# Diagnosis and management of left valvular heart disease with advanced echocardiography and cardiac computed tomography

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# CHAPTER 1

# General Introduction and Outline of the Thesis

# TYPES OF LEFT VALVULAR HEART DISEASE

**Prevalence and spectrum of the disease**

Left-sided significant valvular heart disease is a fast growing worldwide problem that expands proportionally to the increment of the life expectancy of the population and its prevalence is expected to double by 2050.[1] In a large-scale community screening cohort study that enrolled 2500 participants aged ≥65 years, the prevalence of moderate or severe valvular heart disease was 11.3%.[1] According to the Euro-Heart survey II on valvular heart disease, aortic stenosis (AS) and mitral regurgitation (MR) are the two most common types of valvular heart disease in adults.[2] Among those who suffer from moderate or severe valvular disease, AS is the most common cause with a prevalence of 41.2% followed by MR with a prevalence of 21.3%.[2] The aetiology of the native valve disease is mainly degenerative in AS for about 90% of cases and in primary MR for about 60% of cases based on the recently reported Euro-Heart survey II.[2] However, 33% of the MR is categorized as secondary and 51.6% of the secondary, as ischemic in origin.[2] Degeneration as a cause of valvular heart disease is highly indicative of its association with the ageing of the population; as age increases from 55 to 75 year-old, the prevalence of AS and MR rises from 2% to 6% and 9% respectively.[3] In a cohort with significant AS, patients older than70 years were 56% and the nonagenarians were 38%, whereas among patients with MR the prevalences were 44% and 17%, respectively.[4] Furthermore, in patients with multiple left-sided valvular heart disease, 33% were older than 80 years.

**Challenges in diagnosis**

Although it has been well established that left-sided valvular heart disease is a problem increasing with age, it is still underdiagnosed in about 10% of patients 75-84 year-old and 20% of patients aged ≥85 years.[1] Thus there is an unmet need for accurate and timely diagnosis of the disease, so that appropriate treatment can be applied.

**Aortic stenosis**

AS is associated with adverse outcomes when there is imbalance between left ventricular hemodynamic load – mainly due to aortic valve obstruction and secondary due to increased arterial pressure- and left ventricular capacity to overcome the increased load.[5] This pathophysiological imbalance in AS leads to left ventricular hypertrophy, concentric remodeling, myocardial fibrosis and heart failure.[6] Hence, in a comprehensive approach of AS, apart from the aortic valve assessment (which is the cornerstone of the assessment), the afterload and the left ventricle have to be evaluated to define the disease severity and prognosis (Figure 1).

AS is considered severe when the peak aortic jet velocity (Vmax) is ≥4m/s, mean pressure gradient (MPG) ≥40mmHg, aortic valve area (AVA) <1cm2 and AVA index <0.6cm2/m2 assessed on echocardiography.7, 8 However the AVA and AVA index have to be evaluated because Vmax and MPG are flow dependent and in case of a high-flow condition such as anaemia, infection, hyperthyroidism, arteriovenous shunt they may overestimate severity.8

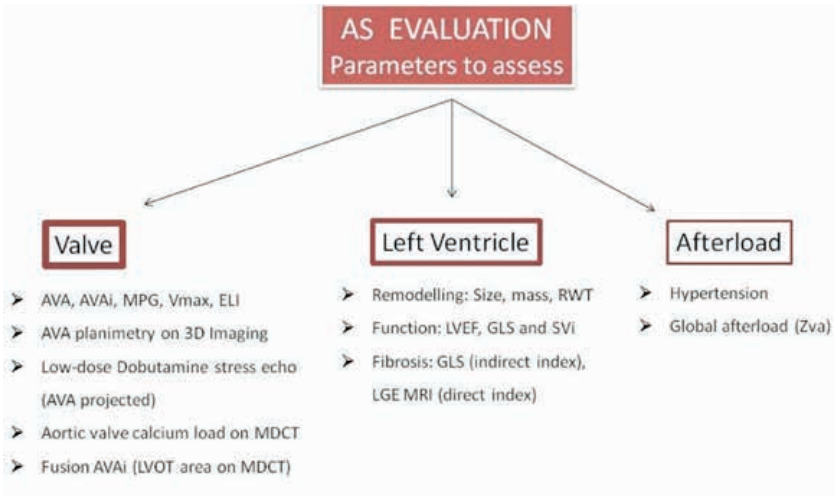


**Figure 1**. Severe aortic stenosis is a disease of the valve that affects the myocardium and the symptoms begin when left ventricular capacity fails to overcome the imposed afterload by the valve and the aorta. Thus for a comprehensive evaluation of AS all three parts involved have to be evaluated: 1. The Valve: by aortic valve area (AVA), AVA index to body surface area (AVAi), mean pressure gradient (MPG), maximum velocity through the valve (Vmax), energy loss index (ELI), AVA planimetry on 3-dimentional (3D) imaging such as 3D echo and cardiac computed tomography, AVA and MPG on low-dose dobutamine stress echo in classical low-gradient AS and AVA projected at normal flow in paradoxical low-gradient AS, aortic valve calcium load in Agatston units on cardiac multidetector computed tomography (MDCT), fusion AVA by combining in the continuity equation Doppler haemodynamics with left ventricular outflow tract (LVOT) planimetry area on MDCT. 2. The Left Ventricle: remodeling by evaluating the size, the relative wall thickness (RWT) and the mass, function by evaluating the left ventricular ejection fraction (LVEF), the global longitudinal strain (GLS) as an estimation of intrinsic myocardial function and the forward stroke volume index (SVi), myocardiac fibrosis evaluated directly by late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (MRI) and indirectly by GLS with the echocardiographic method of speckle tracking. 3. The Afterload: by measuring the blood pressure (systolic arterial pressure (SAP)/ diastolic arterial pressure) and estimating the global afterload with the valvuloarterial impedance (Zva) by the equation Zva = (SAP+MPG)/SVi.

About 40% of patients with severe AS have low-gradient stenosis which has been recently endorsed by the guidelines as severe under specific circumstances.9 This type of AS, also called "discordant grading" (having Vmax<4m/s, MPG<40mmHg and concomitantly AVA <1cm2 and AVA index<0.6cm2/m2), is divided into three subgroups based on the forward flow and the left ventricular ejection fraction (LVEF): 1. Low-flow, low-gradient with low ejection fraction <50% (classical low-flow low gradient), 2. Low-flow, low-gradient with preserved ejection fraction (paradoxical low-gradient) and 3. Normal-flow, low-gradient.9-11 Flow is defined as low when the forward stroke volume index assessed by Doppler echocardiography is <35ml/m2.8 The classical low-gradient type is pathophysiologically attributed to low forward flow due to reduced LVEF.12 The paradoxical low-gradient type is attributed to low-flow due to pronounced concentric remodeling and small left ventricular cavity, to diastolic dysfunction, to atrial fibrillation, to increased afterload, to MR or mitral stenosis and to tricuspid regurgitation.13, 14 Among these low-gradient cases, about 30-70% are proven to be true severe stenosis after double-checking for possible Doppler echocardiography pitfalls underestimating the gradients or undersizing the left ventricular outflow tract area, after using stress echocardiography,

advanced echo techniques or multidetector computed tomography (MDCT) cardiac analysis.[10, 11]

Patients with high-gradient severe AS or with low-gradient AS proved to be severe, if (i) symptomatic with clinically relevant symptoms and (ii) really asymptomatic but with reduced LVEF <50% or aortic Vmax >5.5m/s or Vmax increase rate ≥0.3m/s/year, benefit from surgical or transcatheter aortic valve replacement (AVR).[8, 10, 15, 16] Recently a study of 1678 asymptomatic patients with severe AS and preserved LVEF suggested that even patients with LVEF <55% benefit from AVR.[17] The treatment modality, (transcatheter or surgical) is defined by the Heart Team taking into consideration the surgical risk (Euroscore II >4% or log Euroscore >10%), patient's frailty, the type of stenosis (low-flow, low-gradient), left ventricular flow and systolic reserve (absence of reserve on dobutamine stress echocardiography) and other anatomical aspects (porcelain aorta on MDCT).[8, 10] For the low-flow, low-gradient severe AS patients the preferred treatment option is the transcatheter approach, taking under consideration that these patients have small LV cavity and small annulus and many co-morbidities; in the case of low LVEF the preferred access site is the transfemoral.[10]

Defining the time and type of treatment in AS is mainly designated by the accurate diagnosis of AS type and severity, thus multimodality imaging is the cornerstone for the diagnosis and treatment.

**Challenges in diagnosis**

**Mitral regurgitation**

MR is the second most common valvular heart disease according to EuroHeart Survey II leading to impaired quality of life and increased mortality.[2] The mitral valve has a complex anatomy that includes the mitral annulus, the leaflets, the chorda (primary and secondary), the papillary muscles and the left ventricle.[18] The proper diagnosis of regurgitation involves thorough assessment of all parts of the valvular apparatus. The quantification of the disease severity and the clarification of the regurgitant mechanism are mandatory to guide personalised patient care.[19]

MR moderate or severe (the trivial or mild is not further assessed) is classified as primary, secondary and mixed: 1. In primary type, the aetiology is the abnormal leaflet morphology (also called organic) associated with (i) normal leaflet motion (like in leaflet perforation, in endocarditis, in cleft), (ii) increased leaflet motion (leaflet prolapse or flail) or (iii) decreased leaflet motion in systole and diastole (restriction due to calcification or rheumatic valve). 2. In secondary type (also called functional), the leaflet morphology is normal (trivial leaflet thickening age-related is accepted) and the MR is attributed to pathology of the other parts of the apparatus, (i) with normal leaflet motion due to left atrial remodeling leading to mitral annulus dilatation (e.g. in atrial fibrillation) and (ii) with restricted leaflet motion only in systole due to left ventricular remodeling, ischemic or not, leading to papillary muscle apical dislocation and leaflet tethering (e.g. after myocardial infarction, dilated cardiomyopathy). 3. In mixed type, there is abnormal leaflet morphology, combined with left atrial or ventricular remodeling (e.g. hypertrophic obstructive cardiomyopathy, MR secondary to myocardial infarction and flail leaflet due to chorda rupture).[18-20]

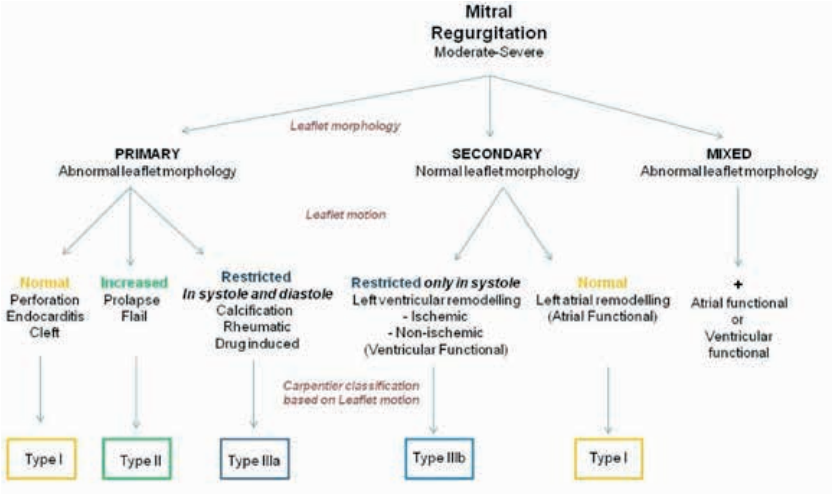


**Figure 2**. Mitral valve regurgitation classification based primarily on leaflet morphology (normal / abnormal) and secondary on leaflet motion (normal / increased / restricted) and their matching with Carpentier classification for surgical use.

Apart from the three types of MR described above, there is another classification proposed by Carpentier based merely on the leaflet motion that allows better communication between cardiologists and surgeons: Type I with normal leaflet motion, Type II with increased leaflet motion (prolapse or flail), Type IIIa with restricted leaflet motion in systole and diastole and Type IIIb with restricted leaflet motion only in systole.[18] The three types of MR endorsing the Carpentier classification are presented in Figure 2.

The impact of severe MR on survival is detrimental for all the disease types.[20] The treatment applied depends on the type of the MR.[8] In the case of primary MR if the patient is symptomatic the best treatment option is surgical mitral valve repair. If the patient is asymptomatic the decision for mitral valve repair relies on the left ventricular function (LVEF ≤60%), size (LVESD ≥45mm), the presence of new onset atrial fibrillation, elevated pulmonary pressures (>50mmHg), flail leaflet or severely dilated left atrium (≥60ml/m$^2$) in the presence of dilated left ventricle (LVESD >40mm).[8] The patients with secondary MR have worse survival than those with primary MR. However, the patients with secondary MR due to left atrial remodeling have better survival and lower incidence of heart failure compared to secondary MR due to left ventricular remodeling.[20] For the former, the optimal treatment is usually surgical restrictive annuloplasty.[21] Patients with secondary MR due to left ventricular remodeling have usually significantly dilated left ventricle and impaired LVEF, and if they are on optimal medical treatment for heart failure including cardiac resynchronisation, if indicated, the decision to operate is ambiguous, considering the lack of robust data demonstrating a survival benefit for surgery compared to medical management.[22, 23] Losartan has been recommended as an option for secondary MR after myocardial infarction because it allows the adaptive leaflet growth and modulates their profibrotic changes.[24] Cardiac resynchronization therapy is indicated not only for left ventricular functional improvement but it has been suggested to reduce functional ventricular MR by at least 1 grade.[25] If the patient remains

symptomatic under medical treatment and resynchronisation, surgical repair has an indication IIb unless concomitant revascularization can be offered upgrading the indication to IIa, according to guidelines.[8]

A community cohort study demonstrated that the patients with severe MR treated surgically are only few; 37% of those with primary MR and 7% of those with secondary MR.[20] Thus there is an unmet need for new treatments of MR. The percutaneous mitral valve edge-to-edge repair with the MitraClip implantation has arisen as an alternative option. For the primary MR patients, MitraClip has been proven in a randomised trial (EVEREST II) to be a safe and effective alternative to surgical repair, with comparable outcomes.[26] Real world studies that followed the initial randomised trial, suggested in line that the short and long term clinical events and survival post MitraClip or surgery are comparable in-between and better than optimal medical treatment alone (including resynchronization).[27, 28] However, these studies included mainly secondary MR population.[27, 28] Randomised trials for patients with secondary MR and reduced systolic function have been performed with conflicting conclusions. MITRA-FR trial suggested no survival benefit and no reduction in heart failure related hospitalisations between MitraClip and medical treatment alone at 1-year follow-up.[29] On the contrary, the COAPT trial demonstrated lower mortality and heart failure related hospitalizations at 2-years follow-up for the MitraClip group.[30] Although the two trials included patients with secondary MR, the COAPT included patients with more severe MR and MITRA-FR with more diseased left ventricle with reference to its dilation and function which could be a reasonable explanation for the opposing results.[31] Thus, is reasonable to perform MitraClip in symptomatic patients on optimal medical treatment who have severe MR (EROA >30mm$^2$ and/or regurgitant volume >45ml) and LVEF 20-50% with left ventricular systolic diameter <70mm.[31]

**Concomitant aortic stenosis and mitral regurgitation**

AS and MR are the 2 most common left heart valvulopathies and they may co-exist in about 20% of patients with severe AS.[32] The two valvulopathies are interrelated to a different extent according to their type. From the cardiac pathophysiology perspective, severe AS is leading to left ventricular remodeling that may cause papillary muscles traction and displacement and leaflet tethering leading to secondary MR. Additionally, it increases left ventricular systolic pressure, leading to increased ventricular-atrial gradient, worsening all types of MR and dilates the left atrium, through diastolic dysfunction, leading to secondary MR (left atrial remodeling).[33, 34] On the contrary, MR reduces the forward flow, by driving blood backwards to low-pressure left atrium and by increasing the prevalence of atrial fibrillation, modifying AS to low-flow, low-gradient.[33, 34] Thus, coinciding MR may be the reason of underestimation of AS and AS may be the reason of worsening MR especially if secondary. Hence, the type of each valvular disease is indicative of their interdependence, which is of paramount importance for the decision making of their treatment. It has been demonstrated that the double operation on both valves is high risk with 5-12.5% in-hospital mortality.[35] To avoid this, the guidelines suggest that surgical intervention on mitral valve is in general not necessary and that secondary MR usually improves post AVR.[8] If the MR is secondary, after AVR the effective regurgitant orifice area and the regurgitant volume are reduced significantly more than in primary MR and

at the same time left ventricular reverse remodeling with greater volume reduction occurs.[36] Apart from the secondary type of MR, other parameters associated with MR reduction post AVR alone are: absence of mitral annular calcification, high gradient AS, dilated left ventricle (left ventricular end-diastolic diameter ≥50mm, left ventricular end-systolic diameter ≥36mm), absence of atrial fibrillation, absence of pulmonary hypertension and successful AVR without aortic regurgitation and with left ventricular pressure reduction, especially if a balloon expandable transcatheter valve is implanted without prosthesis-patient mismatch.[36-38] The reduced MR post-isolated TAVR, but not after surgical AVR, has a positive impact on survival compared with the stable or increased MR.[39, 40] However, the decision of operating on mitral valve has to be taken without the a priori knowledge of the possible MR reduction. Although there are plenty of survival data regarding the impact of untreated significant MR on patients' survival post AVR, they are controversial. Whereas isolated surgical AVR or TAVR is performed some studies support that untreated MR impacts on the survival and others not.[37, 38, 41] It is of note that in low-gradient AS the prevalence of MR is higher compared to high-gradient AS, the presence of significant MR has deleterious impact on survival and TAVR treatment improves survival compared with medical treatment alone.[42] The final treatment decision, keeping in mind the interrelation of the valvular diseases and after a comprehensive evaluation of the AS and MR severity, depends on the type of the mitral valve disease: In primary MR with major anatomic lesions it is highly unlikely to experience MR reduction post AVR. Thus in low/intermediate risk patients, surgical replacement is proposed and in intermediate/high risk patients TAVR followed by transcatheter or minimally invasive surgical mitral repair. In secondary MR, isolated AVR is suggested, surgical AVR or TAVR according to Heart team, trying to avoid prosthesis-patient mismatch which is usually achieved in TAVR.[37, 38]

# MULTIMODALITY IMAGING for the DIAGNOSIS of AORTIC and MITRAL VALVE PATHOLOGY

## Role of advanced echocardiography

### Aortic Stenosis

AS diagnosis is based mainly on echocardiography. Classically, 2-dimensional echocardiography and Doppler are used in every-day clinical practice to assess the severity of AS. Nowadays, with the endorsement of low-gradient stenosis in the spectrum of severe the classical measurements of aortic Vmax, MPG and AVA have to be done even more accurately and have been fortified by new parameters applying cutting-edge echocardiography techniques.

The Vmax and the MPG measured with continuous wave Doppler have to be estimated from the cardiac apex and additionally from the right parasternal side with a stand-alone probe and from subcostal and suprasternal site, wherever the Doppler beam is in line with the blood flow, to ensure that the highest possible Vmax and MPG is obtained, avoiding underestimation of the stenosis or pseudo-low-gradient stenosis.[43] The acceleration time of

this signal is then measured AT>110msec and its ratio over ejection time AT/ET >0.36 are indicative of severe AS.[9] The pulsed wave Doppler signal at the left ventricular outflow tract has to be representative of laminar flow and should be traced after reducing the gain and increasing the reject of the echocardiography device. Afterwards the Doppler velocity index can be estimated from the equation DVI=VTI LVOT / VTI aortic, <0.25 is indicative of severe stenosis.[9] All the aforementioned measurements of transvalvular gradient have to be performed after normalization of the blood pressure, because arterial hypertension may lead to underestimation of the gradient, thus in a pseudo-low-gradient.[44] The left ventricular outflow tract diameter has to be measured at the parasternal long axis at the hinge points or just below in mid-systole avoiding the presence of valve calcium. The area is then estimated from the equation 0.785xdiameter$^2$ assuming that it is circular. However, it has been well demonstrated that LVOT is oval in shape. Thus it is more accurate to evaluate it by direct planimetry at 3-dimentional echo where the real short axis of the LVOT can be seen en-face and measured.[45] This measurement is more accurate when transoesophageal echo is performed. The stroke volume is then estimated from the equation LVOT area x VTI LVOT. After indexing to BSA the flow state can be defined based on the SVi. AVA is estimated from the continuity equation (the flow that goes through LVOT in 1 beat is the same with the flow through aortic valve in 1 beat, preferably measured at stable heart rate) using all the measurements described above. This area corresponds to the effective orifice area, which is the area of the vena contracta of the forward flow jet, i.e. the narrowest area of the jet. However, AVA can be measured with direct planimetry of the valve opening in a short axis view or more accurately at a 3D transoesophgeal short axis view tracing at the tips of the cusps, evaluating the anatomic valve area which is usually bigger, estimating the area at the tips of the cusps and not downstream at the narrowest point of the forward flow.[46] In the case of a small aorta with diameter <3cm the AVA with continuity may overestimate the severity of the stenosis because it doesn't account for the pressure recovery.[47] For such patients the energy loss index = [(AVAxAortaArea)/(AortaArea-AVA)]/BSA is a better measure of the stenosis severity as it estimates the net pressure imposed to left ventricle after the kinetic energy partly convers to static. This pressure is comparable to the pressure measured with the wire in the catheterization laboratory and for this reason energy loss index improved the prediction of events due to AS compared to AVA.[48]

Stress echocardiography is a modality applied in AS for severity assessment in low-gradient patients and for risk stratification in asymptomatic patients.[49] Low dose (till 20mg/Kg/min) dobutamine stress echo is performed in low-gradient patients with reduced ejection fraction for the assessment of severity and risk stratification.[8] If during the test the MPG increases >40mmHg and AVA remains <1cm$^2$ the test is indicative of severe stenosis, if the MPG remains <40mmHg and AVA increases >1cm$^2$ the stenosis is moderate (pseudo-severe) and if MPG remains <40mmHg and AVA remains <1cm$^2$ the test is inconclusive so far, due to lack of flow reserve and the next step is to calculate the AVA projected at normal flow conditions (250ml/min), if the flow increases by 20%, and if AVA projects <1cm$^2$ the stenosis is severe.[50-52] A recent study suggests that AVA projected is the best parameter to clarify severity in dobutamine stress echo.[53] The presence of flow reserve during the test, i.e. increase of the stroke volume >20%, is considered a sign

of good prognosis.[52] However, even patients without flow reserve are doing better after surgical replacement compared to medical treatment and more recently after transcatheter replacement the survival was comparable in between the 2 groups of flow reserve.[54-56] It is of note that after TAVR the LVEF improves independently of the flow reserve.[54, 55] In low-flow, low-gradient patients with preserved ejection fraction, the low-dose stress echo has restricted application. It has been proposed to be used for the evaluation of the AVA projected at normal flow, indicating severe stenosis if AVA <1cm$^2$, or AVA index < 0.55cm$^2$/m$^2$.[57] In asymptomatic patients exercise stress echocardiography may reveal symptoms neglected by the patient or blood pressure fall below baseline indicative of bad prognosis urging to AVR besides the echocardiography findings.[52, 58] An increase of the transaortic MPG by >18mmHg, a systolic pulmonary artery pressure >60mmHg or absence of contractile reserve during exercise defined as drop or increase less than 4-5% of the LVEF are indicative of AS related events and valve replacement should be considered.[52, 58]

**Mitral Regurgitation**

Echocardiography is the cornerstone diagnostic method to assess all the parts of the mitral valve apparatus (left ventricle, papillary muscles, chorda, leaflets and annulus) and to evaluate MR severity and type in order to do a comprehensive assessment of MR. Transthoracic echocardiography is the first step in this approach for assessing mitral valve pathology on grey scale, left ventricular and atrial size and function and then perform qualitative and quantitative MR evaluation.[59] Normal sized left ventricle and left atrium exclude chronic severe MR.[59] MR is a dynamic phenomenon and as such before echo the heart rate, rhythm and blood pressure have to be monitored. In the qualitative assessment the type of MR has to be evaluated as described above (Figure 2) and MR jets have to be described by number, direction and duration in systole. The quantitative assessment is based on the Colour Doppler, continuous wave Doppler and pulsed wave Doppler. An area of the regurgitant jet >50% of the left atrium and a vena contracta width >7mm are indicative of severe MR.[8, 18] Proximal isovelocity surface area (PISA) is used for evaluating the effective regurgitant orifice era >0.4cm2, the regurgitant volume >60ml, the regurgitant fraction >50% and radius >1cm at Nyquist limit 30-40cm/s. These cut-offs are endorsed by the European society of Cardiology for primary MR. For secondary MR the lower cut-offs of effective regurgitant orifice area >0.2cm$^2$ and regurgitant volume >30ml are proposed.[8] However, the American Heart Association/ American College of Cardiology approve the former cut-offs only for both primary and secondary MR.[7] Vena contracta and PISA method may overestimate severity based on EROA in case of non-holosystolic MR, thus regurgitant volume has to be estimated. On the contrary PISA may underestimate severity in case of small size patient with small left ventricular cavity.[18] The continuous wave Doppler used in PISA inform us about the duration of MR in systole and about the peak velocity, considering that the beam is aligned with the blood flow, which is indicative of the left atrial pressure (the lower the velocity the higher the atrial pressure).[18] Pulsed wave Doppler should be used for the mitral inflow with E wave >1.2m/sec indicative of severe MR and for pulmonary vein signal with systolic flow reversal indicative of severe MR.[59]

Transoesophageal echocardiography with the use of 3D imaging is necessary for better visualization of the complex mitral valve apparatus in case the findings on transthoracic are indeterminate or discordant and before any intervention, surgical or transcatheter repair. The 3D imaging enables the operator to specify the type of valve disease, to identify a leaflet cleft or perforation, to name the prolapsing scallop, to check the commissures, to apply PISA method more accurately.[59] It has been demonstrated that 3D echocardiography assesses the effective regurgitant orifice area more accurately than 2D and is comparable to MRI, by planimetry of the vena contracta area, perpendicular to the flow direction at the narrowest position.[60] Subsequently the regurgitant volume is more accurate too.[60] Before the transcatheter repair with MitraClip, 3D transoesophageal echocardiography has to be performed to predict the feasibility of the method. If the segment 2 prolapses, there is no calcification, the flail gap on 4 or 5 chamber view is <10mm, the flail width on short axis is <15mm, the mitral valve area is >4cm$^2$ and the transmitral gradient is <4mmHg there is a high chance of a successful MitraClip implantation.[59]

Exercise stress echocardiography may be applied in primary MR. In asymptomatic patients it may reveal symptoms or systolic pulmonary pressure ≥60mmHg for risk stratification. In symptomatic primary MR that is at least moderate, an increase of MR severity by ≥1 grade, or systolic pulmonary pressure ≥60mmHg are indicative of worse prognosis. Moreover, absence of contractile reserve of left ventricle (LVEF increase <5%) or right ventricle (TAPSE <18mm) are associated with poor outcome.[52,61] In secondary MR, exercise stress echocardiography may predict worse prognosis if an increase of the effective regurgitant area by ≥13mm$^2$ is demonstrated or if dynamic pulmonary systolic pressure ≥60mmHg is measured.[52]

**Role of multidetector computed tomography**

**Aortic Stenosis**

Cardiac computed tomography angiography, including a non-contrast acquisition as the first step of an exam, can be used to calculate the coronary artery calcium with the Agatston method. This technique has been extrapolated to aortic valve calcium. Thus, with a simple acquisition the aortic valve calcium can be estimated in arbitrary units.[62] The more the calcium detected on the valve the more severe the stenosis grade is. This has been endorsed by the guidelines with a cut-off >3000AU for men and >1600AU for women indicating a high likelihood of severe stenosis.[8] Aortic valve calcium evaluation is of paramount importance in the discordant low-gradient group of patients because it can discriminate severe from moderate stenosis after adjustment for the aortic annulus area and for the body surface area in a reproducible and personalized way.[63] The clinical significance of the aortic valve calcium load has been well recognized because it has been associated with the mortality of AS patients beyond clinical parameters and Doppler echocardiographic criteria.[64]

The contrast MDCT has the best spatial resolution among all other imaging modalities. Thus its role in evaluating the aortic valve is gradually evolving. The aortic valve can be seen "en-face" at a double oblique transverse view (the real short axis of the valve) and a complete anatomical analysis can be easily done.[65] The type of valve, tricuspid or bicuspid, the extent of valve

calcification and its exact location (which cusp and where), the length of each leaflet, the left, right and non-coronary sinuses diameter and the AVA with planimetry can be estimated (of note this is the anatomical area not the hemodynamic) in diastole at 75% of the cardiac cycle and in systole at phase 35%.[65, 66] The aortic annulus area and perimeter can be accurately measured by planimetry at the real short axis, allowing accurate sizing of the prosthetic valve in severe AS patients in order to avoid prosthesis patient mismatch and paravalvular regurgitation after the implantation of a transcatheter valve.[67] Then the aortic root can be evaluated, the diameter of sinotubular junction and the distance of the coronaries origin from the annulus in the pre-TAVR assessment to avoid obstruction of the coronaries.[65, 66] An area that always has to be accurately measured for the diagnosis of severe AS is the left ventricular outflow tract. It has been demonstrated that this area is not circular but oval in shape and thus calculating it by one diameter as a circle instead of measuring the area by planimetry on 3-dimentional echocardiography imaging leads to overestimation of AS.[68] The next step evolution is the introduction of the planimetered area on MDCT (Figure 3) in the continuity equation.

**Mitral Regurgitation**

MDCT has been recently applied to illustrate based on its best spatial resolution the complex mitral valve. The quantification of MR by PISA method has been described above and the value of 3D imaging for the more accurate measurement of effective regurgitant area has been annotated. A study including primary and secondary MR proposed the integration of real cross-sectional mitral effective regurgitant area measured on the 3D volume dataset taken by MDCT in the PISA equation and proved that the fusion regurgitant volume estimated significantly reclassified 7/73 patients from severe MR according to echocardiography to non-severe MR and 10/73 from non-severe to severe MR grade.[69] Secondary MR due to atrial remodeling - type I Carpentier – has been studied and confirmed that mitral annulus area and perimeter measured by planimetry on short axis were independently associated with significant MR, shading light to the pathophysiology of atrial functional MR.[70] In primary MR, MDCT can reliably detect the prolapsing scallop by cross-referencing long-axis views with short-axis views of the various scallops and can evaluate left ventricular and left atrial size.[71] Moreover, the use of MDCT has been explored for annulus evaluation of size and calcifications (extent, location) which is important in planning percutaneous mitral prosthesis implantation.[72] Another important role of MDCT is to predict the left ventricular outflow tract obstruction after the implantation of transcatheter prosthesis achieved by 2 means: 1. By evaluating the aorto-mitral angle created by the left ventricular outflow tract long-axis and the mitral annular trajectory line; the risk of obstruction is high at 90° and lowest when the two valves are almost parallel and the angle almost 0°. 2. By using the dedicated software created for evaluating the neo-outflow tract.[73]

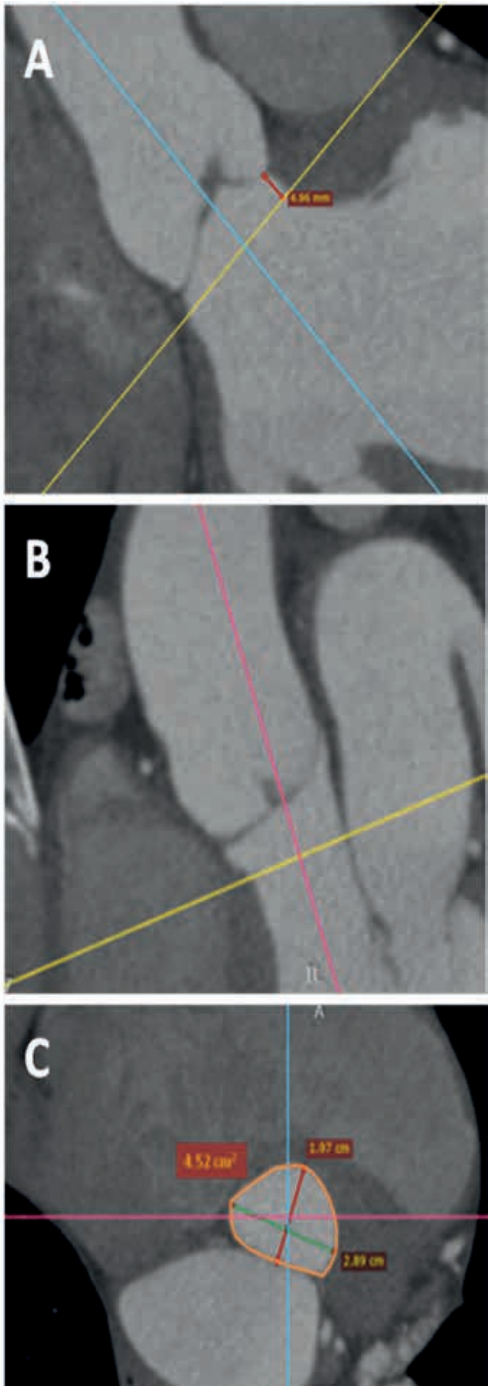


**Figure 3.** Cardiac multidetector computed tomography provides a 3-dimentional cardiac volume and by applying the tri-planar orthogonal system in the coronal (A) and saggital (B) view at the level of left ventricular outflow tract (LVOT) ie 5mm below aortic annulus, the double-oblique view is created (C) where the real LVOT short axis can be seen. Then, the LVOT area can be accurately measured by planimetry of the area.

# LEFT VENTRICULAR SYSTOLIC FUNCTION ASSESSMENT IN LEFT-SIDED VALVULAR HEART DISEASE

**Clinical value of global longitudinal strain**

Global longitudinal strain (GLS) derived by speckle tracking echocardiography has emerged as an alternative way to assess LVEF. This technique is based on detecting and following the movement of myocardial speckles in the longitudinal way. Its advantage is that it is relatively independent of preload and afterload changes compared to LVEF and that it evaluates the intrinsic myocardial function and not on the volumetric changes of left ventricle which is the case in LVEF.[74, 75] Moreover, the changes in pressure and volume loading conditions of the left ventricle may cause myocardial diffuse interstitial fibrosis and focal mid-wall fibrosis starting from the basal parts of the ventricle in AS or subendocardial interstitial fibrosis in MR, which can be indirectly detected by GLS.[76, 77] In this regard, the clinical value of GLS in valvular heart disease should be appreciated.

**Aortic stenosis**

AS is a disease of the valve and myocardium. The increased pressure overload causes left ventricular hypertrophy with excess mass, relative wall thickness increase and concentric hypertrophy. When the left ventricle cannot further compensate for the imbalance with the afterload, LVEF deteriorates, the haemodynamic consequences of the disease become obvious and symptoms become clinically apparent.[78] It has been demonstrated that GLS worsens as the severity of the valve disease progresses, although LVEF remains stable.[79] GLS has been suggested as a more sensitive marker of subtle myocardial dysfunction before the LVEF is reduced and the symptoms appear.[79, 80] This is of paramount importance as it could lead to AVR before any ischemic, systolic and diastolic damage is done to the myocardium and in advance of irreversible structural and functional myocardial changes.[78, 80] Figure 4 demonstrates such a case. The guidelines propose for the asymptomatic severe AS the cut-off 50% for LVEF as an indication to AVR. However, there are studies challenging this cut-off as too low by demonstrating that when LVEF is lower than 60% there is a decline to outcome.[81, 82] Maybe it is time to incorporate in the formal assessment of asymptomatic AS the GLS as an expression of early endomyocardial dysfunction irrespective of left ventricular remodeling that may preserve the LVEF.[78, 80] For such patients the GLS >-18% has been suggested for an integrate approach of stenosis severity, timely treatment decision and better clinical outcome.[78, 83]

AS has been categorised according to forward flow and gradient and the groups of low-flow low-gradient with reduced (classical) or preserved (paradoxical) LVEF have been recognised as severe AS. GLS has a prominent role in enlightening the pathophysiology of low-gradient severe AS with preserved LVEF. Left ventricular remodeling with thick walls and small cavity has a compensatory effect to intrinsic myocardial dysfunction and creates a supernormal LVEF, while the GLS is impaired.[84] This impaired GLS is an

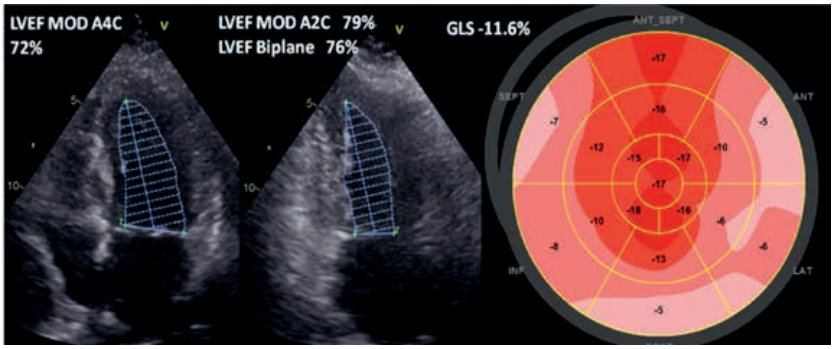


**Figure 4**. In an asymptomatic patient with severe aortic stenosis and preserved left ventricular ejection fraction (LVEF 76%), the global longitudinal strain GLS evaluated by speckle tracking echocardiography is impaired -11.6%, and worse in the basal segments of the left ventricular myocardium, indicating endomyocardial dysfunction.

explanation of the low-flow and thus low-gradient condition although LVEF remains preserved.[14] However, the prognostic value of GLS in these patients is not well elucidated. On the contrary for the patients with low-flow, low-gradient with reduced LVEF, GLS prognostic value has been proven by studies from the TOPAS cohort.[85] GLS is impaired alongside with LVEF but has independent prognostic value measured at rest and stress during the low-dose dobutamine stress echo that the TOPAS patients undergone.[86] Recently, the GLS cut-off of >-12% has been suggested to identify patients with lack of reverse remodeling after TAVR.[87]

GLS not only detects the subtle myocardial changes and defines the prognosis in severe AS with high or low gradient; it has also the ability to elicit subtle changes in myocardial function post AVR when the pressure overload is retracted. After 1.5 years of surgical AVR, GLS improves although LVEF is still stable and this is due to afterload reduction rather than mass reduction or reverse remodeling.[88] After TAVR in AS patients the GLS improved at 1-year follow-up and the greatest the improvement the lower the mortality rate.[89] However, there are scarce data about the left ventricular functional recovery after TAVR in low-gradient AS.

**Mitral regurgitation**

In order to avoid the poor outcome of primary MR it has to be repaired at the proper time, which is defined by symptoms or by LVEF and left ventricular dilation in asymotomatic patients.[8] In severe MR volume overload and emptying of the ventricle partly to a low pressure cavity, left atrium, leads to increased LVEF, because this is merely volume dependent. Thus LVEF may not accurately reflect myocardial performance or may mask myocardial dysfunction. Left ventricular GLS in such patients has been independently associated with survival after mitral valve repair and GLS <-20% has been proposed to define the appropriate timing of surgical repair (Figure 5).[90] Pre-operative GLS has increased prognostic value when added on top of the classical proposed by guidelines factors such as age, left atrial size, LVEF, atrial fibrillation.[91] Thus in primary MR GLS enables early detection of subtle myocardial dysfunction designating the optimal surgical timing for better outcome.

The clinical and prognostic value of GLS has been scarcely investigated in secondary MR. A study of 41 patients with secondary MR, treated with MitraClip demonstrated that GLS was the only independent predictor of cardiac events at 2-years follow-up.

**Clinical value of forward stroke volume**

**Aortic Stenosis**

The forward flow is a parameter of paramount importance in the assessment of AS severity. The low-flow defined as stroke volume index ≤35ml/m$^2$ may be the reason for low-gradient although the AS is severe. Thus, the forward stroke volume has been implemented in the guidelines for the assessment and categorization of AS.[7, 8] The low-flow may be attributed to the low LVEF called "classical low-flow" or to the small left ventricular cavity due to remodeling or diastolic or intrinsic systolic dysfunction, despite the preserved LVEF called "paradoxical low-flow". If the low-flow is associated with high gradient AS, this is indicative of super severe AS, implying that the aortic valve opening is so small that the pressure gradient is elevated even though the forward flow through the valve is low.[14]

The forward stroke volume, having such a prominent role in diagnosis and classification of severe AS, has been inevitably studied for its clinical consequences. The patients with preserved LVEF and low-flow, low-gradient severe AS had worse survival compared with the high-gradient AS patients after AVR and when they followed conservative treatment their survival was as poor as or even worse than the high-gradient AS patients treated medically.[92, 93] The normal-flow, low-gradient, preserved LVEF AS patients had survival comparable to the moderate AS and better that the low-flow, low-gradient.[94] However, in another study, the normal-flow low-gradient AS patients who were treated medically had comparable outcome with the low-flow low-gradient AS patients, creating a controversy.[15] When all AS patients were treated with AVR the 10-year survival was worse for those with low-flow (low-flow, low-gradient 37±10% and low-flow, high gradient 51±8%) and better for those with normal flow (normal-flow low-gradient 61±7% and normal-flow, high-gradient 68±4%).[16]

Patients with low LVEF that leads to low-flow (classical low-flow low-gradient AS) are at very high surgical risk. However, these patients if left untreated (under medical care without AVR), have poor prognosis and very high

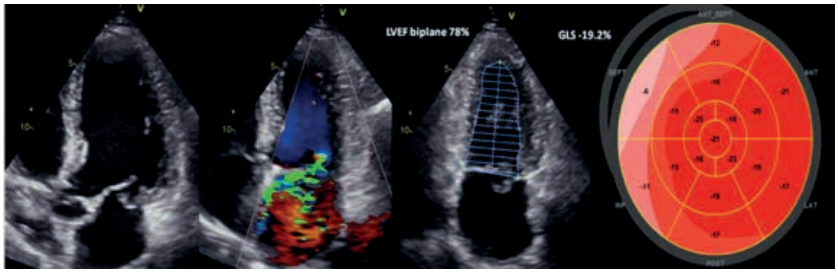


**Figure 5**. A case of an asymptomatic patient with primary organic mitral regurgitation due to posterior leaflet prolapse and preserved left ventricular ejection fraction (LVEF 78%) who has impaired global longitudinal strain by speckle tracking echocardiography (GLS -19.2%). According to the impaired GLS that was worse than -20% the patient was considered for surgical mitral valve repair.

mortality rate.[11, 56] On the other hand their survival is significantly improved with surgical AVR especially if there is flow-reserve, i.e. stroke volume increase by >20%, during the low-dose dobutamine stress echocardiography. Otherwise, there is high operative mortality.[56] This obstacle of the peri-operative mortality for those patients has been surpassed nowadays by treating them with TAVR; the presence or absence of forward flow reserve had no impact on the survival post-TAVR and furthermore, LVEF improved in both patient groups.[54]

When all AS patients were treated with TAVR the low-flow was an independent predictor of poor survival.[95, 96] However, the outcome was significantly better for the low-flow patients if treated with TAVR, which is the preferred method of treatment, compared to medical care alone.[95] Even the patients with heart failure and low-flow with moderate AS may be considered for TAVR, to unload the left ventricle and increase the forward flow, but the answer to these triggering thoughts will be given after the completion of the UNLOAD trial.[97]

In case this low-flow state is not improving after TAVR and remains low at discharge, it is indicative of poor outcome.[98]

**Mitral Regurgitation**

In MR patients LVEF may be increased without corresponding to good left ventricular function, because it merely represents a change in total left ventricular volume from diastole to systole without taking into consideration where the blood goes. In MR the left ventricle partially empties into the low-pressure left atrium, instead of the high-pressure aorta. Thus the forward left ventricular flow and the blood supply to the periphery is reduced. Thus, the forward stoke volume and forward ejection fraction (forward stroke volume expressed as a percentage of left ventricular end-diastolic volume) may be better predictors of left ventricular function and more clinically relevant. Comparing with AS, in MR the patients with preserved LVEF and low-flow state can be identified. Although the impact of forward flow on AS prognosis has been extensively studied and the low-flow has been recognized to be deleterious on survival, its role in MR has not been yet elucidated.

# OBJECTIVES AND OUTLINE OF THE THESIS

The current thesis explores the most common left-sided valvular heart diseases: AS and MR. By applying novel techniques such as deformation imaging by echocardiography and 3-dimentional imaging with excellent spatial resolution by MDCT the diagnosis of left-sided valvular heart disease and its prognosis after surgical or novel transcatheter treatment, is enlightened through this thesis.

**Part I** focuses on aortic valve stenosis diagnosis and management. Chapter 2, explores the use of fusion AVA for reclassification of AS severity in patients with low-gradient AS and preserved LVEF, by implementing the planimetered left ventricular outflow tract area on MDCT in the continuity equation. In chapter 3 the diagnosis and management of AS in patients with heart failure and reduced ejection fraction are reviewed. Chapter 4, aims to prove that left ventricular functional recovery and reverse remodeling occurs after TAVR in patients with low-flow and low-gradient AS with reduced or preserved ejection fraction. Chapter 5 refers to the management of severe AS with surgical sutureless or transcatheter aortic valves and aims to compare the hemodynamic performance of the two different valve types and the impact clinical outcomes in propensity score-matched high-risk populations.

**Part II** focuses on secondary mitral valve regurgitation diagnosis and management. Chapter 6 aims to investigate whether in patients with secondary MR, speckle tracking GLS is an alternative and better, than LVEF, way to assess left ventricular systolic function. Chapter 7 studies patients with non-ischemic dilated cardiomyopathy and secondary MR and evaluates left ventricular reverse remodeling and increase of forward flow after mitral valve repair.

**Part III** studies the prognosis of AS and MR. Chapter 8, evaluates the calcium of aortic and mitral valve detected on contrast-enhanced MDCT and its association with the outcome in patients with suspected coronary artery disease. Chapter 9 studies the impact of left ventricular forward flow and GLS on outcome post AVR in patients with low-gradient severe AS and preserved LVEF. In chapter 10, patients with severe secondary MR are evaluated with the aim to identify the prognostic implications of left ventricular forward flow after surgical mitral valve repair.

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