profound disturbances in preoperative LV function may only be partially reversible after AVR or may be limited to patients with less severe LV disease (148). For patients who demonstrate irreversible LV dysfunction, the cause of post-operative morbidity and mortality may be related to the ventricle itself, and thus may underestimate a successful life saving surgical procedure, and hence the need for early referral. In our study, the patients who died had all received a stented valve. However, we are unable to exclude valve type as a confounding factor. Since stentless valves, especially in the subcoronary position, normally require longer cross-clamp times. There is most likely a selection bias regarding the distribution of the different valve types rather than a causal relationship between valve type and mortality. Further studies are required to test the potential benefit of stentless valves in this patient group.
Age is not a predictor of mortality in septuagenarians and octogenarians undergoing AVR for severe AS

Co-existing coronary artery disease (20,149), a low transaortic valve gradient, LV systolic dysfunction (150) (151) and age (152,153) are known predictors of clinical and surgical outcome for AS. In this study age was not a predictor of surgical outcome but anaemia, long cardiopulmonary bypass time, significant PPM and raised left atrial pressure predicted 30-day mortality. Also, significant pulmonary hypertension in addition to the above-mentioned variables predicted long term mortality. Age was identified as a major adverse predictor of outcome (152) by Logeais Yet. al, in 1994 and a recent small surgical series echoed such finding (153). Given the improvement in surgical techniques, advances in cardiopulmonary bypass strategies and peri-operative care in recent years, the observation of an advanced age failing to predict early and long term mortality with our relatively large and recent surgical cohort warrants a large-scale multi-centre study for a definitive answer. Our findings are supported by few studies questioning the prognostic value of age (154,155). These results are compatible with Gjertsson's finding in highlighting the role of LV diastolic dysfunction after AVR for AS in predicting late mortality (156). The non-survivors of our elderly AS patients had higher E/A ratios, shorter DT, more frequent atrial fibrillation and higher PASP than those survived. The persistent elevation of LV filling pressure undoubtedly leads to significant pulmonary vascular disease that carries a poor long term prognosis. We demonstrated with a cut off value of PASP of 40 mmHg, we could predict long term mortality with a sensitivity and specificity of 85% and 64% respectively.

Another important finding in our study is the lack of predictive value of baseline coronary artery disease in contrast to what has previously been known [14]. Again, our finding is supported by a recently published surgical report (157). Our cohort included a relatively small number of patients with low transvalvular gradient and LV systolic dysfunction that any conclusion drawn about their prognostic value would not be accurate. Yet the prognostic values of age, NYHA functional class and co-existing coronary artery disease need to be retested in a large cohort.

Pre-operative LV end-systolic dimension predicts ventricular recovery

Our findings in this paper confirmed that even patients with reduced LV function and severe AS benefit from SAVR (149). Surgical relief of afterload resulted in favorable LV remodeling as evidenced by reduction in function. Previous studies showed that the majority of LV mass regression after SAVR occurs during the first
six month (158). Thus our measurements obtained from a median of 48 months after surgery represent an established process of reverse LV remodeling and functional recovery that are likely to be clinically significant. Our data suggest that even patients with severe LV dysfunction should not be denied the potential benefit of SAVR. Furthermore, pre-operative LV dimensions seem to reflect the degree of cavity function impairment, a smaller end-systolic index was associated with a higher incidence of LV functional recovery on multivariate analysis. Our results echoed the findings of Vaquette et al., which identified pre-operative semi-quantitative cardio-thoracic ratio in predicting subsequent acute LV functional recovery in a large surgical cohort (157). The prognostic relevance of LV size has also been reported by Trantini et al., who identified LV end-systolic volume index as the only independent predictor of cardiac death (57).

LV dilatation as a result of long standing AS may imply that the myocardium has reached a state of decompensation, if not irreversible dysfunction. This hypothesis was supported by our findings of lack of functional recovery after surgery in patients with larger pre-operative LV dimensions and more severe LV long axis dysfunction. We have previously addressed the question of reduced long axis function in patients with hypertrophic cardiomyopathy arising secondary to underlying myocardial fiber disarray or fibrosis (159). We have also discussed the significant contribution of long axis shortening to the overall fattening of the posterior wall and normal fall of minor axis (160). A recent histological study illustrated that the more depressed the LV function, the higher the collagen load within the hypertrophied ventricle in aortic stenosis (161). We therefore postulated that LV dilatation in patients with severe AS and LV dysfunction could indicate a more severe degree of myocardial fibrosis and subsequent loss of contractile reserve. This presentation of LV dilatation with high trans-aortic gradient results in lower probability of recovery of LV function after valve replacement surgery.

Another interesting observation is that the presence of moderate to severe prosthesis-patient mismatch was not predictive of recovery of LV function in the intermediate term. Previous studies addressed PPM as a strong predictor for short term morbidities and mortality especially in patients with LV systolic dysfunction (136,162). The long term impact of PPM on survival, however, remains controversial (162-164). In the current study we aimed at identifying predictors for med-term LV recovery and hence those patients with early deaths after AVR were excluded. 12 of 21 patients (57%) with moderate to severe PPM in our study exhibited med-term LV recovery. A large prospective study for re-visiting this
The relation between PPM and long-term LV function (a surrogate marker for late mortality) is therefore warranted.

**Effect of trans-apical (TA) and trans-femoral (TF) TAVI on LV function**

Despite similar clinical, demographic, risk factors and LV structure and function in our two patient groups who received TAVI for AS, the procedure they underwent had different effect on LV cavity function. EF increased only in TF patients along with significant improvement of lateral wall function and cavity twist function. These findings seem to reflect pure LV cavity response to removal of afterload, in line with previously shown response after surgical AVR (165). TF then seems to reflect similar effect of SAVR, where the LV myocardium is not touched and only the ascending aorta is slit. TA patients, on the other hand, underwent an additional myocardial intervention, with apical puncture for antegrade aortic valve implantation. Such minor surgical intervention seems to have resulted in delayed LV overall cavity and segmental function recovery. The exaggerated apical rotation, known in AS, reduced equally in the two patient groups suggesting that it was related to the presence of AS, as we have previously shown (166), but the response of the remaining components of cavity function to individual procedure seem to be directly related to the TAVI approach used. Finally, the lagging of LV function recovery in the TA patients could be contributed to by the significantly worse diastolic dysfunction as shown by the larger left atrium and the higher estimated peak systolic pulmonary artery pressure in the TA patients with respect to the TF group.

**Clinical implications**

SAVR results in significantly improved survival and functional recovery in the majority of severer AS, even in the patients with LV dysfunction. A decision making of SAVR in severe AS is currently based on the presence, rather than the degree, of LV dysfunction. However, asymptomatic patients may remain undetected for many years, and often present late in the natural history of the disease due to the development of symptoms secondary to ventricular disease. Our findings represent a group of elderly patients with an advanced form of AS, with a high prevalence of heart failure, coronary disease, and other significant comorbidities. Surgical mortality and long term mortality are acceptable. Survival was intricately linked to the degree of LV dysfunction at the time of surgery. Patients with moderate LV dysfunction (LVEF >40%, PSPAP < 45 mmHg, and a lack of restrictive LV filling) had significantly better survival than those with severe LV dysfunction (LVEF<40%, PSPAP ≥45 mmHg, and the presence
restrictive LV filling). These are in agreement with data from patients with dilated cardiomyopathy, in whom development of restrictive filling (167,168) and pulmonary hypertension (169) are both features of sicker ventricles and are therefore associated with poorer outcomes. A lower prevalence of LV functional recovery in patients with large pre-operative LV end systolic dimension index might signify the loss of contractile reserve and unlikely post-op functional recovery. Early and long-term mortality in elderly is associated CBP time, valve chosen and developed diastolic dysfunction, all predict poor long term outcome. Therefore early identification of patients for AVR, before myocardial damage becomes decompensated or irreversible, better protection of myocardium during bypass surgery, and be careful of valve choice should be considered. TAVI can improve the outcome in high risk patients from SAVR. If given a procedural choice transfemoral approach seems to result in faster recovery of ventricular function. In addition, worse diastolic LV function seems to be related to the delayed recovery of cavity performance.

**Limitations**

The sample size and event rate in this study were modest for definitive conclusions to be drawn. However, we did include a relatively large and recent cohort of uncommon but clinically important subset of AS patients (low flow and high gradient). The acceptable mortality rates suggest that surgery should still be offered to these patients after careful evaluation of risks. Pre-operative data on myocardial contractile reserve by stress echocardiography were not available in all of our patients. Having studied only surgical patients in the first three studies, we were unable to compare our results with a control group treated medically. We could not exclude concomitant CAD as a cause for LV myocardial damage. None of our patients had evidence of recurrence of significant CAD during follow-up. Furthermore, relatively outdated echocardiographic instruments were used in the SAVR studies. Current state of the art machines with myocardial tissue-Doppler imaging and speckle tracking techniques could have provided in depth regional quantitative assessment of LV dysfunction in patients for better prediction of outcome (170). Finally, different valve types were used which, although is to be expected in conventional clinical practice, limits the assessment of any possible effects of valve type on outcome. Another potential limitation is the retrospective nature of the studies. Cardiac MRI to quantify the degree of myocardial fibrosis by late gadolinium enhancement could have provided further insight into the mechanism of diastolic dysfunction in AS patients. A larger prospective
investigation, incorporating cardiac MRI and dobutamine stress echocardiogram to quantify contractile reserve, may shed more light on the exact mechanism of myocardial dysfunction in these patients. We did not have mid-term or long term follow up assessment in all TAVI patients, which might have demonstrated delayed recovery of LV function in the trans-apical group. We do not have a similar group of TA patients in whom LV diastolic function was maintained to compare with the TF group. Our results reflect early changes which we and others have shown, to change few months after procedure (25,87,171).

Conclusions

Our findings suggest that the severity of LV dysfunction should be considered when planning AVR surgery for low-flow and high-gradient AS, irrespective of increasing age and co-morbidity. Aortic valve replacement related survival in septuagenarians and octogenarians with severe AS is encouraging. Early identification of patients for AVR, before myocardial damage becomes irreversible and surgical risk increases, should improve survival. TAVI, has become an alternative option to SAVR, and has resulted in satisfactory survival and improvement of LV function, particularly the transfemoral approach. Finally, in addition to transaortic valve pressure drop follow up in AS, LV systolic and diastolic function should always be critically assessed in order to identify fast deteriorating patients who should benefit from early intervention.
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