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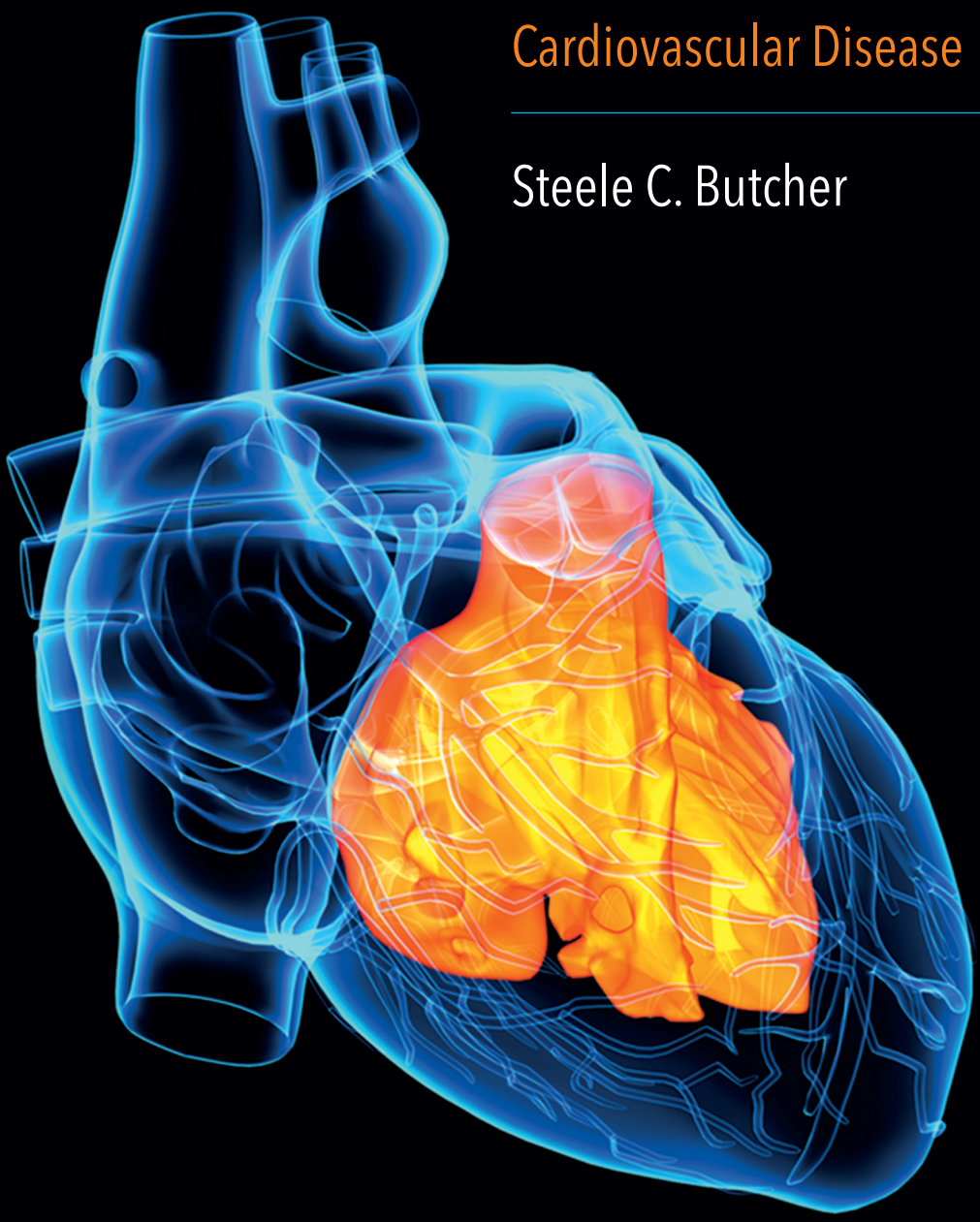

Novel Imaging Insights into Cardiac Remodeling, Myocardial Function and Risk Stratification in Cardiovascular Disease

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The studies presented in this thesis were performed in the Department of Cardiology of Leiden University Medical Center, Leiden, The Netherlands.

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Novel Imaging Insights into Cardiac Remodeling, Myocardial Function and Risk Stratification in Cardiovascular Disease

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General introduction and outline of the thesis

GENERAL INTRODUCTION

Non-invasive imaging has revolutionized the way clinicians evaluate patients with cardiovascular disease. Multimodal non-invasive imaging has facilitated significant advances in the diagnosis of cardiac disease, while also providing new opportunities for the prediction of patient outcomes. In clinical practice, echocardiography remains the first imaging technique of choice to evaluate cardiac dimensions and function. However, in recent years, there has been a shift from use of conventional echocardiographic parameters (such as left ventricular ejection fraction (LVEF) and cardiac chamber volumes) to the use of advanced strain imaging by speckle tracking echocardiography, which provides a more sensitive and robust evaluation of cardiac function[1, 2].

New developments based on strain imaging have allowed for the non-invasive assessment of myocardial work of the left ventricle, providing a deeper insight into myocardial performance and energetics[3, 4]. Indeed, by accounting for afterload and myocardial work efficiency, myocardial work evaluation with left ventricular (LV) pressure-strain loops (Figure 1) has been demonstrated to offer incremental prognostic value over LV global longitudinal strain[5, 6]. Due to the greater afterload dependency of the right ventricle compared to the left ventricle, the evaluation of noninvasive right ventricular (RV) myocardial work could improve the non-invasive understanding of RV performance[7]. However, despite this, current imaging parameters of RV function used in clinical practice, such as tricuspid annular plane systolic excursion (TAPSE), RV longitudinal strain and RV fractional area change (FAC), do not account for RV afterload and do not provide an estimate of mechanical efficiency[8, 9]. RV pressure-strain loop analysis has the potential to non-invasively improve a clinician's understanding of the RV pathophysiology of an individual patient and enhance risk stratification in those with RV pathology, such as patients with pulmonary arterial hypertension. In addition, measurements of myocardial work and strain may be influenced by the type of cardiac remodeling, which may also vary according to the underlying disease[10]. Indeed, greater understanding of cardiac remodeling may improve understanding of concomitant or future changes in myocardial function.

Valvular heart disease accounts for a significant burden of disease in Western countries and likely remains undetected in a significant proportion of the population[11]. Indeed, at present it is estimated that approximately 41 million people worldwide are affected by rheumatic heart disease, with 24 million affected by degenerative mitral valve disease and 9 million by calcific aortic stenosis[12]. There is promise that non-invasive imaging techniques evaluating myocardial remodeling and function may identify patients with valvular heart disease who could benefit most from specific therapies. For example, the use of imaging techniques to establish the extent of cardiac involvement may be particularly important for the development of algorithms that facilitate referral

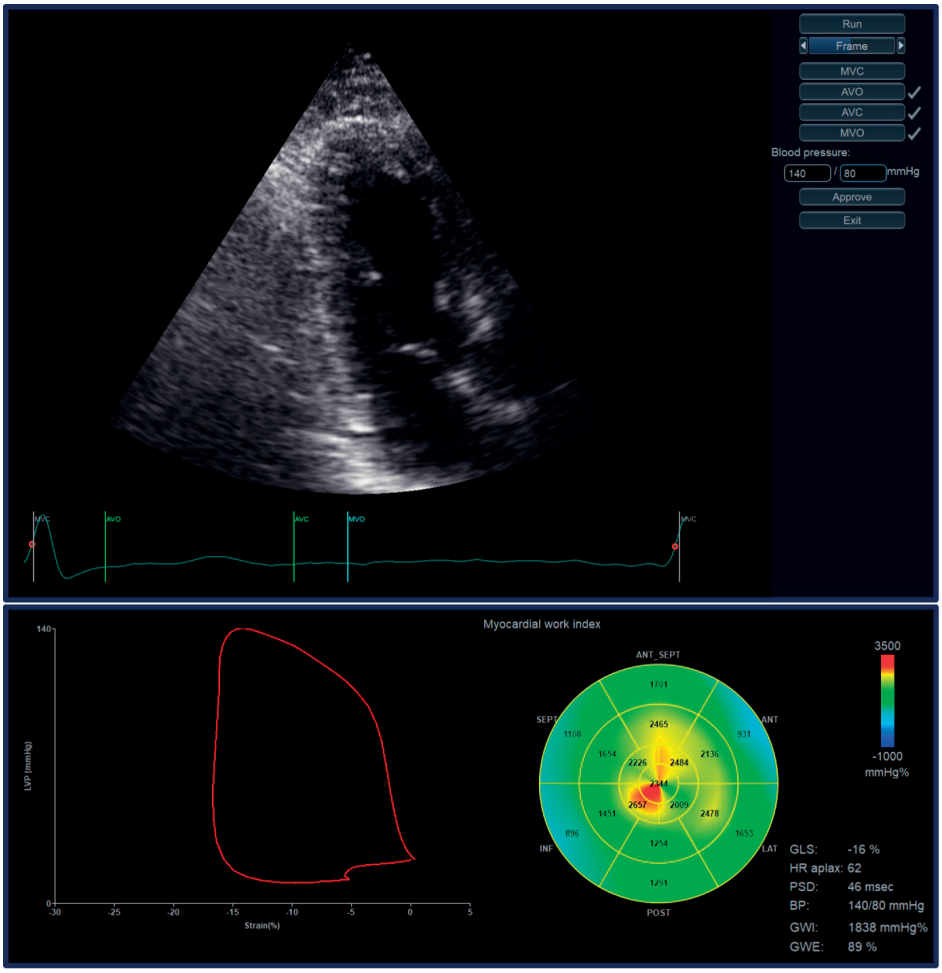

Figure 1: The upper panel demonstrates the synchronization of valvular event timings with LV strain and incorporation of systolic blood pressure. A LV pressure-strain loop (red outline) and bulls-eye plot of LV myocardial work index are displayed in the lower panel. LV pressure strain loops are used to provide a quantitative estimate of LV function that accounts for afterload and mechanical efficiency.

for timely intervention. At present, most guideline recommendations for intervention in valvular heart disease are based on observational data and depend on either the presence of symptoms or specific thresholds of isolated imaging parameters. However, the recognition of high-risk phenotypes with multiple abnormal parameters of cardiac structure and/or function may identify patients at even higher risk than patients who meet the traditional thresholds for intervention. The identification of such a phenotype may also increase the clinician's certainty of the significance of the hemodynamic consequences and severity of the underlying valvular lesion.

In addition, guideline recommendations for patients with bicuspid aortic valve are frequently extrapolated from data from patients with a tricuspid aortic valve. Indeed,

despite the availability of extensive data regarding the risk stratification and management of patients with tricuspid aortic valve disease, there is limited data which supports that identical recommendations should be applied to patients with a bicuspid aortic valve, a cohort who are considerably younger, with fewer comorbidities, and whom may have important differences in cardiac remodeling and function[13, 14]. Further understanding of myocardial remodeling and function for this important patient group is urgently needed, to enhance risk stratification and facilitate appropriate timing for intervention.

OUTLINE OF THE THESIS

The objective of this thesis was two-fold: (i) To investigate the utility of the non-invasive evaluation of RV myocardial work and, (ii) to investigate the role of echocardiography for the risk stratification of patients with valvular heart disease. In this thesis, novel and established imaging techniques have provided new insights into the pathophysiology and outcomes of various cardiac diseases.

In **part I**, a novel method of evaluating RV function is described and validated. **Chapter 2** provides a proof of concept for the feasibility of RV myocardial work assessment on 2-dimensional speckle tracking strain echocardiography. This concept was validated in **chapter 3** with hemodynamic parameters and outcome in a population with precapillary pulmonary hypertension who underwent right heart catheterization.

Part II includes six chapters focused on novel insights into the risk stratification of patients with valvular heart disease. **Chapter 4** demonstrates the differences and prognostic implications of LV remodeling in different types of bicuspid aortic valve disease, while **chapter 5** shows the association between left atrial enlargement and outcome in patients with aortic regurgitation due to a bicuspid aortic valve. **Chapter 6** evaluates the prevalence and prognostic relevance of mitral regurgitation in patients with a bicuspid aortic valve and **chapter 7** investigates the importance of LV ejection fraction in patients with significant bicuspid aortic stenosis, aortic regurgitation, and mixed aortic valve disease. **Chapter 8** evaluates the mechanisms linking renal function and significant tricuspid regurgitation and associated prognostic implications. **Chapter 9** evaluates the prognostic role of the number of secondary outcome determinants (left atrial enlargement, pulmonary hypertension, tricuspid regurgitation, and atrial fibrillation) on post-surgical survival in patients with degenerative mitral regurgitation.

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PART I

NON-INVASIVE RIGHT VENTRICULAR MYOCARDIAL WORK ANALYSIS

2

Right ventricular myocardial work: proof-of concept for non-invasive assessment of right ventricular function

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ABSTRACT

Aims

Right ventricular myocardial work (RVMW) is a novel method for non-invasive assessment of right ventricular (RV) function utilizing RV pressure–strain loops. This study aimed to explore the relationship between RVMW and invasive indices of right heart catheterization (RHC) in a cohort of patients with heart failure with reduced left ventricular ejection fraction (HFrEF), and to compare values of RVMW with those of a group of patients without cardiovascular disease.

Methods and results

Non-invasive analysis of RVMW was performed in 22 HFrEF patients [median age 63 (59–67) years] who underwent echocardiography and invasive RHC within 48 h. Conventional RV functional measurements, RV global constructive work (RVGCW), RV global work index (RVGWI), RV global wasted work (RVGWW), and RV global work efficiency (RVGWE) were analysed and compared with invasively measured stroke volume and stroke volume index. Non-invasive analysis of RVMW was also performed in 22 patients without cardiovascular disease to allow for comparison between groups. None of the conventional echocardiographic parameters of RV systolic function were significantly correlated with stroke volume or stroke volume index. In contrast, one of the novel indices derived non-invasively by pressure–strain loops, RVGCW, demonstrated a moderate correlation with invasively measured stroke volume and stroke volume index ($r = 0.63$, $P = 0.002$ and $r = 0.59$, $P = 0.004$, respectively). RVGWI, RVGCW, and RVGWE were significantly lower in patients with HFrEF compared to a healthy cohort, while values of RVGWW were significantly higher.

Conclusion

RVGCW is a novel parameter that provides an integrative analysis of RV systolic function and correlates more closely with invasively measured stroke volume and stroke volume index than other standard echocardiographic parameters.

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (i.e. dyspnoea, oedema, and fatigue) caused by a structural and/or functional cardiac abnormality resulting in a reduced cardiac output and/or elevated filling pressures.[1] With an estimated global prevalence of 38 million individuals,[2] HF is a leading cause of hospitalization and morbidity.[3]

While many echocardiographic parameters provide important prognostic information for patients with HF and reduced left ventricular (LV) ejection fraction (HFrEF) (i.e. LV ejection fraction (EF), LV global longitudinal strain),[4] the value of indices evaluating the function of the right ventricle have become increasingly recognized.[5] Right ventricular (RV) speckle tracking echocardiography-derived longitudinal strain is angle-independent and less load-dependent than other conventional parameters of RV systolic function [such as RV fractional area change (FAC) or tricuspid annular plane systolic excursion (TAPSE)][6] and has been demonstrated to have an important role in the prediction of outcomes for individuals with HFrEF.[7]

Despite demonstrating superiority over conventional two-dimensional echocardiography parameters for the evaluation of RV systolic function,[5,8] RV longitudinal strain is a more afterload-dependent parameter than LV global longitudinal strain, due to the thinner walls and lower ventricular elastance of the right ventricle.[9] Furthermore, RV longitudinal strain does not integrate RV dyssynchrony or post-systolic shortening into its quantitative output, components of RV function that have been demonstrated to correlate with invasively derived cardiac index.[10]

Recently, LV myocardial work, a non-invasive estimate of the LV pressure–volume loop, was proposed as method to provide a comprehensive evaluation of LV systolic function, accounting for both afterload and LV dyssynchrony. LV myocardial work is calculated from LV pressure–strain loop analysis, incorporating speckle tracking echocardiography-derived LV global longitudinal strain and non-invasive brachial cuff blood pressure measurements.[11] However, no such technique has been applied for the estimation of RV function, neither for individuals with HFrEF nor for any other patient group. Therefore, the present study aimed to explore the relationship between the non-invasive estimation of RV myocardial work (RVMW) and invasive indices of right heart catheterization (RHC) in a cohort of patients with HFrEF, utilizing software dedicated for myocardial work analysis of the left ventricle. An additional aim was to compare the values of RVMW in a cohort with HFrEF with those of a group of patients without cardiovascular disease.

METHODS

Study population

From the departmental electronic records of the Leiden University Medical Center (Leiden, The Netherlands), all patients with HFrEF who underwent RHC during the period of January 2006–July 2020 were selected. Those who had an echocardiogram performed within 48 h of RHC were included for further evaluation (Figure 1). Patients with active endocarditis, severe tricuspid regurgitation (TR), and congenital heart disease were excluded. Additionally, a healthy population consisting of individuals without cardiovascular disease who underwent echocardiography during the same period as the HF patients were selected for derivation of the normal reference values for RVMW indices.[12] Patient demographics and clinical data were collected from the departmental electronic medical record (EPD-vision; Leiden University Medical Center, Leiden, The Netherlands). As this study involved the retrospective analysis of clinically acquired data, the institutional review board of the Leiden University Medical Center waived the need for written patient informed consent. The data that supports the findings of this study are available on reasonable request to the corresponding author.

Right heart catheterization

All procedures were performed in the catheterization laboratory by an experienced interventional cardiologist. A standard 7.5 Fr triple lumen Swan Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted via an 8 Fr introducer sheath through the right femoral or right internal jugular vein at the operator's discretion and advanced to the left or right pulmonary artery under fluoroscopic guidance. Right atrial (RA) pressure, systolic and diastolic RV pressure, systolic, diastolic, and mean pulmonary artery pressure (mPAP), and pulmonary capillary wedge pressure (PCWP) were obtained at end-expiration. Cardiac output was obtained by thermodilution, as the average of three measurements. Stroke volume index and cardiac index were calculated by indexing stroke volume and cardiac output to body surface area, respectively (estimated using the Dubois formula). RV stroke work was calculated according to methods previously described.[13]

Echocardiographic data acquisition and standard measurements

Comprehensive transthoracic echocardiography was performed utilizing a Vivid 7 or E9 ultrasound system (General Electric Vingmed Ultrasound, Milwaukee, WI, USA) with patients at rest in the left lateral decubitus position. Electrocardiogram-triggered echocardiographic data were acquired with 3.5MHz or M5S transducers. Data were stored digitally in a cine-loop format for offline analysis with EchoPAC software (EchoPAC 204, General Electric Vingmed Ultrasound). LVEF was calculated using the biplane Simpson

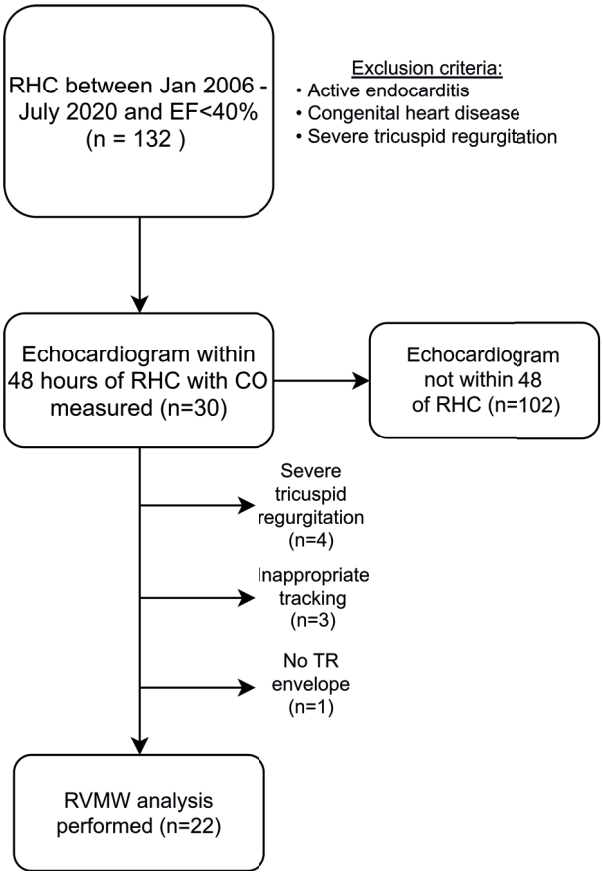

Figure 1: Study flow chart. EF, ejection fraction; RHC, right heart catheterization; RVMW, right ventricular myocardial work; TR, tricuspid regurgitation.

method, while LV mass was calculated using the standard linear two-dimensional approach.[14] TAPSE was measured on M-mode recordings of the lateral tricuspid annulus in an RV-focused apical view, while peak systolic myocardial velocity of the RV lateral annulus (RV S') was measured using tissue Doppler imaging, according to guideline recommendations.[14] RV end-systolic and end-diastolic areas were acquired in an RV-focused apical view, with RV FAC calculated as: RV FAC = [(RV end-diastolic area - RV end-systolic area)/RV end-diastolic area] X 100%.[14] Systolic pulmonary artery pressure (PASP) was estimated from the TR jet peak velocity applying the modified Bernoulli equation and adding mean RA pressure. Estimated mean RA pressure was derived from the inferior vena cava diameter and its collapsibility.[15] Pulmonary artery mean pressure (PAMP) was obtained by the formula: mean RV-RA gradient+ mean RA pressure. The mean RV-RA gradient was calculated by tracing the TR velocity-time integral.[16] Pulmonary artery diastolic pressure (PADP) was calculated as: PADP = 1.5 X [PAMP - (PASP/3)].[15] All other

standard measurements were performed according to the American Society of Echocardiography guidelines.[14]

Quantification of RVMW

The novel indices of RVMW were analysed utilizing proprietary software originally developed for the assessment of LV myocardial work by two-dimensional speckle tracking echocardiography (EchoPAC Version 204). This software has been validated for a variety of different patient subgroups for the measurement of LV myocardial work.[11,17] The non-invasive evaluation of LV myocardial work was first developed by Russell et al.[11] as a tool for the estimation of LV myocardial oxygen consumption. In this non-invasive model, an estimate of the area of the myocardial force-segment length loop was approximated by non-invasive brachial cuff blood pressure recordings (as a substitute for myocardial force) and global longitudinal strain by speckle-tracking echocardiography (as a substitute for segment length), and was validated with pressure–volume loops derived invasively with micromanometer-tipped catheters. Similar principles may be applied to the right ventricle, allowing for the approximation of RV myocardial force-segment length loops with pressure– strain loops. Pulmonary pressures may be used to derive an estimate of myocardial force, while strain derived by speckle tracking echocardiography can be used to estimate changes in segment length.

An RV-focused apical four chamber view was used to evaluate RV global longitudinal strain, with the region of interest including both the RV free wall and interventricular septum.[18] Analysis of RV global rather than free wall strain was performed because the left ventricle, via the septum, is estimated to contribute up to 20–40% to overall RV stroke volume and pulmonary flow.[19,20] Measurements of RV strain and pulmonary systolic and diastolic pressures were then synchronized by cardiac cycle timings (determined by pulmonic and tricuspid valve events) to produce noninvasively derived pressure–strain loops for the right ventricle (Figure 2). The event timings of the pulmonic valve were determined by pulsed-wave interrogation in the basal parasternal short-axis view, while tricuspid valve event timings were derived from direct visualization in the RV-focused apical four-chamber view. Whenever both valve timings were adequately visualized in the parasternal short-axis view at the level of the aortic valve, this was used preferentially.

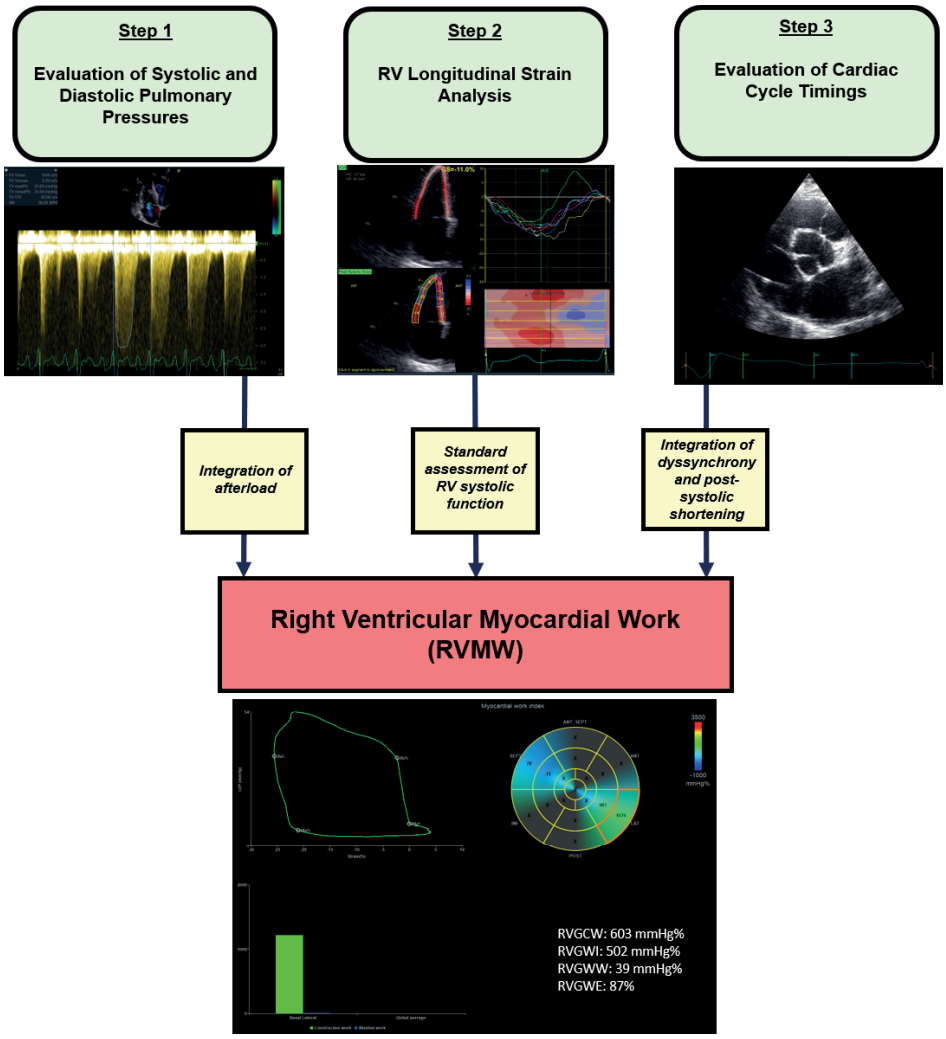

Figure 2: Method for the calculation of RVMW. RVMW provides an integrative analysis of RV function, incorporating speckle tracking echocardiography- derived RV strain, pulmonary pressures, and cardiac cycle timings. Cardiac cycle timings are determined by pulmonic and tricuspid valve opening and closure events, identified through either direct visualization of two-dimensional images or by pulsed-wave Doppler interrogation. Integration of event timings allows for the quantitative evaluation of RV dyssynchrony and post-systolic contraction. Indices of RVMW are calculated based on non-invasively derived pressure–strain loops for the right ventricle. RV, right ventricular; RVGCW, right ventricular global constructive work; RVGWE, right ventricular global work efficiency; RVGWI, right ventricular global work index; RVGWW, right ventricular global wasted work; RVMW, right ventricular myocardial work.

Four parameters of RVMW were derived:

(1) RV global work index (RVGWI, mmHg%): the area within the global RV pressure–strain loop, calculated from tricuspid valve closure to opening.
(2) RV global constructive work (RVGCW, mmHg%): defined as the work contributing to the shortening of the cardiac myocytes during systole and the lengthening during isovolumic relaxation.
(3) RV global wasted work (RVGWW, mmHg%): defined as the work contributing to the lengthening of the cardiac myocytes during systole and the shortening during isovolumic relaxation.
(4) RV global work efficiency (RVGWE, %): defined as RVGCW divided by the sum of RVGCW and RVGWW.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., IBM Corp). Categorical variables are expressed as numbers and percentages. Adherence to a normal distribution was verified using the Kolmogorov–Smirnov test and visual assessment of histograms. Normally distributed continuous variables are presented as mean ± standard deviation while variables that are non-normally distributed are presented as median and interquartile range. Categorical variables were compared using the $\chi 2$ test. Continuous variables were compared using the Student's t-test if normally distributed, while the Mann–Whitney U test was utilized for non-normally distributed variables. Spearman correlation was used to investigate the relationship between invasively derived stroke volume and stroke volume index, and the parameters of RV systolic function (including the novel indices of RVMW). Ten random individuals were selected for evaluation of intraobserver and interobserver agreement using intraclass correlation coefficients (ICCs) and Bland–Altman analysis. Intraobserver measurements were performed offline after a 4-week interval. The second observer was blinded to the measurements of the first observer for interobserver measurements. All tests were two-sided and P-values <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Twenty-six patients with HFrEF fulfilled the inclusion criteria. Four patients were excluded from RVMW analysis due to inappropriate tracking or the absence of a measurable TR envelope (feasibility, 85%). An additional 22 individuals without cardiovascular disease were selected for comparison of the non-invasively derived parameters of RVMW with HFrEF patients. Patients with HFrEF were older (62.5 vs. 53.5 years, P= 0.037) and

more frequently male (77% vs. 32%, P = 0.004) compared to the individuals without cardiovascular disease. Of the HFrEF patients, 73% were in New York Heart Association Class III or IV and 50% had ischaemic cardiomyopathy. Additional patient demographic and clinical data are presented in Table 1.

Table 1: Patient characteristics of HFrEF and no CVD groups

Variable:	HFrEF (n=22)	No CVD (n=22)	P- value
Age (years)	62.5 (59.0-67.3)	53.5 (35.0-65.5)	0.037
Male Sex	17 (77%)	15 (68%)	0.004
Obesity (BMI>30kg/m^2)	3 (14%)	2 (9%)	0.634
CKD (eGFR<60ml/min/1.73m^2)	12 (55%)		
Diabetes	7 (32%)		
COPD	2 (9%)		
Hypertension	6 (27%)		
Dyslipidemia	8 (36%)		
Indication for RHC			
LVAD Workup	16 (73%)		
Evaluation of Cardiomyopathy	6 (27%)		
Aetiology of Heart Failure			
Ischemic	11 (50%)		
Non-Ischemic	11 (50%)		
NYHA Class			
III or IV	16 (73%)		
Medication			
ARB/ACEi/ARNi	18 (82%)		
MRA	18 (82%)		
Diuretics	22 (100%)		
Beta-blocker	17 (77%)		
Oral Anticoagulation	17 (77%)		

Data are presented as median (25th–75th percentile) if not normally distributed.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitors; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RHC, right heart catheterization

Conventional echocardiographic parameters

Patients with HFrEF had a lower LVEF [18.4% (±6.8) vs. 59.9% (±4.6), P< 0.001], LV global longitudinal strain [-3.5% (±1.7) vs. -20.5% (±2.1), P< 0.001], and RV global longitudinal strain [-9.6% (±4.7) vs. -21.8% (±3.0), P< 0.001] when compared to the individuals without cardiovascular disease. In addition, estimated PASP, LV mass index, RV end-diastolic area, RV basal diameter, RV mid-diameter, and indexed RA volume were significantly higher in the HFrEF group, while stroke volume index derived from echocardiography

was significantly lower compared to individuals without cardiovascular disease (Table 2).

Table 2: Echocardiographic characteristics of HFrEF vs no CVD patient groups

Variable	HFrEF (n=22)	No CVD (n=22)	P value
RVGWI (mmHg%)	241.4 (±124.6)	381.2 (±103.6)	<0.001
RVGCW (mmHg%)	344.0 (±125.9)	414.2 (±103.4)	0.017
RVGWW (mmHg%)	70.0 (42.8-134.1)	14.8 (9.3-20.6)	<0.001
RVGWE (%)	73.5 (66.4-86.5)	95.5 (93.4-96.6)	<0.001
LVEF (%)	18.4 (±6.8)	59.9 (±4.6)	<0.001
LV GLS (%)	-3.5 (±1.7)	-20.5 (±2.1)	<0.001
LV mass index (g/m^2)	187.3 (±54.5)	90.2 (±20.9)	<0.001
TAPSE (mm)	14.8 (±3.7)	24.0 (±3.7)	<0.001
RV GLS (%)	-9.6 (±4.7)	-21.8 (±3.0)	<0.001
RV FWLS (%)	-13.3 (±6.6)	-25.3 (±4.2)	<0.001
PASP (mmHg)	41.5 (±12.6)	22.6 (±3.8)	<0.001
Echocardiography-derived stroke volume index (ml/m^2)	27 (22-43)	41 (38-46)	0.009
RV S' (cm/s)	6.8 (±1.7)	10.2 (±1.7)	<0.001
RV FAC (%)	30.9 (±12.5)	49.0 (±9.3)	<0.001
RV EDA (cm^2)	24.4 (±8.6)	19.6 (±4.5)	0.029
RV basal diameter (mm)	49.2 (±12.4)	36.1 (±5.4)	<0.001
RV mid-diameter (mm)	33.5 (±9.0)	27.7 (±5.0)	0.014
TA diameter (mm)	33.5 (±6.5)	26.8 (±5.3)	0.001
RAVI (ml/m^2)	33.6 (23.4-56.3)	22.2 (17.8-27.6)	0.002

Data are presented as mean ± SD if normally distributed or median (25th–75th percentile) if not normally distributed.
CVD, cardiovascular disease; EDA, end-diastolic area; FAC, fractional area change; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; RV FWLS, right ventricle free wall longitudinal strain; RV GLS, right ventricle global longitudinal strain; RV S' , right ventricular S prime; RVGCW, right ventricular global constructive work; RVGWE, right ventricular global work efficiency; RVGWI, right ventricular global work index; RVGWW, right ventricular global wasted work; TA, tricuspid annular; TAPSE, tricuspid annular plane systolic excursion.

Parameters of RVMW by two-dimensional speckle tracking echocardiography

Table 2 compares the values of RVMW indices between HFrEF patients and individuals without cardiovascular disease. As expected, RVGWI [241.4mmHg% (±124.6) vs. 381.2mmHg% (±103.6), P< 0.001], RVGCW [344.0mmHg% (±125.9) vs. 414.2mmHg% (±103.4), P= 0.050], and RVGWE [73.5% (66.4–86.5) vs. 95.5% (93.4–96.6), P < 0.001] were significantly lower, while RVGWW [70.0mmHg% (42.8–134.1) vs. 14.8mmHg% (9.3–20.6), P< 0.001] was significantly higher in the HFrEF group when compared to individuals without cardiovascular disease. Examples of RVMW measurements are demonstrated

in Figure 4. Correlations of parameters of RVMW with standard parameters of RV systolic function are presented in Supplementary data online, Table S1.

RHC parameters

For the 22 patients with HFrEF who underwent invasive RHC, median stroke volume [52.9 (42.8–64.1) mL], stroke volume index [26.4 (22.1–31.3) mL/m^2], and mean cardiac index were reduced (2.1± 0.63 L/min/m^2), while median mPAP [34.7 (18.7–47.0) mmHg], PCWP [20.5 (12.0–34.0) mmHg], and RA pressure [10 (4–17) mmHg] were increased. Additional RHC data are summarized in Table 3.

Table 3: HFrEF patient right heart catheterization characteristics

Variable	n = 22
Right Atrial Pressure (mmHg)	10 (4-17)
sPAP (mmHg)	48.0 ± 19.1
dPAP (mmHg)	26 (12.5-35.5)
mPAP (mmHg)	34.7 (18.7-47.0)
Stroke Volume (ml)	52.9 (42.8-64.1)
Stroke Volume Index (ml/m^2)	26.4 (22.1-31.3)
Cardiac Index (L/min/m^2)	2.1 ± 0.63
RV stroke work (mmHg X ml)	25.8 (14.8-37.3)
PCWP (mmHg)	20.5 (12.0-34.0)

Data are presented as mean ± SD if normally distributed or median (25th–75th percentile) if not normally distributed.
dPAP, diastolic pulmonary artery pressure; HFrEF, heart failure with reduced ejection fraction; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RV, right ventricular; sPAP, systolic pulmonary artery pressure.

Relationship between RHC parameters and parameters of RV systolic function

The correlations between stroke volume and stroke volume index measured on RHC and the various echocardiographic parameters of RV systolic function were evaluated in the cohort of HFrEF patients. None of the standard echocardiographic parameters of RV systolic function were significantly correlated with stroke volume or stroke volume index, including FAC (r= -0.23, P=0.33 and r= -0.13, P= 0.57, respectively), RV global longitudinal strain (r = -0.11, P=0.63 and r= -0.27, P = 0.23, respectively), RV free wall longitudinal strain (r= -0.07, P=0.75 and r = -0.22, P= 0.32, respectively), TAPSE (r=0.25, P=0.27 and r=0.27, P= 0.22, respectively), and echocardiography-derived stroke volume (r=0.25, P=0.27 and r= 0.29, P= 0.19, respectively) (Figure 3). The echocardiographically derived parameters of LVEF, LV global longitudinal strain, RVGWI, RVGWW, RVGWE, and PASP did not significantly correlate with invasively derived stroke volume or stroke volume index. However, one of the novel indices derived non-invasively by pressure–strain

loops, RVGCW, demonstrated a significant correlation with invasively measured stroke volume and stroke volume index (r=0.59, P= 0.004 and r=0.63, P= 0.002, respectively). Additionally, RVGCW was also correlated with cardiac index (r=0.42, P= 0.049) measured during RHC.

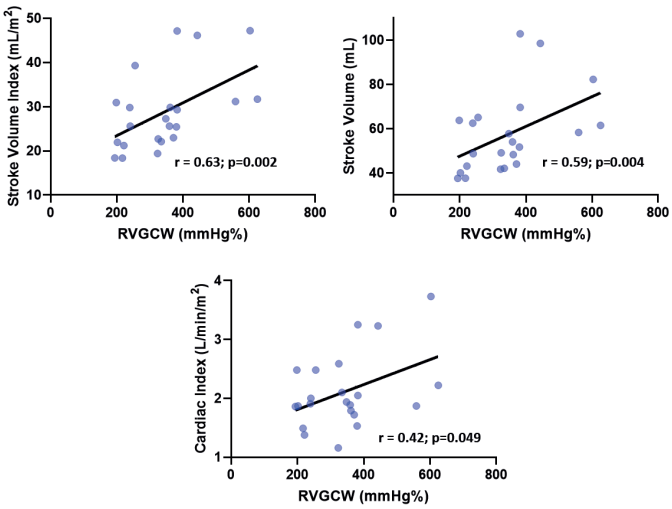

Figure 3: Correlation of RVGCW with invasive parameters of RV systolic function. Significant correlations between RVGCW and invasively derived stroke volume index, stroke volume, and cardiac index are evident. RV, right ventricular; RVGCW, right ventricular global constructive work.

Intraobserver and interobserver variability

The ICC for intraobserver variability was 0.915 for RVGCW (P< 0.001), 0.959 for RVGWI (P< 0.001), and 0.967 for RVGWE (P< 0.001), demonstrating excellent reliability (Table 4). The ICC for intraobserver variability for RVGWW indicated good reliability at 0.868 (P < 0.001). The ICC for interobserver variability for RVGWW was 0.938 (P < 0.001), demonstrating excellent reliability, while the interobserver variability was 0.858 for RVGCW (P = 0.001), 0.802 for RVGWI (P= 0.001), and 0.826 for RVGWE (P< 0.001) indicating good reliability. Bland–Altman analysis for assessing the intraobserver and interobserver variability of the four novel parameters of RVMW is shown in Figure 5.

Table 4: Intraclass correlation coefficients for intra- and interobserver variability for RVMW parameters

	Interobserver variability (n=10)		Intraobserver variability (n=10)	
Variables	**Intraclass correlation coefficient**	**95% confidence interval**	**Intraclass correlation coefficient**	**95% confidence interval**
RVGWI (mmHg%)	0.802	0.394-0.946	0.959	0.845-0.990
RVGCW (mmHg%)	0.858	0.523-0.963	0.915	0.703-0.978
RVGWW (mmHg%)	0.938	0.729-0.985	0.868	0.580-0.965
RVGWE (%)	0.826	0.380-0.956	0.967	0.880-0.992

RVGCW, right ventricular global constructive work; RVGWW, right ventricular global wasted work; RVGWE, right ventricular global work efficiency; RVGWI, right ventricular global work index; RVMW, right ventricular myocardial work.

DISCUSSION

The present study is a proof-of-concept of the feasibility of RVMW indices measurements in HFrEF and its correlation with invasively measured stroke volume and stroke volume index. Compared to a healthy cohort, RVGWI, RVGCW, and RVGWE were demonstrated to be significantly lower in patients with HFrEF, while values of RVGWW were significantly higher. Non-invasively measured RVGCW was the only echocardiographic parameter that showed an association with invasively measured stroke volume and stroke volume index in patients with HFrEF. RVMW indices may enhance the non-invasive understanding of the pathophysiology of patients with HFrEF and improve the non-invasive characterization of their response to therapies.

RVMW in HFrEF vs. patients without cardiovascular disease

Several small studies evaluating LV myocardial work in individuals with HFrEF have demonstrated reduced values of LV global work index, constructive work, and work efficiency when compared to those of healthy controls.[21,22] Furthermore, values of LV wasted work were observed to be higher in those with HFrEF. These differences appeared to be secondary to a combination of increased wasted work due to LV dyssynchrony and a reduction in LV global longitudinal strain.[22] However, non-invasive measurements of RVMW indices have not been published before. The present study shows for the first time the feasibility of the measurement of RVMW indices and compares them between HFrEF patients and individuals without structural heart disease. In patients with HFrEF, a reduction in RVGWI, RVGCW, and RVGWE was observed when compared to a healthy population. Similar to the LV, the lower values of RVGCW, RVGWI, and RVGWE observed in those with HFrEF can be explained by the presence of RV dyssynchrony and increased wasted work. In contrast to the left ventricle, the higher levels of wasted work observed for the right ventricle were likely due to a combination of post-systolic shortening

secondary to pulmonary hypertension and septal dyssynchrony due to ventricular interdependence.

Superiority of RVMW over standard parameters of RV systolic function

Theoretically, the calculation of the indices of RVMW through the estimation of non-invasive pressure–strain loops provides a more comprehensive estimation of RV function when compared to standard echocardiographic measures. In contrast with RV longitudinal strain, TAPSE and RV FAC, the parameters of RVMW integrate contractility, RV dyssynchrony and pulmonary pressures into their quantitation. In addition to providing a more comprehensive assessment of RV function, RVMW is not subject to the technical limitations of other standard parameters of RV systolic function. TAPSE is angle-dependent, load-dependent, and varies according to the degree of cardiac translation,[6,14] while RV FAC is limited by increased load dependency and only fair interobserver reproducibility.[14]

Both experimental and clinical studies have demonstrated that RV longitudinal strain measured by speckle tracking echocardiography is afterload dependent, although less than other standard measures of RV systolic function.[23,24] Therefore, by accounting for afterload, RVMW provides an insight into RV-pulmonary arterial coupling, potentially delivering a more precise estimate of RV systolic function. For example, Figure 4B demonstrates the parameters of RVMW for a patient with HFrEF and an RV global longitudinal strain of -13.2%, while Figure 4C displays the same measurements for an individual with HFrEF and an RV global longitudinal strain of -5.8%. If examining only the difference in RV global longitudinal strain, one would conclude that the patient in Figure 4B has better RV systolic function. However, in this case, much of the difference is secondary to differences in afterload, with invasively measured stroke volume index demonstrating comparable RV systolic function, despite the significant discrepancy in RV global longitudinal strain. Likewise, as RVMW accounts also for pulmonic pressures, estimates of RVGCW were comparable between patients despite the disparity in RV global longitudinal strain. In another example, a comparison can be made between the patients in Figure 4A and B: both had similar RV global longitudinal strain, yet the patient in Figure 4A was generating an equivalent value of RV global longitudinal strain despite a significantly higher afterload. The increased pulmonic pressures were accounted for in RVMW analysis, reflected by the higher values of RVGCW and RVGWI for the individual in Figure 4A. As expected, this patient also had a higher stroke volume index when compared to the patient in Figure 4B.

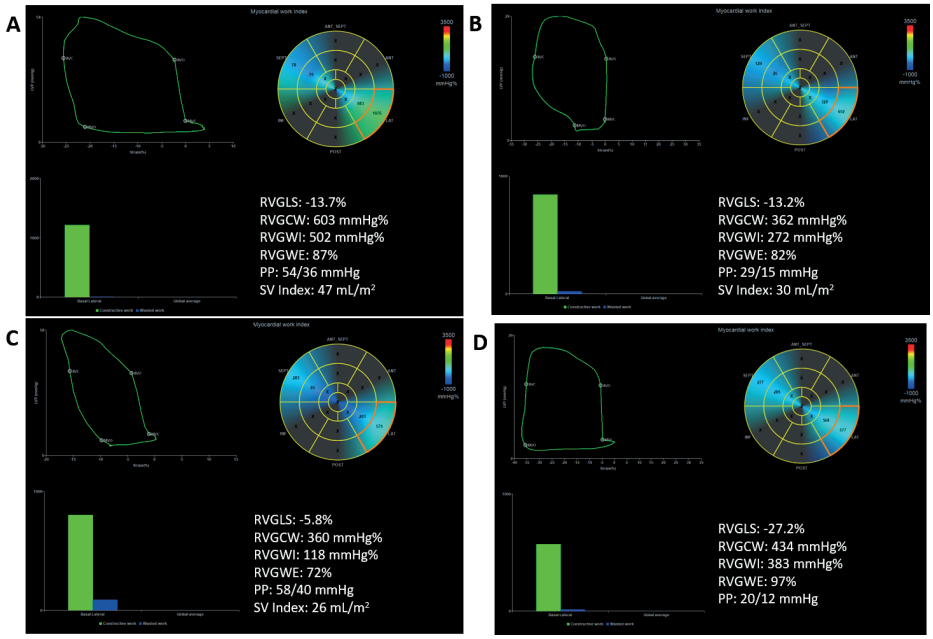

Figure 4: Comparison of RVMW parameters and cardiac index in three patients with HFrEF (A–C) and in one individual without cardiovascular disease (D), demonstrating the important impact of afterload on parameters of RVMW. PP, pulmonary pressures; RVGCW, right ventricular global constructive work; RVGLS, right ventricle global longitudinal strain; RVGWE, right ventricular global work efficiency; RVGWI, right ventricular global work index; RVGWW, right ventricular global wasted work.

RVMW also integrates RV dyssynchrony and post-systolic shortening into its non-invasive estimate of RV function, through the synchronization of pulmonic and tricuspid valvular events with RV longitudinal strain. Any myocardial lengthening occurring during systole and shortening during isovolumic relaxation are recorded as RV wasted work and do not contribute to RV constructive work. Therefore, any inefficient post-systolic shortening does not contribute to estimates of RVGCW, explaining at least in part, the stronger association of RVGCW with stroke volume and stroke volume index compared to conventional parameters of RV systolic function. The impact of RV dyssynchrony on RV function has been demonstrated in a study of 60 consecutive patients with idiopathic pulmonary arterial hypertension, where a significant negative correlation between post-systolic shortening time and invasively measured cardiac index was observed.[10] Similarly, in a cohort of patients with pulmonary arterial hypertension, Marcus et al.[25] observed that a dyssynchronous left-to-right delay of RV myocardial shortening was correlated with a reduced RV stroke volume, an association best explained by the phenomenon of ventricular interdependence. Conventional echocardiographic and speckle tracking echocardiography-derived parameters do not account for the impact of left-to-right delay and ventricular interdependence on RV stroke volume, possibly explaining

the absence of any correlation between these indices and invasively measured stroke volume and stroke volume index. On the other hand, RVMW indices integrate all of these elements of RV dyssynchrony, providing an estimate of the myocardial constructive work that effectively contributes to RV stroke volume.

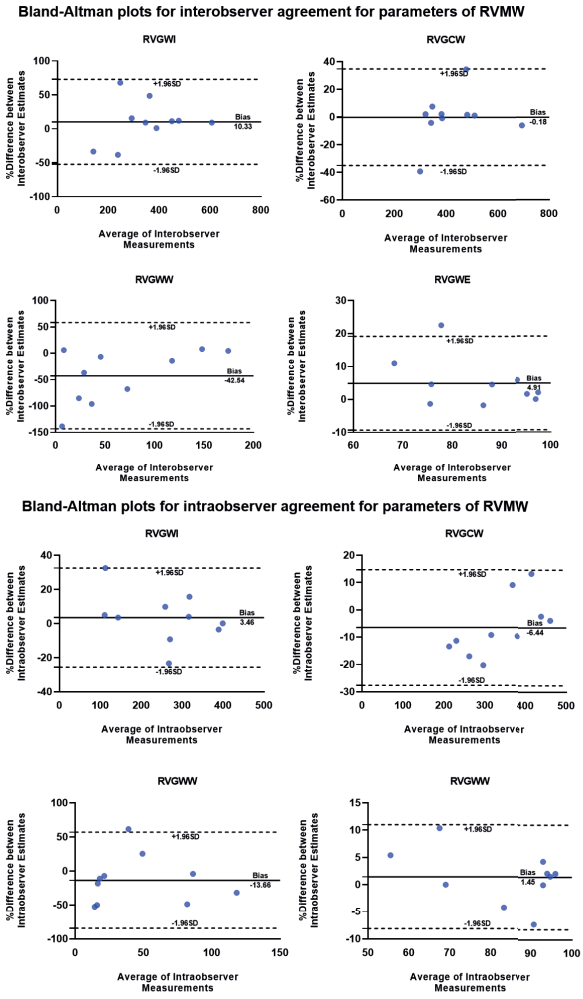

Figure 5: Bland–Altman Plots for interobserver and intraobserver agreement for parameters of right ventricular myocardial work. RVGCW, right ventricular global constructive work; RVGWE, right ventricular global work efficiency; RVGWI, right ventricular global work index; RVGWW, right ventricular global wasted work.

Clinical implications

In this study, we have demonstrated that parameters of RVMW could provide a non-invasive estimate of stroke volume and stroke volume index in individuals with HFrEF.

For serial examinations evaluating treatment response, utilizing speckle tracking echocardiography-derived RV pressure–strain loops could provide a safer alternative than repeating invasive RHC to determine stroke volume or stroke volume index, a procedure with a rate of serious complications of 1.1%.[26] Furthermore, RVMW could be used as a tool to define the prognosis and better characterize a range of RV pathologies by providing a radiation-free, non-invasive estimate of regional RV myocardial energetics and pressure–volume loops. Previously, Russell et al.[11] demonstrated that regional myocardial work distribution derived from the area of non-invasive LV pressure–strain loops strongly correlated with myocardial glucose metabolism by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET). Several studies have demonstrated that the extent of RV glucose uptake on 18F-FDG PET in patients with pulmonary hypertension (including in those with group II pulmonary hypertension) is associated with pressure overload and RV dysfunction[27,28] and may be associated with poor prognosis.[29] This suggests that the non-invasive estimation of RVMW may provide an insight into altered RV energetics in patients with HFrEF, possibly enhancing risk stratification. While speckle tracking echocardiography-derived RV longitudinal strain provides important prognostic information for patients with HFrEF,[5] RVMW could potentially offer incremental predictive benefit through the integration of afterload, quantification of RV dyssynchrony, and estimation of RV myocardial energetics.

Limitations

This study is limited by its single-centre, retrospective design. Furthermore, only a small number of patients were evaluated. Therefore, larger studies will be required to define the normal values of RVMW and to confirm its clinical utility for patients with HFrEF. The generalizability of these results to other RV pathological entities also requires further investigation. In addition, the new echocardiographic measurements were not tested against cardiovascular magnetic resonance or radionuclide ventriculography (considered reference standard for the measurement of RV systolic function). Another important limitation is that the commercial software required for the measurement of RVMW is only provided by a single vendor and was specifically designed for the assessment of myocardial work of the left ventricle. The derivation of LV pressure– strain loops is based on Laplace's law, which makes simple geometric assumptions, therefore, the irregular and complex geometry of the right ventricle could result in calculated values of myocardial work that are less precise than for those of the left ventricle.[30] In the future, validation of non-invasive RV pressure–strain loops with invasively derived RV pressure–volume loops may be required, as these are different from those of the left ventricle.[30] Finally, the limited number of patients precluded us from investigating the association between RVMW parameters and survival (due to the high probability of type II errors).

CONCLUSION

RVGCW, a novel parameter of RVMW, was the only non-invasively derived echocardiographic index that correlated with invasively derived stroke volume and stroke volume index in patients with HFrEF. A potential role in aiding clinical decision-making merits further investigation.

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SUPPLEMENTARY MATERIALS

Table S1: Correlations between indices of RVMW and standard parameters of RV systolic function

r	RV FWS	RV GLS	RV FAC	TAPSE	RV S'
RVGCW	-0.44*	-0.51*	-0.02	0.15	0.16
RVGWI	-0.76**	-0.78**	0.20	0.22	0.46*
RVGWE	-0.70**	-0.78**	0.31	0.30	0.51*
RVGWW	0.49*	0.49*	-0.37	-0.36	-0.49*

RV = Right ventricular, RVGCW = Right ventricular global constructive work, RVGWE = Right ventricular global work efficiency, RVGWI = Right ventricular global work index, RVGWW = Right ventricular global wasted work, RVMW = Right ventricular myocardial work, RV FAC = Right ventricular fractional area change, RV FWLS = Right ventricular free wall longitudinal strain, RV GLS = Right ventricular global longitudinal strain, RV S'= Right ventricular S prime; TAPSE = Tricuspid annular plane systolic excursion.

*p<0.05

**p<0.01

3

Right Ventricular Myocardial Work Characterization in Patients With Pulmonary Hypertension and Relation to Invasive Hemodynamic Parameters and Outcomes

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ABSTRACT

Noninvasive evaluation of indexes of right ventricular (RV) myocardial work (RVMW) derived from RV pressure-strain loops may provide novel insights into RV function in precapillary pulmonary hypertension. This study was designed to evaluate the association between the indexes of RVMW and invasive parameters of right heart catheterization and all-cause mortality. Noninvasive analysis of RVMW was completed in 51 patients (mean age 58.1 ± 12.7 years, 31% men) with group I or group IV pulmonary hypertension. RV global work index (RVGWI), RV global constructive work (RVGCW), RV global wasted work (RVGWW), and RV global work efficiency (RVGWE) were compared with parameters derived invasively during right heart catheterization. Patients were followed-up for the occurrence of all-cause death. The median RVGWI, RVGCW, RVGWW, and RVGWE were 620 mmHg%, 830 mmHg%, 105 mmHg% and 87%, respectively. Compared with conventional echocardiographic parameters of RV systolic function, RVGCW and RVGWI correlated more closely with invasively derived RV stroke work index ($R = 0.63$, $p < 0.001$ and $R = 0.60$, $p < 0.001$, respectively). Invasively derived pulmonary vascular resistance correlated with RVGWW ($R = 0.63$, $p < 0.001$), RVGWE ($R = 0.48$, $p < 0.001$), and RV global longitudinal strain ($R = 0.58$, $p < 0.001$). RVGCW (hazard ratio 1.42 per 100 mmHg% <900 mmHg%, 95% confidence interval 1.12 to 1.81, $p = 0.004$) and RVGWI (hazard ratio 1.46 per 100 mmHg% <650 mmHg%, 95% confidence interval 1.09 to 1.94, $p = 0.010$) were significantly associated with all-cause mortality, whereas RV global longitudinal strain, RVGWE, and RVGWW were not. In conclusion, indexes of RVMW were more closely correlated with invasively derived RV stroke work index and peripheral vascular resistance than conventional echocardiographic parameters of RV systolic function. Decreased values of RVGCW and RVGWI were associated with all-cause mortality, whereas conventional echocardiographic parameters of RV function were not.

INTRODUCTION

A recently developed echocardiographic method of evaluating left ventricular (LV)[1] myocardial work to provide an estimate of right ventricular (RV) myocardial work,[2] using noninvasively derived pressure-strain loops, provides a quantitative estimate of ventricular deformation that accounts for afterload, dyssynchrony, and postsystolic shortening. The quantitative integration of these important components of RV function may provide the clinician a more comprehensive evaluation of the status of the right ventricle than standard echocardiographic evaluation of RV function. However, this novel method has not been investigated in patients with precapillary pulmonary hypertension. Therefore, this study was designed to (1) evaluate the association between the novel indexes of RV myocardial work and the invasively derived parameters and (2) to evaluate the association of RV myocardial work parameters with all-cause mortality in patients with precapillary pulmonary hypertension.

METHODS

Between January 2016 and March 2020, patients with pulmonary arterial hypertension (group I) or chronic thromboembolic pulmonary hypertension (group IV) who underwent right heart catheterization (RHC) at the AHEPA University General Hospital (Thessaloniki, Greece) were identified. Patients who underwent echocardiography within 6 weeks of the RHC were included for further evaluation. Diagnostic confirmation of group I or group IV pulmonary hypertension was performed according to the European Society of Cardiology guidelines on pulmonary hypertension, including RHC (pulmonary hypertension was defined by a mean pulmonary artery pressure [mPAP] ≥25 mmHg), nuclear ventilation/perfusion scan, pulmonary function tests, and the diffusing capacity of the lung for carbon monoxide.[3] Patients with pulmonary hypertension because of left heart disease (group II, n = 7) or because of lung diseases and/or chronic hypoxia (group III, n = 4) and patients with an echocardiogram performed outside the specified time window (n = 2) or where RV myocardial work could not be analyzed (n = 6) were excluded. Because this study was designed to evaluate the effect of isolated elevated pulmonary pressure on RV work and invasive hemodynamics, patients with group II pulmonary hypertension were excluded. Additionally, patients with group III pulmonary hypertension were excluded because of the important association between hyperinflation, impaired LV filling, and reductions in stroke volume.[4]

Additionally, to create a control group with no structural cardiac disease to compare values of RV myocardial work with invasive hemodynamics, patients with systemic sclerosis referred for RHC at Leiden University Medical Center with normal diastolic function,[5]

normal systolic function (LV ejection fraction ≥50%), no significant (≥moderate) valvular heart disease, and with an mPAP <25 mmHg on RHC were selected. Demographic and clinical data were prospectively collected. Due to the retrospective study design, the institutional review boards of AHEPA University General Hospital and Leiden University Medical Center waived the need for written informed consent.

All RHC procedures were performed by an experienced interventional cardiologist. A 7.5 French triple lumen Swan Ganz CCOmbo V thermodilution catheter (Edwards Lifesciences) was inserted by way of an 8 French introducer sheath through the right femoral or internal jugular vein under fluoroscopic guidance. Right atrial pressure, pulmonary artery wedge pressure, mPAP, systolic pulmonary artery pressure, and diastolic pulmonary artery pressure were obtained at end-expiration. Cardiac output was determined by thermodilution, according to guideline recommendations.[3] Stroke volume was calculated by dividing cardiac output by heart rate, whereas cardiac index and stroke volume index were calculated by indexing cardiac output and stroke volume by body surface area. RV stroke work index was calculated using the following equation[6]: stroke volume index X (mPAP right atrial pressure) X 0.0136. Peripheral vascular resistance (PVR) was calculated as[7]: (mPAP − pulmonary artery wedge pressure)/cardiac output. Transthoracic echocardiography was performed with a Vivid 7, E9 or E95 ultrasound system (General Electric Vingmed Ultrasound, Milwaukee, Wisconsin) equipped with a 3.5-MHz or M5S transducer, with patients at rest in the left lateral decubitus position. Electrocardiogram-triggered echocardiographic data were stored offline in a cineloop format for analysis with EchoPac software (EchoPac 204, General Electric Vingmed Ultrasound). LV ejection fraction, LV end-diastolic, and LV end-systolic volumes were calculated using the biplane Simpson method, with LV mass calculated using a linear 2-dimensional approach.[8] Tricuspid annular plane systolic excursion (TAPSE) was derived from M-mode recordings of the lateral tricuspid annulus in an RV-focused apical view according to guideline recommendations.[8] RV end-systolic and end-diastolic areas were measured in an RV-focused apical view, whereas RV fractional area change (FAC) was calculated with the following equation: ([RV end-diastolic area – RV end-systolic area]/RV end-diastolic area) X 100. Pulmonary artery systolic pressure (PASP) was estimated from the tricuspid regurgitation jet peak velocity using the modified Bernoulli equation (PASP = 4 X [tricuspid regurgitation jet velocity]^2 + estimated right atrial pressure). Estimated right atrial pressure was calculated on the basis of the evaluation of the inferior vena cava diameter and its collapsibility.[9] All other standard measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines.[8]

The quantification of parameters of RV myocardial work was performed using proprietary software (Echo-PAC version 204, GE Healthcare, Horten, Norway), which was originally developed for the assessment of LV myocardial work by 2-dimensional speck-

le-tracking echocardiography,[1] adapted for RV work analysis, as previously described.[2] Initially, an RV-focused apical 4-chamber view was used to derive RV global longitudinal strain (RVGLS) (including the regions of the RV free wall and interventricular septum) (Figure 1). Pulsed-wave Doppler was used to define the pulmonary valve opening and closure timings, whereas event timings of the tricuspid valve were derived from direct visualization of the valve leaflets on an RV-focused apical 4-chamber view. Subsequently, RVGLS and pulmonary arterial pressures were synchronized by valvular event timings, producing pressure-strain loops of the right ventricle. RV myocardial work was then calculated by integrating the product of the rate of segmental shortening and instantaneous RV pressure overtime to obtain myocardial work as a function of time during isovolumic contraction, ejection, and isovolumic relaxation. A total of 4 parameters of RV function were then derived from the analysis of the RV pressure-strain loops: (1) RV global work index (RVGWI), derived from the area within the global RV pressure-strain loop; (2) RV global constructive work (RVGCW), equal to the work contributing to myocardial shortening during systole and lengthening during isovolumic relaxation; (3) RV global wasted work (RVGWW), equal to the work contributing to myocardial lengthening during systole and shortening during isovolumic relaxation; and (4) RV global work efficiency (RVGWE), calculated by the following formula: (RVGCW/[RVGCW + RVGWW]) X 100%.

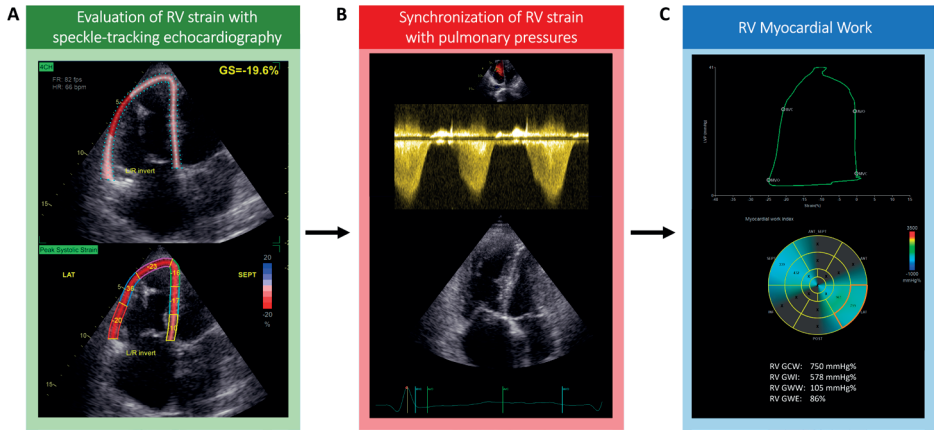

Figure 1: **Method of acquisition of RV myocardial work parameters.** RV myocardial work incorporates speckle-tracking echocardiography derived RV strain, pulmonary pressures, and cardiac valve opening and closure events to generate non-invasive pressure-strain loops of the right ventricle. Panel A depicts the acquisition of RV global longitudinal strain utilizing speckle-tracking echocardiography. The upper image in Panel B demonstrates an image used for the estimation of PASP from the TR jet peak velocity using the modified Bernoulli's equation. The lower image in Panel B demonstrates the synchronization of cardiac valvular event timings, performed through either direct visualization of the two-dimensional image presented, or using event timings established by pulsed-wave Doppler interrogation. Panel C demonstrates the non-invasive estimation of RV myocardial work indexes and a pressure-strain loop of the basal segment of the free wall of the right ventricle. TR = tricuspid regurgitation.

The primary end point of the study was all-cause mortality at follow-up. Mortality data were complete for all patients. Follow-up began from the date of echocardiography and data for all patients were included up to the last date of follow-up.

Statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Adherence to normality was verified through visual assessment of histograms of the sample data. Normally distributed continuous variables are presented as mean ± SD, whereas non-Gaussian variables are presented as median and interquartile range. Categoric variables are expressed as numbers and percentages. Spearman correlation was used to evaluate the association between prespecified invasive RHC (RV stroke work index, stroke volume index, and PVR) and echocardiographic variables (including indexes of RV myocardial work, standard parameters of RV systolic function, and PASP). Additionally, to evaluate the difference in the estimation of RV myocardial work indexes with invasively derived pulmonary pressures versus echocardiographically derived pulmonary pressures, intraclass correlation (ICC) coefficients were calculated. All analyses were performed only in patients in whom RV myocardial work analysis was feasible. For the evaluation of the end point of all-cause mortality, restricted cubic spline curve analysis was used to investigate the hazard ratio (HR) change for all-cause mortality across a range of values of RV myocardial work parameters. Likelihood ratio tests were used to determine the significance of nonlinearity. A threshold of RVGCW and RVGWI to dichotomize the population for Kaplan–Meier analysis was estimated using the fitted spline curves. Cumulative survival rates were calculated using the Kaplan–Meier method and the log-rank test was used to compare groups. The association of clinical, RHC, and echocardiographic variables with all-cause mortality was investigated by univariable Cox proportional hazards regression models. To optimize the balance between bias and variance while accounting for nonlinearity, RVGCW and RVGWI were refitted in the Cox proportional hazards regression models with linear spline terms, reducing variance and minimizing model overfitting.[10] The proportional hazards assumption was verified through the assessment of scaled Schoenfeld residuals. The HR and 95% confidence intervals (CIs) were calculated and reported for each variable. To examine the reproducibility of indexes of RV myocardial work, 10 individuals were randomly selected for the evaluation of intra- and interobserver agreement using ICCs. The second observer was blinded to the measurements of the first observer for interobserver measurements. All tests were 2-sided and $p < 0.05$ were considered statistically significant.

RESULTS

A total of 57 patients (mean age 58 ± 13 years, 31% men) fulfilled the study inclusion criteria, with RV myocardial work analysis feasible in 51 patients. The median time between echocardiogram and RHC was 1 (0 to 10) day. A total of 21 patients with systemic sclerosis and without structural cardiac disease were included to facilitate comparison with the precapillary pulmonary hypertension group. A summary of clinical and RHC characteristics of both groups are presented in Table 1.

Table 1: Clinical and right heart catheterization characteristics

Variable	Overall (N = 72)	Pre-Capillary Pulmonary Hypertension (N = 51)	No Structural Cardiac Disease (N = 21)	P-value
Age (years)	56 (±13)	58 (±13)	49 (±10)	0.003
Men	27 (38%)	16 (31%)	11 (52%)	0.094
Systolic blood pressure (mmHg)	124 (20)	126 (21)	116 (16)	0.044
PDE-5 inhibitor	18 (25%)	18 (35%)	0 (0%)	0.002
Endothelin receptor antagonist	17 (24%)	17 (33%)	0 (0%)	0.002
Guanylate cyclase stimulator	7 (9.9%)	7 (14%)	0 (0%)	0.18
Prostacyclin	3 (4.2%)	3 (5.9%)	0 (0%)	0.55
Right atrial pressure (mmHg)	7 (4 to 9)	7 (5 to 10)	6 (4 to 7)	0.033
sPAP (mmHg)	56 (±25)	67 (±20)	28 (±5)	<0.001
dPAP (mmHg)	20 (13 to 27)	23 (18 to 30)	11 (9 to 13)	<0.001
mPAP (mmHg)	34 (20 to 45)	41 (34 to 48)	16 (14 to 19)	<0.001
Stroke volume index (ml/m^2)	38 (±11)	38 (±12)	40 (±7)	0.34
Cardiac index (L/min/m^2)	2.95 (±0.90)	2.92 (±1.00)	3.02 (±0.63)	0.62
RV stroke work index (ml.mmHg/m^2)	12 (7 to 17)	16 (12 to 20)	6 (5 to 7)	<0.001
PVR (WU)	4.1 (2.0 to 6.8)	5.4 (4.0 to 8.2)	1.5 (1.0 to 1.8)	<0.001
PAWP (mmHg)	10 (8 to 12)	10 (8 to 12)	9 (6 to 11)	0.089

Values are presented as mean ± SD, median (IQR) or n (%).
dPAP = Diastolic pulmonary artery pressure, mPAP = Mean pulmonary artery pressure, PAWP = Pulmonary artery wedge pressure, PDE5 = phosphodiesterase type 5 inhibitor; PVR = peripheral vascular resistance; sPAP = Systolic pulmonary artery pressure; WU = Wood units

Table 2 provides a summary of the echocardiographic characteristics of the study population. Conventional parameters of RV systolic function were decreased, with a mean RVFAC of 30 ± 11% and mean RVGLS of -15.5 ± 5.5%. Median RVGWI, RVGCW, and RVGWW were 620 (446 to 848) mmHg%, 830 (660 to 1,201) mmHg%, and 105 (56 to 166) mmHg%, respectively; whereas median RVGWE was 87 (82 to 93)%. The ICCs for intraobserver variability were 0.96 for RVGWI, 0.92 for RVGCW, and 0.90 for RVGWE demonstrating excellent reliability (Supplementary Table S1). The ICC for intraobserver

variability for RVGWW was 0.78, signifying good reliability. Similarly, the ICCs for interobserver variability were 0.97 for RVGWI and 0.97 for RVGCW, indicating excellent agreement, whereas the interobserver variability was 0.87 for RVGWE and 0.76 for RVGWW, indicating good reliability (Supplementary Table S1).

Table 2: Echocardiographic characteristics

Variable	Overall (N = 72)	Pre-Capillary Pulmonary Hypertension (N = 51)	No Structural Cardiac Disease (N = 21)	P-value
RV basal diameter (mm)	44 (±10)	46 (±10)	39 (±7)	<0.001
RV mid-diameter (mm)	36 (±11)	39 (±10)	27 (±7)	<0.001
Tricuspid annulus diameter (mm)	32.7 (±6.3)	32.3 (±6.6)	33.7 (±5.6)	0.39
Moderate or severe tricuspid regurgitation	7 (9.7%)	7 (14%)	0 (0%)	0.10
Right atrial volume index (ml/m^2)	32 (21 to 44)	37 (26 to 49)	23 (18 to 33)	0.001
RV end-diastolic area (cm^2)	26 (20 to 31)	30 (22 to 36)	21 (15 to 24)	<0.001
RV FAC (%)	36 (±14)	30 (±11)	51 (±7)	<0.001
TAPSE (mm)	20.3 (±4.4)	19.2 (±4.4)	22.8 (±3.1)	<0.001
RV GLS (%)	-17.0 (±5.4)	-15.5 (±5.5)	-20.7 (±2.8)	<0.001
RV FWLS (%)	-20 (±7)	-18 (±7)	-24 (±4)	<0.001
PASP (mmHg)	48 (39 to 74)	65 (47 to 81)	29 (25 to 39)	<0.001
Right ventricular global work index (RV GWI) (mmHg%)	564 (442 to 691)	620 (446 to 848)	544 (403 to 591)	0.047
Right ventricular global constructive work (RV GCW) (mmHg%)	708 (592 to 998)	830 (660 to 1,201)	588 (489 to 651)	<0.001
Right ventricular global wasted work (RV GWW) (mmHg%)	68 (38 to 134)	105 (56 to 166)	38 (21 to 51)	<0.001
Right ventricular global work efficiency (RV GWE) (%)	90 (85 to 94)	87 (82 to 93)	93 (91 to 96)	0.001
LV mass index (g/m^2)	77 (±22)	77 (±23)	77 (±18)	0.88
LV end-diastolic volume (ml)	99 (±33)	96 (±34)	104 (±30)	0.34
LV end-systolic volume (ml)	38 (27 to 50)	39 (28 to 55)	34 (26 to 47)	0.45
LV ejection fraction (%)	63 (55 to 68)	60 (53 to 65)	66 (62 to 70)	0.006
Left atrial volume index (ml/m^2)	32 (21 to 38)	29 (21 to 38)	35 (25 to 38)	0.57

Values are presented as mean±SD, median (IQR) or n (%).
LV = Left ventricular; LVEF = Left ventricular ejection fraction; PASP = Pulmonary artery systolic pressure; RV = right ventricular; RV FAC = right ventricular fractional area change; RV FWLS = Right ventricular free wall longitudinal strain; RV GLS = Right ventricular global longitudinal strain; TAPSE = Tricuspid annular plane systolic excursion

Compared with PASP and conventional echocardiographic parameters of RV systolic function (including RVGLS, TAPSE, and RVFAC), RVGCW and RVGWI correlated more closely with invasively derived RV stroke work index (R = 0.63, p <0.001 and R = 0.60, p <0.001, respectively) (Figure 2, Figure S1). In contrast, RVGLS (R = 0.57, p <0.001) cor-

related more closely with invasively derived stroke volume index than RVGCW, RVGWI and RVGWE (R = 0.34, p = 0.016, R = 0.48, p<0.001 and R = 0.47, p <0.001, respectively) (Figure 3). Invasively derived PVR correlated with RVGWW (R = 0.63, p <0.001), RVGWE (R = 0.48, p<0.001), RVGLS (R = 0.58, p <0.001), and PASP (R = 0.66, p<0.001) (Figure 4). Moreover, similar correlations were observed in the patient cohort without structural cardiac disease: RVGCW and RVGWI demonstrated an association with RV stroke work index (R = 0.62, p=0.003 and R = 0.48, p = 0.028, respectively), RVGLS showed an association with invasively derived stroke volume index (R = 0.49, p = 0.023), and RVGWW was correlated with invasively derived PVR (R = 0.51, p = 0.017).

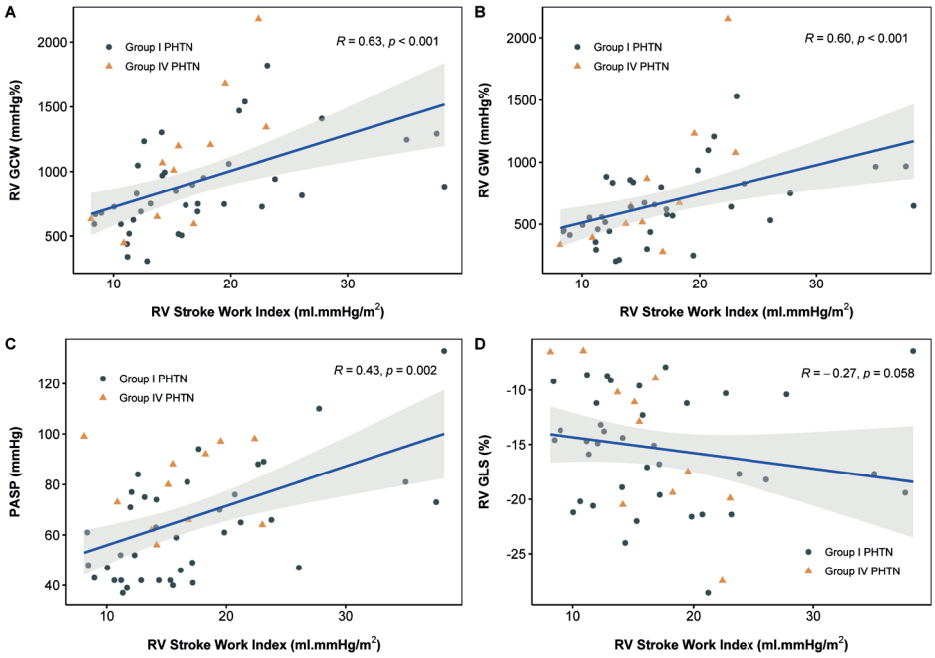

Figure 2: Correlation between invasively derived right ventricular stroke work index and echocardiographic parameters. RV stroke work index assessed with right heart catheterization demonstrated a significant association with RVGCW (A), RVGWI (B) and PASP (C). The association between RVGLS and RV stroke work index was not significant (D). PHTN = pulmonary hypertension.

Over a median follow-up of 35 (interquartile range 25 to 45) months, a total of 17 patients (33%) died. Spline curve analyses showed significant increases in the hazard for all-cause mortality with progressively lower values of RVGCW (Figure 5) and RVGWI (Figure 5), although not for RVGWE, RVGWW, or RVGLS (Supplementary Figure 2). Likelihood ratio tests demonstrated that there was significant nonlinearity for RVGCW (p = 0.031) and RVGWI (p = 0.043), with an increasing hazard for mortality, evident from values of <900 mmHg% for RVGCW and for values of <700 mmHg% for RVGWI. To dichotomize

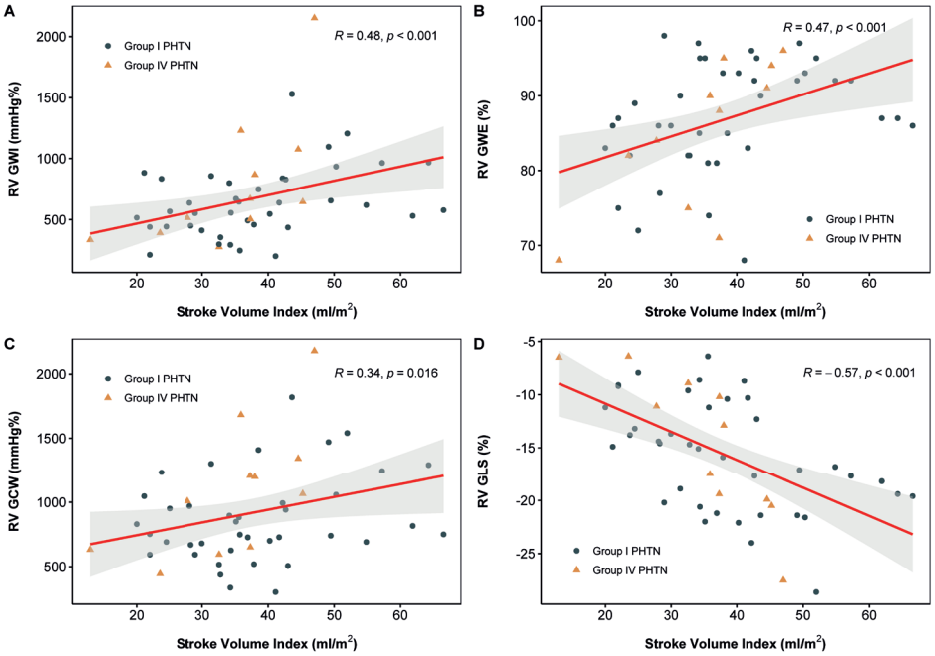

Figure 3: **Correlation between invasively derived stroke volume index and echocardiographic parameters.** Stroke volume index assessed with right heart catheterization demonstrated a significant association with RVGWI (A), RVGWE (B), RVGCW (C) and RVGLS (D). PHTN=pulmonary hypertension.

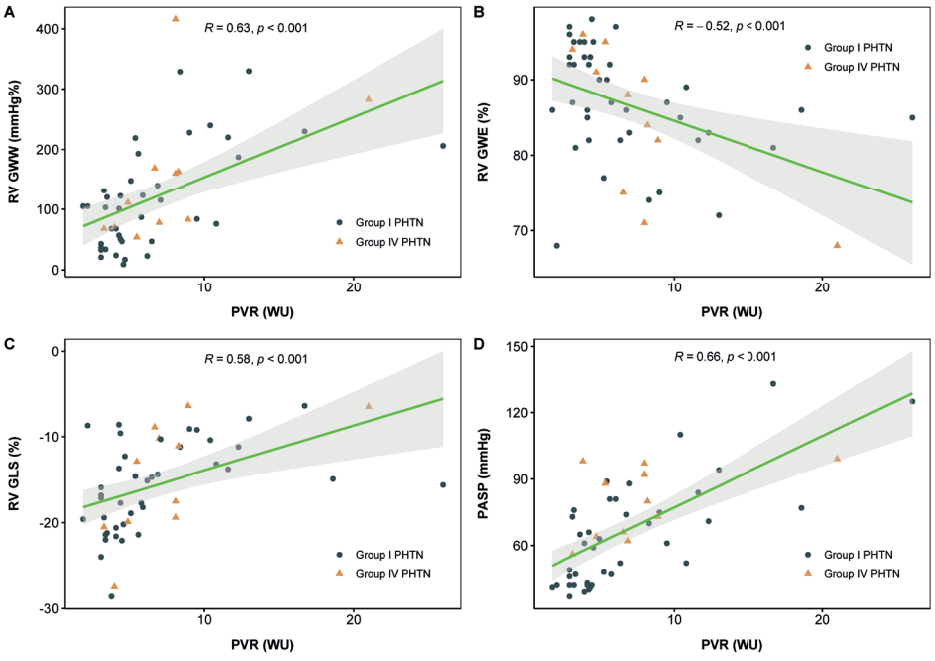

Figure 4: Correlation between invasively derived PVR and echocardiographic parameters. PVR assessed with right heart catheterization demonstrated a significant association with RVGWW (A), RVGWE (B), RVGLS (C) and PASP (D). PHTN = pulmonary hypertension.

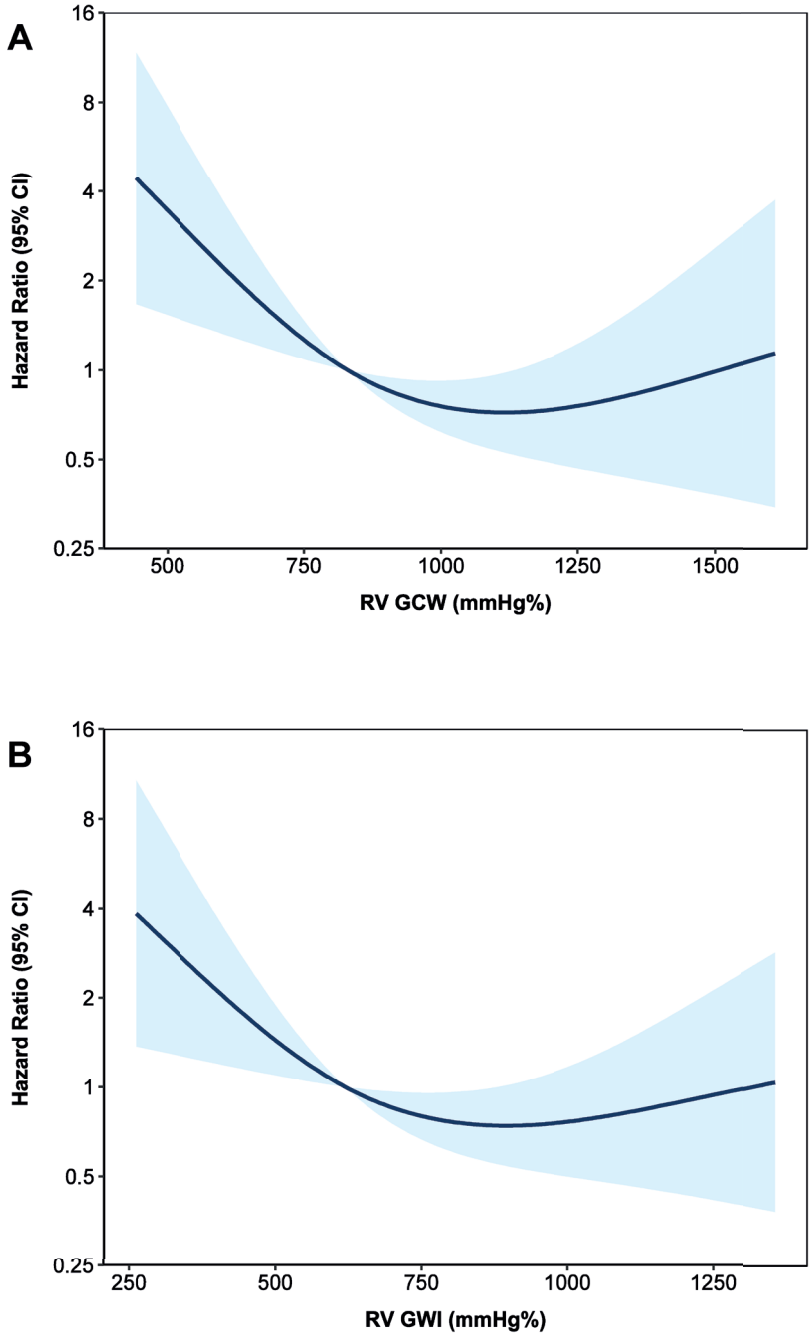

Figure 5: Spline curves demonstrating the hazard ratio for all-cause mortality according to RVGCW (A) and RVGWI (B). The curves in (A) and (B) demonstrate the hazard ratio change for all-cause mortality with 95% confidence intervals (blue shaded areas) in patients with precapillary pulmonary hypertension, across a range of values of RVGCW (A) and RVGWI (B) at the time of echocardiography.

the population for Kaplan–Meier analyses, cut-offs of 550 mmHg% for RVGCW and 500 mmHg% for RVGWI were estimated from the respective spline curves. Kaplan–Meier analysis demonstrated significantly worse survival for patients with RVGCW <550 mmHg% than patients with an RVGCW ≥550 mmHg% (96% and 64% vs 71% and 14%, at 1 and 5 years of follow-up, respectively, p = 0.0007; Figure 6). Additionally, patients with an RVGWI <500 mmHg% had significantly worse estimated survival than those with

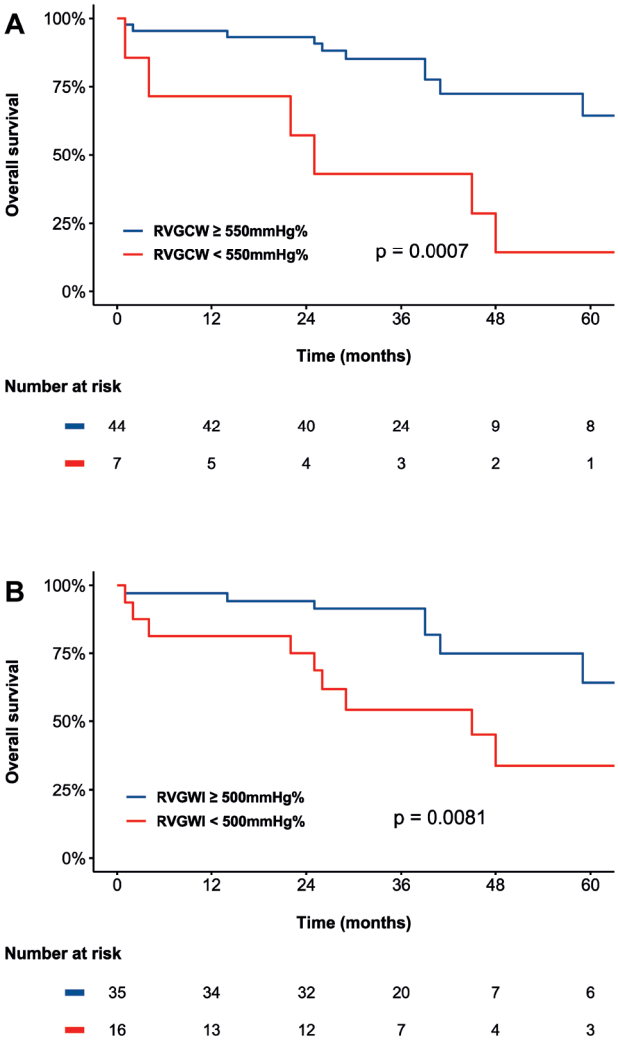

Figure 6: Kaplan–Meier curves for all-cause mortality for RV myocardial work parameters for patients with precapillary pulmonary hypertension. Panel A demonstrates the Kaplan–Meier curve for RVGCW of 550 mm Hg%, while Panel B shows the Kaplan–Meier curve for RVGWI at a cut-off of 500 mmHg%.

an RVGWI ≥500 mmHg% (97% and 64% vs 81% and 34%, at 1 and 5 years of follow-up, respectively, p = 0.008; Figure 6). Univariable Cox regression analysis demonstrated an association between all-cause mortality and RVGCW (HR 1.42 per 100 mmHg% <900 mmHg%, 95% 1.12 to 1.81, p = 0.004) and all-cause mortality and RVGWI (HR 1.46 per 100 mmHg% <650 mmHg%, 95% CI 1.09 to 1.94, p = 0.010). Additionally, an association was observed between age, RV stroke work index, and all-cause mortality. However, no association was observed between RVGLS, RVFAC, TAPSE, PASP, PVR, RVGWE, or RVGWW and all-cause mortality (Table 3).

Table 3: Univariable Cox Regression for Association with All-Cause Mortality

Variable	HR (95% CI)	P-value
Age (per year)	1.05 (1.00 to 1.10)	0.045
PDE-5 inhibitor	0.73 (0.25 to 2.10)	0.55
Endothelin receptor antagonist	0.83 (0.30 to 2.30)	0.72
Guanylate cyclase stimulator	0.61 (0.14 to 2.72)	0.52
Right atrial pressure (per mmHg)	0.88 (0.74 to 1.06)	0.18
sPAP (per mmHg)	0.98 (0.95 to 1.01)	0.11
mPAP (per mmHg)	0.95 (0.90 to 1.00)	0.064
Stroke volume index (per ml/m^2)	0.97 (0.92 to 1.02)	0.19
RV stroke work index (per ml.mmHg/m^2)	0.89 (0.80 to 0.99)	0.038
PVR (per WU)	0.93 (0.83 to 1.05)	0.26
PAWP (per mmHg)	0.90 (0.74 to 1.10)	0.30
≥ Moderate tricuspid regurgitation	0.26 (0.03 to 2.14)	0.21
Right atrial volume index (per ml/m^2)	0.99 (0.98 to 1.01)	0.59
RV end-diastolic area (per cm^2)	1.03 (0.98 to 1.09)	0.19
RV FAC (per %)	0.98 (0.94 to 1.03)	0.45
TAPSE (per mm)	1.03 (0.92 to 1.16)	0.56
RV GLS (per %)	1.07 (0.98 to 1.17)	0.13
PASP (per mmHg)	0.99 (0.97 to 1.01)	0.21
LV ejection fraction (per %)	0.99 (0.95 to 1.04)	0.78
Left atrial volume index (per ml/m^2)	1.01 (0.97 to 1.05)	0.77
Right ventricular global work index (RV GWI) (per 100mmHg% below 650mmHg%)	1.46 (1.09 to 1.94)	0.010
Right ventricular global constructive work (RV GCW) (per 100mmHg% below 900mmHg%)	1.42 (1.12 to 1.81)	0.004
Right ventricular global wasted work (RV GWW) (per mmHg%)	1.00 (0.99 to 1.00)	0.18
Right ventricular global work efficiency (RV GWE) (per %)	1.00 (0.95 to 1.07)	0.88

CI = Confidence Interval; HR = Hazard Ratio; LV = Left ventricular; LVEF = Left ventricular ejection fraction; mPAP = Mean pulmonary artery pressure; PASP = Pulmonary artery systolic pressure; PAWP = Pulmonary artery wedge pressure; PDE5 = phosphodiesterase type 5 inhibitor; PVR = peripheral vascular resistance; RV = right ventricular; RV FAC = right ventricular fractional area change; RV GLS = Right ventricular global longitudinal strain; sPAP = Systolic pulmonary artery pressure; TAPSE = Tricuspid annular plane systolic excursion; WU = Wood units

DISCUSSION

RV performance is a major determinant of prognosis in patients with precapillary pulmonary hypertension and may be evaluated with invasive techniques, including RHC or non-invasive methods, such as echocardiography or cardiac magnetic resonance.[11] Current guidelines state that RHC is the gold standard for the evaluation and diagnosis of group I and group IV pulmonary hypertension.[3,12] PVR and mPAP provide an evaluation of RV afterload and stroke volume index provides an indirect estimate of RV contractility, whereas RV stroke work index estimates RV workload through the incorporation of both RV function and hemodynamics.[13] However, because of cost, training requirements, and associated risks, there is a driving interest in the development of non-invasive alternatives for the serial monitoring and assessment of RV performance in pulmonary hypertension.[14] Although conventional echocardiographic parameters of RV function have been demonstrated to be prognostically important in precapillary pulmonary hypertension[15] they reflect the interaction between pulmonary vascular load and the contractility of the right ventricle, providing a significantly afterload dependent evaluation of RV performance.[16] Indeed, because right heart failure is often a direct consequence of increased afterload and not only the consequence of primary myocardial disease, a full physiologic analysis of the cardiopulmonary unit is necessary to correctly interpret clinical and imaging data.[16] For instance, parameters such as RV ejection fraction and TAPSE are typically decreased in patients with group I pulmonary hypertension, despite evidence of increased contractility when RV end-systolic elastance is evaluated.[17] Contrarily, RV myocardial work derived noninvasively from pressure-strain loops provides an estimate of RV performance that accounts for afterload and mechanical efficiency. Unlike RVGLS, TAPSE, and RVFAC, these novel indexes do not only reflect system function[16] but also provide an evaluation of RV performance that accounts for afterload and myocardial work efficiency.

In the future, the non-invasive evaluation of RV myocardial work may have the potential to enhance echocardiographic monitoring of patients with precapillary pulmonary hypertension. Hemodynamic parameters derived from RHC during follow-up after treatment (such as PVR and stroke volume index) have been shown to be independently associated with adverse prognosis.[18,19] Monitoring with serial RHC may improve the risk stratification and management of patients with group I pulmonary hypertension.[3,20] However, with a rate of serious complications of approximately 1%, cheaper , non-invasive alternatives to serial RHC are needed.[21] Changes in conventional echocardiographic parameters of RV performance, such as RVGLS, have been independently associated with clinical deterioration and all-cause mortality in patients with group I pulmonary hypertension, implying a possible role for the monitoring of these patients with speckle-tracking echocardiography.[22] However, simultaneous evaluation

of indexes of RV myocardial work may contextualize any changes in RVGLS by providing an estimate of RV performance that also accounts for afterload and mechanical work efficiency.

Several studies have demonstrated that pressure-strain loops of the left ventricle derived from speckle-tracking echocardiography strongly correlate with myocardial glucose metabolism by 18F-fluorodeoxyglucose positron emission tomography.[1,23] RV myocardial work may also provide a non-invasive estimate of regional myocardial energetics and could be useful for the evaluation of the right ventricle, considering that the extent of RV glucose uptake on 18F-fluorodeoxyglucose positron emission tomography in patients with precapillary pulmonary hypertension has been associated with pressure overload, RV dysfunction, and poor prognosis.[24,25] The present study showed that RVGCW and RVGWI were associated with all-cause mortality, and that this relation was significantly nonlinear. Conversely, RVGLS, TAPSE, RVFAC, and PASP, conventional parameters of RV function, were not associated with all-cause mortality.

This study is limited by its retrospective, observational design and limited sample size. Additional large prospective studies are required to confirm the prognostic value of RV myocardial work parameters in patients with precapillary pulmonary hypertension. Additionally, RHC was not performed simultaneously with echocardiography and hemodynamics may change substantially over relatively short time periods in patients with precapillary pulmonary hypertension. Importantly, the software used for the analysis of RV myocardial work was originally designed for the evaluation of LV pressure-strain loops rather than for those of the right ventricle. However, in patients with severe group I and group IV pulmonary hypertension, pressure volume loops of the right ventricle change with increasing pulmonary arterial pressure, closely resembling those of the left ventricle.[26,27]

CONCLUSION

In conclusion, in a patient cohort with group I and group IV pulmonary hypertension, indexes of RV myocardial work were more closely correlated with invasively derived RV stroke work index and PVR than conventional echocardiographic parameters of RV systolic function. Decreased values of RVGCW and RVGWI were associated with all-cause mortality, whereas conventional echocardiographic parameters of RV function were not.

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SUPPLEMENTARY MATERIAL

Table S1: Intraclass correlation coefficients for intra-observer measurements, inter-observer measurements and RV myocardial work indices derived from invasive versus non-invasive systolic pulmonary artery pressure

Variable	Intraclass correlation coefficient (95% CI)	*P*
RV myocardial work derived from invasive vs non-invasive pulmonary pressures		
RV GWI (mmHg%)	0.942 (0.901 to 0.966)	<0.001
RV GCW (mmHg%)	0.916 (0.857 to 0.951)	<0.001
RV GWW (mmHg%)	0.947 (0.909 to 0.969)	<0.001
RV GWE (%)	1 (1 to 1)	<0.001
Intra-observer variability		
RV GWI (mmHg%)	0.956 (0.832 to 0.989)	<0.001
RV GCW (mmHg%)	0.919 (0.707 to 0.979)	<0.001
RV GWW (mmHg%0	0.781 (0.345 to 0.940)	0.001
RV GWE (%)	0.898 (0.645 to 0.974)	<0.001
Inter-observer variability		
RV GWI (mmHg%)	0.969 (0.889 to 0.992)	<0.001
RV GCW (mmHg%)	0.971 (0.893 to 0.992)	<0.001
RV GWW (mmHg%)	0.759 (0.271 to 0.935)	0.005
RV GWE (%)	0.871 (0.565 to 0.966)	<0.001

CI = confidence interval; RV = right ventricular; RV GCW = right ventricular global constructive work, RV GWW = right ventricular global wasted work, RV GWE = Right ventricular global work efficiency, RV GWI = Right ventricular global work index

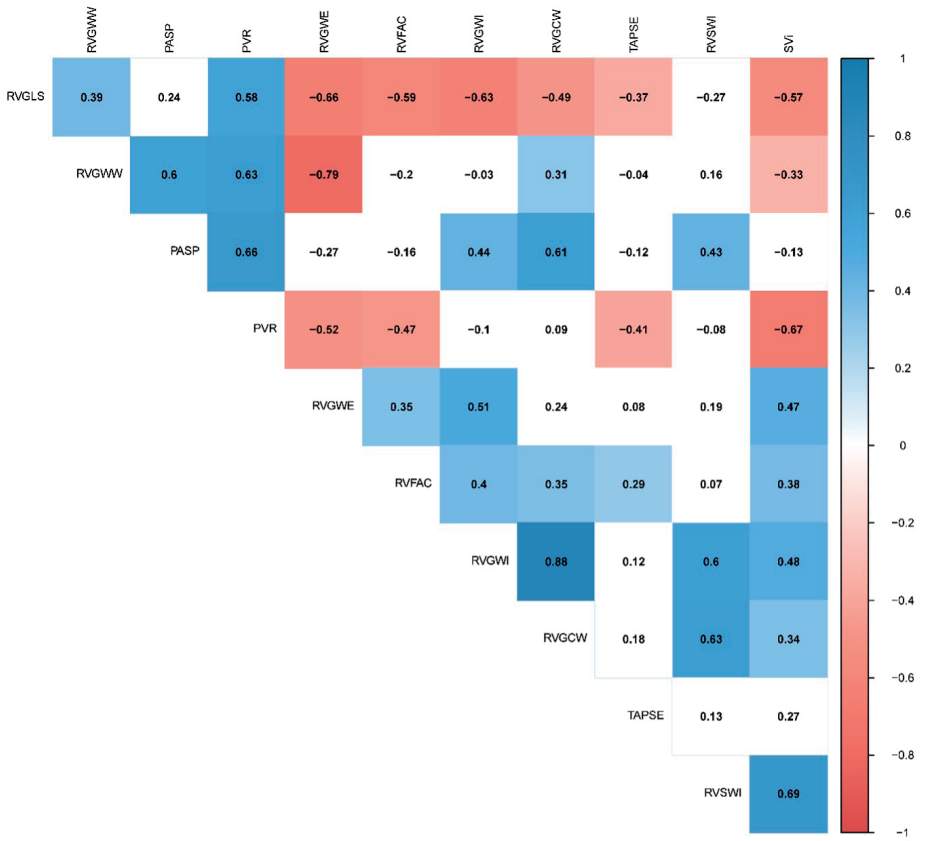

Figure S1: Correlation matrix of echocardiographic and RHC parameters of interest. White colored squares in the correlation matrix indicate a p-value ≥ 0.05, while red or blue colored squares indicate correlation coefficients with a p-value < 0.05. PASP = pulmonary artery systolic pressure, PVR = pulmonary vascular resistance, RHC = right heart catheterization, RVFAC = right ventricular fractional area change, RVGCW = right ventricular global constructive work, RVGLS = right ventricular global longitudinal strain, RVGWE = right ventricular global work efficiency, RVGWI = right ventricular global work index, RVGWW = RV global wasted work, RVSWI = right ventricular stroke work index, TAPSE = tricuspid annular plane systolic excursion, SVi = stroke volume index

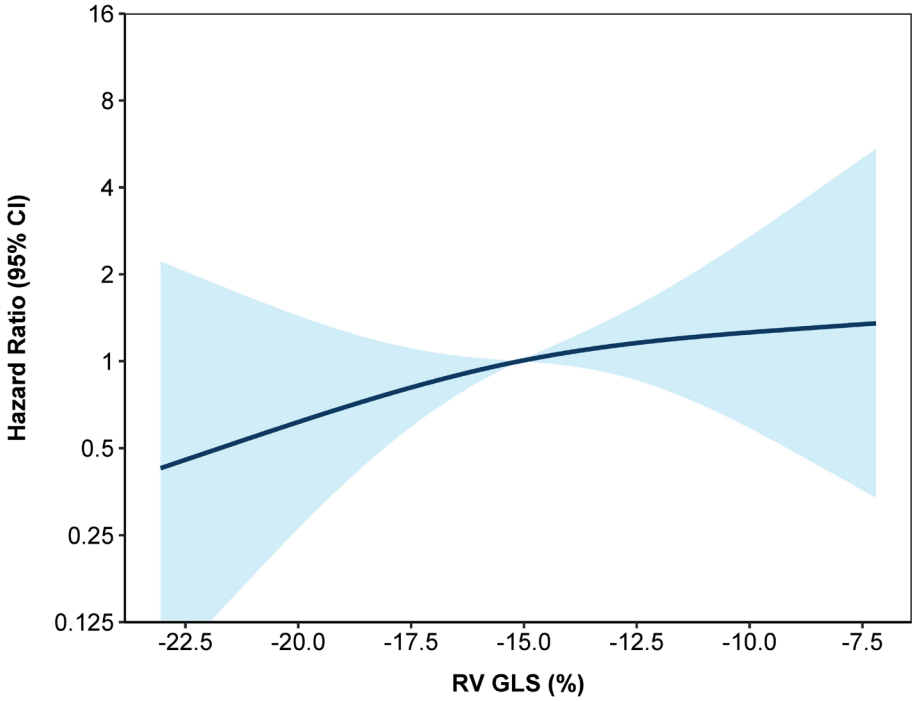

Figure S2: Spline curve demonstrating the hazard ratio for all-cause mortality according to RV GLS. The curve demonstrates the hazard ratio change for all-cause mortality with 95% confidence intervals (blue shaded areas) in patients with pre-capillary pulmonary hypertension, across a range of values of RV GLS at the time of echocardiography.

PART II

NEW INSIGHTS INTO RISK STRATIFICATION OF PATIENTS WITH VALVULAR HEART DISEASE

4

Left ventricular remodelling in Bicuspid Aortic Valve Disease

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ABSTRACT

Background

Characterization of left ventricular (LV) geometric pattern and LV mass could provide an important insight into the pathophysiological adaptations of the left ventricle to pressure and/or volume overload in patients with bicuspid aortic valve (BAV) and significant (≥moderate) aortic valve (AV) disease. This study aimed to characterize LV remodelling and its prognostic impact in patients with BAV according to the predominant type of valvular dysfunction.

Methods

In this international, multicenter BAV registry, 1,345 patients (51.0 [37.0 to 63.0] years, 71% male) with significant AV disease were identified. Patients were classified as having isolated aortic stenosis (AS) (n=669), isolated aortic regurgitation (AR) (n=499) or mixed aortic valve disease (MAVD) (n=177). LV hypertrophy was defined as a LV mass index >115 g/m^2 in males and >95 g/m^2 in females. LV geometric pattern was classified as (i) normal geometry: no LV hypertrophy, relative wall thickness (RWT) ≤0.42, (ii) concentric remodelling: no LV hypertrophy, RWT >0.42, (iii) concentric hypertrophy: LV hypertrophy, RWT >0.42, and (iv) eccentric hypertrophy: LV hypertrophy, RWT ≤0.42. Patients were followed-up for the endpoints of event-free survival (defined as a composite of aortic valve repair/replacement and all-cause mortality) and all-cause mortality.

Results

Type of AV dysfunction was related to significant variations in LV remodelling. Higher LV mass index, i.e. LV hypertrophy, was independently associated with the composite endpoint for patients with isolated AS (HR 1.08 per 25g/m^2, 95% CI 1.00 to 1.17, p=0.046) and AR (HR 1.19 per 25g/m^2, 95% CI 1.11 to 1.29, p<0.001), but not for those with MAVD. The presence of concentric remodeling, concentric hypertrophy and eccentric hypertrophy were independently related to the composite endpoint in patients with isolated AS (HR 1.54, 95% CI 1.06 to 2.23, p=0.024; HR 1.68, 95% CI 1.17 to 2.42, p=0.005; HR 1.59, 95% CI 1.03 to 2.45, p=0.038, respectively), while concentric hypertrophy and eccentric hypertrophy were independently associated with the combined endpoint for those with isolated AR (HR 2.49, 95% CI 1.35 to 4.60, p=0.004 and HR 3.05, 95% CI 1.71 to 5.45, p<0.001, respectively). There was no independent association observed between LV remodelling and the combined endpoint for patients with MAVD.

Conclusions

LV hypertrophy or remodelling were independently associated with the composite endpoint of aortic valve repair/replacement and all-cause mortality for patients with isolated AS and isolated AR, although not for patients with MAVD.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most frequent type of congenital heart disease[1], and is a common cause of aortic stenosis (AS) and aortic regurgitation (AR)[2, 3]. Patients with BAV may have a higher prevalence of left ventricular (LV) diastolic dysfunction and reduced LV deformation compared to those with a tricuspid aortic valve (AV)[4, 5]. In addition, individuals with BAV typically develop moderate or severe (significant) AV disease at a considerably younger age[2]. These differences suggest that there could be important differences in LV remodeling in patients with BAV compared to those with a tricuspid AV.

Characterization of LV geometric pattern and LV mass could provide an important insight into the pathophysiological adaptations of the left ventricle to pressure and/or volume overload in patients with BAV and significant AV disease. Although changes in LV mass and geometry may represent a physiological response to altered loading, they may also imply a greater hemodynamic burden on the left ventricle and a higher likelihood of future symptom development[6-8]. In addition, increasing LV mass and changes in LV geometric pattern have been associated with the development of myocardial fibrosis, irreversible LV dysfunction and poor long-term prognosis in patients with significant AV disease[9-12]. Identifying the extent and phenotype of LV remodeling could potentially allow for the identification of patients with BAV and significant AV disease who may benefit from earlier AV surgery or intervention. However, until now, there has only been limited investigation of LV remodeling in patients with BAV and significant AV disease.

Therefore, this study aimed to (i) characterize LV remodelling in patients with BAV and significant AR, AS or mixed AV disease (MAVD), and (ii) investigate the prognostic implications of LV hypertrophy and remodelling according to the type of aortic valve dysfunction for individuals with BAV.

METHODS

Study population

Individuals with BAV and at least moderate AS and/or AR were selected from an international multicenter BAV registry[13]. Patients with previous or current endocarditis, complex congenital heart disease, previous AV surgery, or without moderate or severe (significant) AV disease were excluded. Demographic and clinical data were obtained from medical records corresponding to the time of first diagnosis of BAV by transthoracic echocardiography. Body surface area was calculated using the Mosteller method[14]. Data were obtained according to regulations specified by the institutional review board of each center, and were retrospectively analysed. Due to the retrospective nature of the study design, the ethical committee of each participating center waived the require-

ment for written informed consent. The data that support these findings are available on reasonable request to the corresponding author.

Echocardiography

Echocardiographic studies were performed with commercially available ultrasound systems, with the first transthoracic echocardiogram confirming a diagnosis of BAV considered the index study. Images were retrospectively analyzed by experienced investigators from each center, with BAV morphology classified according to the system proposed by Sievers and Schmidtke[15]. AS severity was classified as none, mild, moderate or severe based on aortic valve area, peak aortic velocity and mean pressure gradient, as per contemporary guideline recommendations[16]. The severity of AR was graded as none, mild, moderate or severe according to AR jet size, pressure half-time and vena-contracta width, according to guideline recommendations[17]. Individuals with significant AS and AR were considered to have MAVD, while patients with significant AS and less than moderate AR were classified as isolated AS. Individuals with significant AR and less than moderate AS were classified as isolated AR. The diameters of the sinus of Valsalva, sinotubular junction and ascending aorta were measured on a parasternal long-axis view from leading-edge to leading-edge, perpendicular to the centerline of the aorta in end-diastole[18]. The aortic annulus was conventionally measured from inner-edge to inner-edge on a parasternal long-axis view[18]. LV ejection fraction (LVEF) was estimated using the biplane Simpson method. LV end-diastolic diameter (LVEDD), posterior wall thickness (PWT) and interventricular septal thickness (IVST) were measured using the 2D linear method, as per guideline recommendations[18]. Relative wall thickness (RWT) was calculated as: (2 X PWT) / LVEDD (18). LV mass was calculated by the following formula: LV mass = 0.8 X 1.04 X [(IVST + LVEDD + PWT)^3 - LVEDD^3] + 0.6 [18]. LV mass was subsequently indexed to body surface area. LV hypertrophy was defined as a LV mass index >115 g/m^2 in males and >95 g/m^2 in females. LV geometric pattern was classified according to guideline recommendations as[18] (i) normal geometry: no LV hypertrophy, RWT ≤0.42, (ii) concentric remodelling: no LV hypertrophy, RWT >0.42, (iii) concentric hypertrophy: LV hypertrophy, RWT >0.42, and (iv) eccentric hypertrophy: LV hypertrophy, RWT ≤0.42. All other measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines[18].

Follow-up

Follow-up started at the time of the first echocardiogram that confirmed a diagnosis of BAV. The primary endpoint of the study was a composite of aortic valve repair/replacement and all-cause mortality. Indications for aortic valve repair/replacement were according to recommendations of contemporary guidelines, including patients with symptomatic severe aortic valve dysfunction or asymptomatic severe aortic valve

dysfunction with a reduced LVEF (≤50%)[19, 20]. The secondary endpoint was all-cause mortality. Follow-up data were available for 613 (92%) patients with isolated AS, 163 (92%) patients with MAVD and 415 (83%) patients with isolated AR. Data for all patients were included up to the last date of follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation if normally distributed and median and interquartile range (IQR) if non-normally distributed. Data were evaluated for normality by comparing histograms to superimposed normal probability curves. Normally distributed variables were compared using one-way ANOVA, while non-normally distributed variables were compared with the Kruskal-Wallis test. Multiple comparisons for continuous variables were tested using the Bonferroni correction. Categorical data are expressed as counts and percentages and were compared using the Pearson χ^2 test. The association between presence of a dilated aortic root or aorta (≥ 50mm) and LV geometric pattern was evaluated with binary logistic regression.

Cumulative 1- and 5- year event-free survival for the composite endpoint of all-cause mortality and aortic valve repair/replacement were calculated using the Kaplan Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was used to evaluate the associations between LV mass index and LV geometric pattern with the composite endpoint of all-cause mortality and aortic valve repair/replacement. In addition, to further investigate the relationship between LV mass index and the hazard ratio (HR) change for the combined endpoint of aortic valve repair/replacement and all-cause mortality, a spline curve was fitted for each type of AV disease (isolated AS, MAVD and isolated AR). Multivariable Cox proportional hazards regression analyses were performed adjusting for pre-specified clinical and echocardiographic variables associated with event-free survival specific to each patient group (isolated AS, MAVD, isolated AR). HR and 95% confidence intervals (CI) were reported for each model. The proportional hazards assumption was confirmed through the evaluation of scaled Schoenfeld residuals.

In a sensitivity analysis, univariable Cox regression was used to evaluate the association between LV geometric pattern, LV mass index and the secondary endpoint of all-cause mortality. Multivariable models were constructed adjusting for age and LV ejection fraction only, to avoid overfitting. All tests were two-sided and *P* values <0.05 were regarded as statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient population

Of the 1345 patients with significant AV disease and BAV (median age 51 [37-63] years, 71% male), 669 had isolated AS, 177 MAVD and 499 isolated AR (Figure 1). Individuals with isolated AS were older, more frequently had hypertension, diabetes mellitus and dyslipidemia compared to patients with MAVD or isolated AR. In addition, patients with MAVD more frequently had a type 1 R-N raphe BAV compared to those with isolated AR or AS. A summary of the clinical characteristics of the population is presented in Table 1.

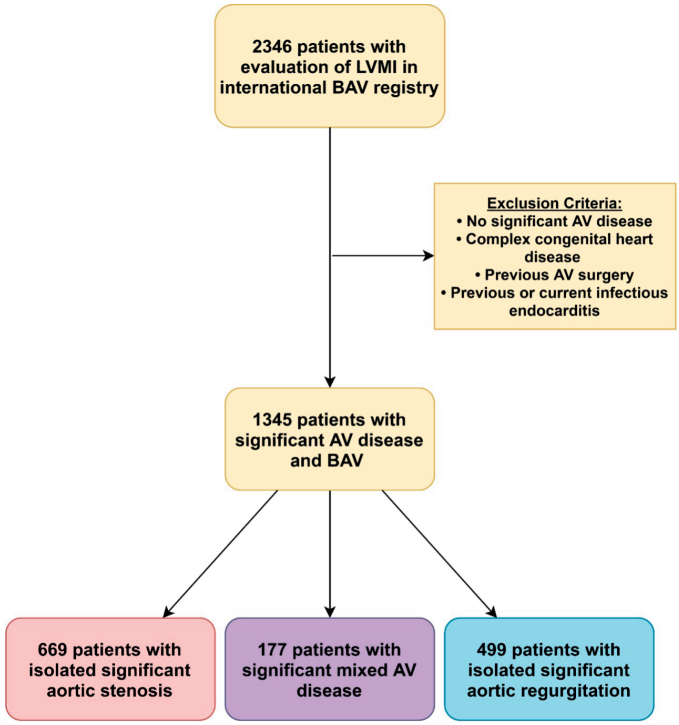

Figure 1: Study flow chart. AV = aortic valve; BAV = bicuspid aortic valve; LVMI = LV mass index.

Echocardiographic characteristics

The echocardiographic characteristics of the study population are displayed in Table 2. Individuals with isolated AR had larger LV dimensions, aortic annulus and sinus of Valsalva diameters compared to the other groups, whereas those with MAVD had larger LV dimensions, aortic annulus and sinus of Valsalva diameters compared to those with isolated AS. In addition, although patients with isolated AR had larger sinotubular junction diameters than those with isolated AS or MAVD, there was no difference observed between ascending aorta diameters.

Table 1: Clinical and BAV characteristics according to AV dysfunction type

	Total Population (n=1345)	Isolated significant AS (n=669)	Significant mixed AV disease (n=177)	Isolated significant AR (n=499)	*P* value
Clinical characteristics					
Age (years)	51.0 (37.0 to 63.0)	57.0 (45 to 67)	51.0 (38.5 to 63.0)*	41.0 (31.0 to 54.0)*†	<0.001
Male (%)	951 (70.7%)	417 (62.3%)	123 (69.5%)	411 (82.4%)*	<0.001
Hypertension (%)	470 (37.5%)	277 (43.7%)	57 (33.7%)*	136 (30.3%)*	<0.001
Current smoker (%)	202 (16.5%)	92 (15.5%)	30 (17.8%)	80 (17.4%)	0.645
Dyslipidemia (%)	385 (29.7%)	249 (38.1%)	40 (23.1%)*	96 (20.5%)*	<0.001
Prior CAD (%)	111 (9.1%)	62 (10.0%)	18 (11.0%)	31 (7.1%)	0.172
Diabetes mellitus (%)	143 (11.7%)	107 (18.0%)	15 (8.9%)*	21 (4.6%)*†	<0.001
BAV characteristics					
No raphe (%)	102 (8.3%)	45 (7.6%)	10 (5.9%)	47 (10.2%)	0.002
Type 1 raphe (L-R), (%)	852 (69.6%)	410 (68.9%)	107 (63.3%)	335 (72.7%)†	
Type 1 raphe (R-N), (%)	207 (16.9%)	104 (17.5%)	42 (24.9%)*	61 (13.2%)†	
Type 1 raphe (L-N), (%)	52 (4.2%)	28 (4.7%)	6 (3.6%)	18 (3.9%)	
Type 2 raphe (%)	12 (1.0%)	8 (1.3%)	4 (2.4%)	0 (0.0%)*†	

Values are median (IQR) and n (%).
AV = aortic valve; AR = aortic regurgitation; AS = aortic stenosis; CAD = coronary artery disease; L-N = left – non-coronary; L-R = left – right; R-N = right – non-coronary.
*p<0.05 vs Group I;†p<0.05 vs Group II

LV remodelling characteristics

Patients with isolated AS had a higher RWT and lower LV mass index compared to those with MAVD or isolated AR (Table 2). However, individuals with MAVD also had a higher RWT than patients with isolated AR. In addition, the distribution of LV geometric patterns differed significantly between groups (Figure 2). Patients with MAVD were less likely to exhibit normal geometry compared to patients with isolated AR. Individuals with isolated AS more frequently had concentric remodelling compared to those with MAVD or isolated AR. Patients with isolated AR more frequently had eccentric hypertrophy than those with MAVD, who in turn, demonstrated this pattern more often than individuals with isolated AS. The patient groups with MAVD and isolated AS had a higher prevalence of concentric hypertrophy when compared to individuals with isolated AR.

There was no significant association between BAV morphology and LV geometric pattern observed in patients with isolated AS, MAVD or isolated AR. However, a significant association between the presence of a dilated aortic root or aorta (≥ 50mm) and LV geometric pattern was observed in patients with isolated AS (concentric remodelling versus normal geometry, OR 0.61, 95% CI 0.10 to 3.70, p=0.59; concentric hypertrophy versus normal geometry, OR 4.13, 95% CI 1.18 to 14.42, p=0.026; eccentric hypertrophy versus normal geometry, OR 5.79, 95% CI 1.49 to 22.43, p=0.011), although not in patients with MAVD or isolated AR.

Table 2: Echocardiographic characteristics

	Total population (n=1345)	Isolated significant AS (n=669)	Significant mixed AV disease (n=177)	Isolated significant AR (n=499)	*P* value
Left ventricle and atrium					
LV EDD, mm	52.6 (±9.6)	48.0 (±7.2)	54.6 (±8.7)*	58.2 (±9.4)*†	<0.001
LV ESD, mm	35.4 (±10.0)	31.7 (±8.4)	36.6 (±10.2)*	39.4 (±10.2)*†	<0.001
LV EDVi, ml/m^2	67.9 (54.2 to 88.5)	57 (47 to 70)	76 (61 to 94)*	83 (67 to 104)*†	<0.001
LV EF, %	63 (55 to 69)	65 (57 to 70)	61 (52 to 71)	61 (54 to 67)*	<0.001
LV EF <50%	205 (15.3%)	86 (12.9%)	34 (19.2%)	85 (17.1%)	0.045
LAVI, ml/m^2	27 (20 to 36)	27 (21 to 36)	30 (21 to 42)	25 (19 to 35)†	0.002
Mitral inflow E velocity, m/s	0.80 (±0.25)	0.81 (±0.26)	0.84 (±0.29)	0.77 (±0.23)*†	0.003
Mitral inflow E/A ratio	1.14 (0.83 to 1.56)	1.00 (0.78 to 1.49)	1.14 (0.82 to 1.67)	1.25 (0.88 to 1.61)*	<0.001
LV remodelling parameters					
LV mass index, g/m^2	117 (93 to 150)	107 (85 to 134)	132 (101 to 168)*	127 (102 to 169)*	<0.001
RWT	0.43 (±0.12)	0.47 (±0.12)	0.42 (±0.11)*	0.38 (±0.09)*†	<0.001
LV geometric pattern					
Normal geometry	339 (25.2%)	170 (25.4%)	34 (19.2%)	135 (27.1%)†	<0.001
Concentric remodelling	229 (17.0%)	184 (27.5%)	12 (6.8%)*	33 (6.6%)*	
Concentric hypertrophy	408 (30.3%)	231 (34.5%)	72 (40.7%)	105 (21.0%)*†	
Eccentric hypertrophy	369 (27.4%)	84 (12.6%)	59 (33.3%)*	226 (45.3%)*†	
Aortic valve and aortic root					
Aortic annulus diameter, mm	23.1 (±3.6)	21.6 (±2.7)	23.0 (±3.3)*	25.0 (±3.7)*†	<0.001
SOV diameter, mm	34.8 (±6.3)	33.0 (±5.6)	34.6 (±5.9)*	37.2 (±6.6)*†	<0.001
STJ diameter, mm	30.0 (±6.6)	28.7 (±5.4)	29.8 (±6.1)	31.7 (±7.6)*†	<0.001
Ascending aorta diameter, mm	37.6 (±7.4)	37.2 (±6.8)	37.9 (±6.8)	38.0 (±8.2)	0.149
Dilated aortic root or tubular aorta (≥ 50mm), %	75 (5.6%)	29 (4.4%)	8 (4.5%)	38 (7.6%)*	0.046
Severe aortic stenosis, %	444 (33%)	369 (55.2%)	75 (42.4%)*	0 (0%)*†	<0.001
Severe aortic regurgitation, %	241 (17.9%)	0 (0%)	51 (28.8%)*	190 (38.8%)*†	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; AR = aortic regurgitation; EDD = end-diastolic diameter; EDVi = end-diastolic volume index; EF = ejection fraction; ESD = end-systolic diameter; LAVI = left atrial volume index; LV = left ventricle; MR = mitral regurgitation n; RWT = relative wall thickness; SOV = sinus of Valsalva; STJ = sinotubular junction
*p<0.05 vs Group I;†p<0.05 vs Group II

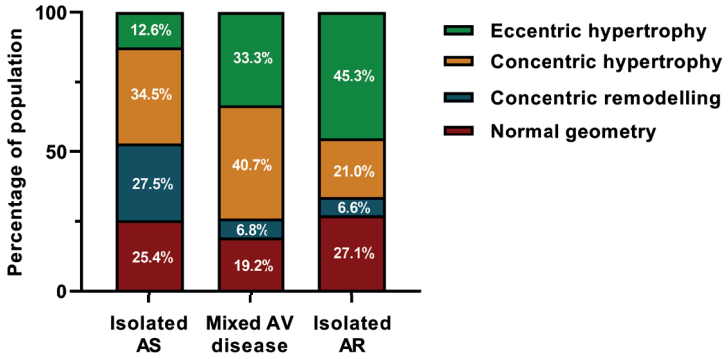

Figure 2: LV geometric pattern according to type of AV dysfunction in patients with BAV. AV = aortic valve; AR = aortic regurgitation; AS = aortic stenosis; BAV = bicuspid aortic valve

Prognostic implications of LV remodelling in isolated AS

Of the individuals with isolated AS, 344 died (n=31, 4.6%) or underwent aortic valve repair/replacement (n=313, 46.8%) over a median follow-up of 20 (IQR 3 to 60) months. The 1- and 5- year cumulative event-free survival rates were 70% and 48% for the composite endpoint of all-cause death and aortic valve repair/replacement, respectively (Figure 3A). Kaplan-Meier analysis demonstrated a significant reduction in event-free survival for the composite endpoint in individuals with concentric remodelling, concentric hypertrophy and eccentric hypertrophy compared to those with normal LV geometry (χ^2=48.44, p<0.001)(Figure 3B). On multivariable Cox regression analysis, following adjustment for possible confounding variables (age, smoking, coronary artery disease, aortic root or ascending aorta dilation, aortic valve area, left atrial volume index (LAVI) and LVEF), concentric remodelling (HR 1.54, 95% CI 1.06 to 2.23, p=0.024), concentric hypertrophy (HR 1.68, 95% CI 1.17 to 2.42, p=0.005) and eccentric hypertrophy (HR 1.59, 95% CI 1.03 to 2.45, p=0.038), remained independently associated with the composite endpoint (Figure 4, Figure 5, C, panel 1, Table S1). To examine the relationship between LV mass index and the combined endpoint for each patient group (isolated AS, MAVD and isolated AR), spline curves were fitted, demonstrating a continuous increase in HR across a range of values of LV mass index for all groups (Figure 5, B). Multivariable Cox regression analysis demonstrated that LV mass index remained independently associated with the combined endpoint for patients with isolated AS and BAV (HR 1.08 per 25g/m^2, 95% CI 1.00 to 1.17, p=0.046) (Figure 4, Table S1).

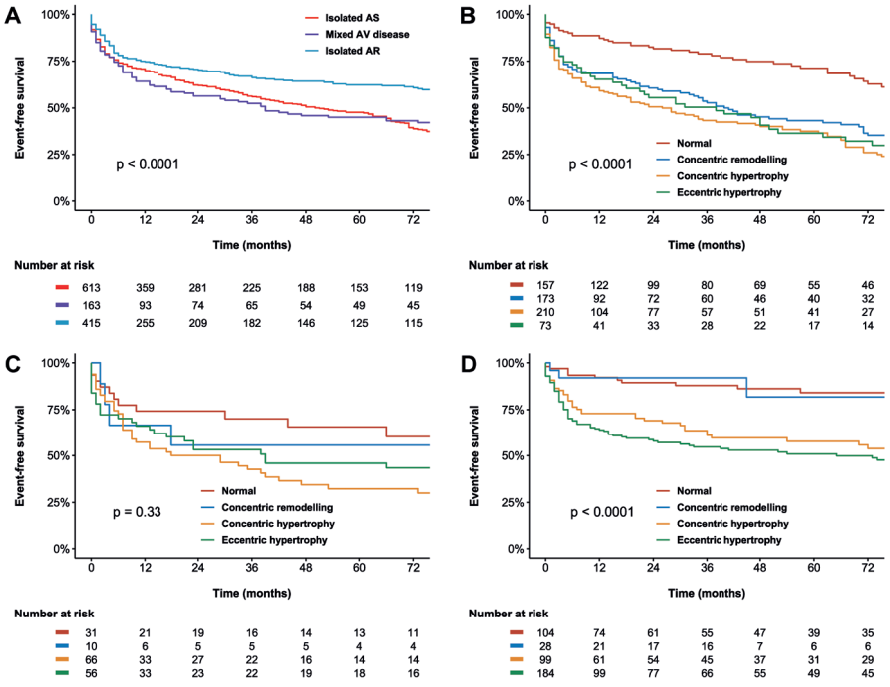

Figure 3: Kaplan-Meier curves demonstrating event-free survival for the composite endpoint of all-cause mortality and aortic valve repair/replacement according to the type of AV dysfunction in patients with BAV, and according to LV geometric pattern within each group. Panel A demonstrates that patients with significant aortic stenosis or mixed AV disease have reduced event-free survival compared to those with significant aortic regurgitation. Panels B, C and D demonstrate Kaplan Meier survival estimates according to LV geometric pattern for aortic stenosis, mixed AV disease and aortic regurgitation, respectively.
AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricular

Prognostic implications of LV remodelling in MAVD

For those with MAVD, after a median follow-up of 18 (IQR 2 to 76) months, 107 (60.4%) patients died (n=12, 6.8%) or underwent aortic valve repair/replacement (n=95, 54.6%). Kaplan-Meier and univariable Cox regression analysis did not demonstrate an association between LV geometric pattern and the composite endpoint of all-cause mortality and aortic valve repair/replacement for patients with MAVD (χ^2=3.44, p=0.33) (Figure 3C), including after adjustment in a multivariable model (Figure 4, Figure 5, C, panel 2). Although on univariable Cox regression analysis, LV mass index was associated with the combined endpoint in patients with MAVD (HR 1.17 per 25g/m^2, 95% CI 1.08 to 1.27, p<0.001), an independent association was not observed following adjustment (HR 0.97 per 25g/m^2, 95% CI 0.85 to 1.10, p=0.62).

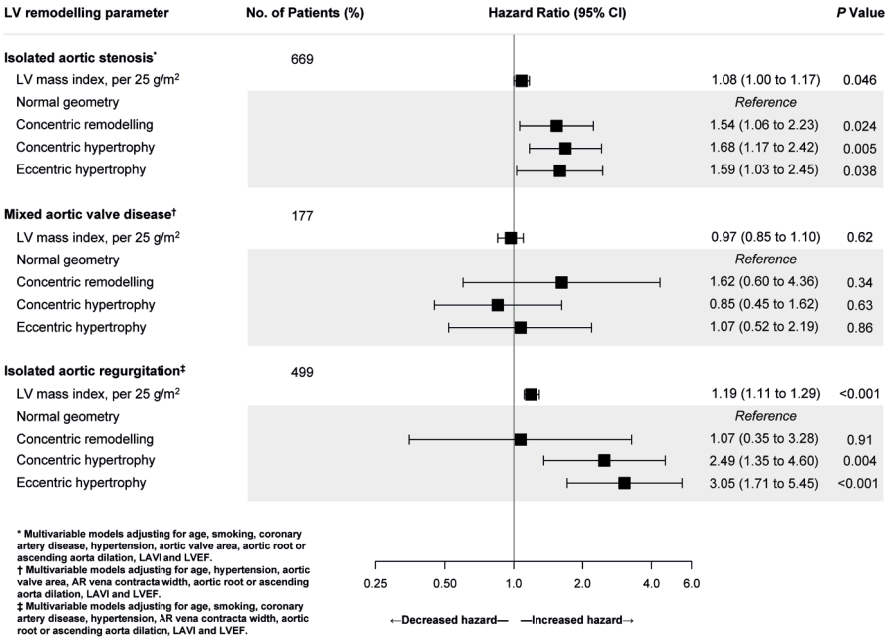

Figure 4: Forest plot of Cox regression models investigating the association between parameters of LV remodelling and event-free survival according to type of aortic valve disease. AR = aortic regurgitation; AV = aortic valve; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction

Prognostic implications of LV remodelling in isolated AR

Over a median follow-up of 24 (4 to 79) months, 170 patients with isolated AR died (n=14, 2.8%) or underwent aortic valve repair/replacement (n=156, 31.3%). Univariable Cox regression and Kaplan-Meier analyses demonstrated reduced event-free survival for the composite endpoint for patients with concentric hypertrophy and eccentric hypertrophy compared to those with normal geometry (χ^2=34.90, p<0.001) (Figure 3D). In a multivariable model, concentric and eccentric hypertrophy (HR 2.49, 95% CI 1.35 to 4.60, p=0.004 and HR 3.05, 95% CI 1.71 to 5.45, p<0.001, respectively) remained independently associated with the combined endpoint (Figure 4, Figure 5, C, panel 3). Likewise, LV mass index remained significantly associated with the composite endpoint in an adjusted model (HR 1.19 per 25g/m^2, 95% CI 1.11 to 1.29, p<0.001).

LV remodelling and all-cause mortality

In sensitivity analyses, the association between LV geometric pattern, LV mass and all-cause mortality were evaluated for each type of AV dysfunction (Table S2, Figure S1). A total of 59 (8.8%) patients with isolated AS (median follow-up 53 [IQR 23 to 86] months), 17 (9.6%) with MAVD (median follow-up 69 [IQR 29 to 127] months) and 23 (4.6%) with isolated AR (median follow-up 57 [IQR 21 to 122] months) died during follow-up. LV

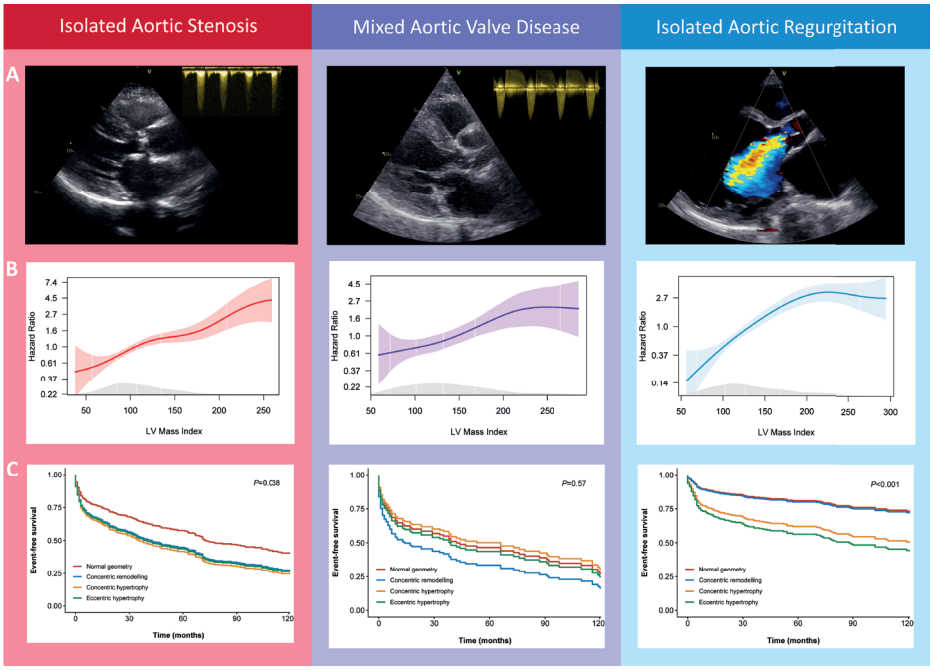

Figure 5: Prognostic implications and differences in LV remodelling according to type of AV dysfunction in BAV. Panel A demonstrates the typical LV geometric patterns according to the type of AV dysfunction. Patients with significant isolated aortic stenosis are more likely to have lower LV mass compared to those with significant isolated aortic regurgitation or mixed AV disease. Individuals with significant isolated aortic stenosis and mixed AV disease typically have a higher relative wall thickness compared to those with significant isolated aortic regurgitation. The spline curves in panel B show the hazard ratio change for event-free survival with 95% confidence intervals (shaded red, purple and blue areas) across a range of values of LV mass index for each patient group. The density plots beneath the curves shows the distribution of the study population according to values of LV mass index. Panel C demonstrates adjusted event-free survival curves according to LV geometric pattern. LV geometric pattern was independently associated with event-free survival in individuals with isolated aortic stenosis and aortic regurgitation, but not for those with mixed AV disease.
AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricular

geometric pattern was associated with all-cause mortality in patients with isolated AS, but not with MAVD or isolated AR on univariable analysis. In a multivariable model adjusting for age and LVEF, concentric hypertrophy remained significantly associated with all-cause mortality for patients with isolated AS (HR 2.87, 95% CI 1.09 to 7.54, p=0.032). Although LV mass index was associated with increased all-cause mortality for each type of AV dysfunction, following adjustment for age and LVEF, an association was only observed for patients with isolated AR (HR 1.19 per 25g/m^2, 95% CI 1.00 to 1.40, p=0.044). For patients with isolated AS and AR, subgroup analyses and interactions for the association between LV remodelling and all-cause mortality and the combined endpoint are displayed in supplementary tables S3-S8.

DISCUSSION

In this large, international, multicenter BAV study, the type of AV dysfunction (isolated AS, isolated AR or MAVD) was related to significant variations in LV mass and geometric pattern. In addition, for patients with isolated AS and AR, increasing LV mass index was independently associated with the composite endpoint of aortic valve repair/replacement and all-cause mortality. The presence of concentric hypertrophy or concentric remodeling was independently related to worse event-free survival in patients with isolated AS, while eccentric hypertrophy and concentric hypertrophy LV geometric patterns were independently associated with the composite endpoint for those with isolated AR. There was no independent association observed between indices of LV remodelling and the composite endpoint for BAV patients with MAVD.

Differences in LV remodelling in patients with BAV according to type of AV disease

BAV is a common congenital valvular disease with different AV, aortic root and ascending aorta phenotypes, leading to valvular dysfunction and/or aortic dilatation at a younger age compared to those with tricuspid AV morphology[21]. This dysfunction imposes varying degrees of pressure and volume overload on the left ventricle according to the predominant valvular lesion/s, which may lead to changes in LV mass and geometric pattern.

In patients with isolated AS, pressure overload triggers cardiomyocyte hypertrophy in order to reduce wall stress and maintain adequate systolic function[22]. The result is myocardial thickening with comparatively smaller changes in LV dimensions, leading to predominantly concentric LV geometry. The predominance of LV concentric hypertrophy observed in those with isolated AS in the present study is in accordance with previous reports, although a lower prevalence was observed in our population[23, 24]. Notably, the majority of preceding reports included mostly patients with degenerative calcific aortic stenosis, who are significantly older and have higher prevalence of clinical comorbidities, important risk factors for LV hypertrophy. Conversely, patients with AR are subject to a combination of volume and pressure overload, typically resulting in considerable LV dilation, myocyte elongation and compensatory increases in LV mass, although without substantial increases in myocardial thickness, translating as eccentric hypertrophy[25]. Our study is consistent with prior literature, demonstrating a prevalence of eccentric hypertrophy of approximately 50% in patients with isolated AR[8, 26]. In patients with MAVD, substantial pressure and volume overload coexist, and the consequent LV remodelling is a result of the additional hemodynamic burden imposed on the myocardium[27, 28]. Consistent with the literature, the present study demonstrates a high prevalence of LV hypertrophy in patients with MAVD[28], with increased relative wall thickness compared to those with isolated AR, and increased LV mass index compared to those with isolated AS.

Prognostic implications of LV remodelling in patients with BAV

LV remodelling can produce diastolic dysfunction and sub-endocardial ischemia due to an imbalance between myocardial oxygen supply and demand, and may be related to myocardial fibrosis and the onset of symptoms[25]. It is possible that changes in LV remodelling may anticipate the onset of symptoms (currently the major indication for surgery in individuals with BAV and significant AV disease) and foreshadow a future need for AV intervention. It is also possible that these findings may be extrapolated to patients with a tricuspid AV, with the caveat that these patients are usually older with greater comorbidity profile, which could somewhat confound the underlying etiology of LV hypertrophy and remodeling.

High LV mass index has been associated with adverse outcomes in patients with isolated AS[6, 7, 29]. In addition, Debry et al. previously demonstrated that concentric LV remodelling and hypertrophy, compared to normal LV geometry, were independently associated with decreased survival in patients with moderate and severe AS[24]. Likewise, Capoulade et al. analyzed the impact of LV remodelling patterns in patients with AS (peak velocity > 2.0 m/s) and preserved LVEF, demonstrating that concentric hypertrophy was independently associated with all-cause mortality when compared to other LV geometric patterns[23]. However, tricuspid AV morphology was the predominant phenotype in these studies. Our results confirm that patients with concentric geometry, isolated AS and BAV have reduced event-free survival compared to those with normal geometry.

The present study also demonstrates that elevated LV mass index, concentric hypertrophy and eccentric hypertrophy are independently related to a composite endpoint of aortic valve repair/replacement and all-cause mortality in patients with isolated AR. Furthermore, higher LV mass index was associated with all-cause mortality at long-term follow-up. Data investigating the prognostic implications of LV remodelling in significant isolated AR remain scarce. In a study including 130 patients undergoing surgery for significant AR due to a variety of etiologies, post-operative, but not pre-operative LV mass index was associated with all-cause mortality on univariable analysis[30]. Contrarily, in a study of 113 patients with significant AR, no preoperative hemodynamic or echocardiographic variables (including LV mass) were related to long-term outcome, although preoperative echocardiographic data were only available in 44 patients[31]. Providing a possible pathophysiological mechanism linking elevated LV mass index with poorer outcome, Taniguchi et al. demonstrated that substantial increases in LV mass index, but not LV geometric pattern, were associated with a deterioration in LV contractility that persisted post-operatively[32]. Nonetheless, further research is required to confirm the role of LV mass index for the risk stratification of patients with isolated AR.

Interestingly, we did not observe an independent association between LV mass index or LV geometric pattern and the composite endpoint in the patient subgroup with MAVD. However, our findings are consistent with most previous studies. In three studies of

patients with MAVD of a variety of etiologies, increasing LV mass index or LV hypertrophy were not independently associated with event-free survival[27, 33, 34], although one study did observe an independent association[28]. Likewise, in a study of 138 patients with unicuspid or bicuspid aortic valves and MAVD, LV mass index was not related to event-free survival[35]. It is possible that increased LV mass in MAVD is principally an adaptive (rather than maladaptive) physiological response to the combination of extreme volume and pressure overload imposed on the left ventricle, a concept which may provide an explanation for the absence of an association between indices of LV remodelling and the primary endpoint in this study.

Limitations

This study is subject to the limitations of its retrospective, observational design. Furthermore, several centers involved in this international registry act as referral centers for their respective regions, potentially leading to an imperfect estimation of prevalence data and heterogeneity in the time until surgical intervention across centers. Additionally, data analysis for the secondary endpoint of all-cause mortality was limited by a low-event rate. Although this study had a substantial number of participants, further analysis in studies that are adequately powered to evaluate interactions between LV remodelling and sex are needed for each type of BAV disease. Furthermore, additional studies are required to establish validated prediction models that integrate anatomical LV remodelling (including LV geometry and LV mass index, as appropriate for the type of valvular dysfunction), LV function (LV ejection fraction and/or LV global longitudinal strain), valvular disease severity, and other clinical characteristics, to identify BAV patients at the highest risk for requiring future aortic valve surgery.

CONCLUSION

LV hypertrophy and remodelling were independently associated with the composite endpoint of aortic valve repair/replacement and all-cause mortality for patients with a BAV and isolated AS and isolated AR, although not for patients with MAVD.

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SUPPLEMENTARY MATERIAL

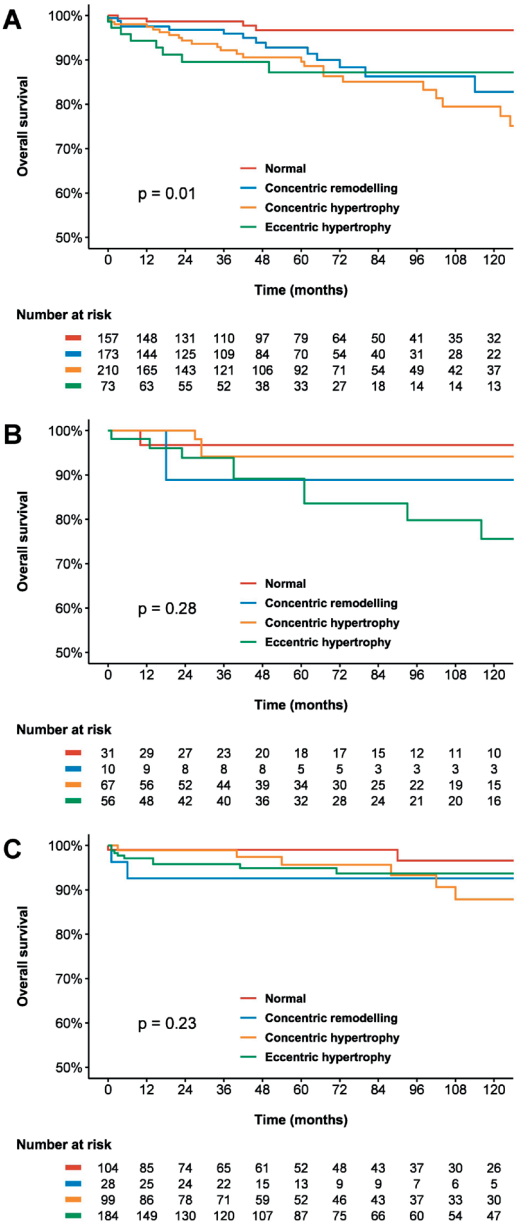

Figure S1: Kaplan-Meier curves for all-cause mortality according LV geometric pattern. Panels A, B and C demonstrate the Kaplan-Meier survival estimates according to LV geometric pattern for aortic stenosis, mixed AV disease and aortic regurgitation, respectively.

AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricular; MR = mitral regurgitation

Table S1: Cox regression models for event-free survival according to AV dysfunction type

	Isolated aortic stenosis[a] (n=669)		Mixed aortic valve disease[b] (n=177)		Isolated aortic regurgitation[c] (n=499)	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Univariable analysis						
LV mass index, per 25g/m^2	1.226 (1.155 to 1.302)	<0.001	1.173 (1.084 to 1.269)	<0.001	1.284 (1.217 to 1.354)	<0.001
LV geometric pattern						
Normal geometry	*Reference*		*Reference*		*Reference*	
Concentric remodelling	2.188 (1.572 to 3.044)	<0.001	1.195 (0.466 to 3.063)	0.711	1.300 (0.476 to 3.551)	0.609
Concentric hypertrophy	2.902 (2.118 to 3.977)	<0.001	1.657 (0.936 to 2.934)	0.083	3.313 (1.878 to 5.843)	<0.001
Eccentric hypertrophy	2.165 (1.453 to 3.226)	<0.001	1.513 (0.842 to 2.718)	0.166	3.952 (2.327 to 6.713)	<0.001
Multivariable models for LV mass index						
LV mass index, per 25g/m^2	1.080 (1.001 to 1.165)	0.046	0.968 (0.849 to 1.102)	0.621	1.194 (1.110 to 1.285)	<0.001
Multivariable models for LV geometric pattern						
LV geometric pattern						
Normal geometry	*Reference*		*Reference*		*Reference*	
Concentric remodelling	1.535 (1.058 to 2.227)	0.024	1.621 (0.603 to 4.360)	0.339	1.066 (0.347 to 3.279)	0.911
Concentric hypertrophy	1.682 (1.168 to 2.423)	0.005	0.854 (0.450 to 1.620)	0.630	2.489 (1.346 to 4.603)	0.004
Eccentric hypertrophy	1.587 (1.026 to 2.454)	0.038	1.067 (0.520 to 2.191)	0.859	3.051 (1.709 to 5.446)	<0.001

[a] Multivariable model adjusting for age, smoking, coronary artery disease, hypertension, aortic valve area, aortic root or ascending aorta dilation, LAVI and LVEF.
[b] Multivariable model adjusting for age, aortic root or ascending aorta dilation, hypertension, aortic valve area, AR vena contracta width, LAVI and LVEF.
[c] Multivariable model adjusting for age, smoking, coronary artery disease, hypertension, aortic root or ascending aorta dilation, AR vena contracta width, LAVI and LVEF.
AR = aortic regurgitation; AV = aortic valve; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction

Table S2: Cox regression models for all-cause mortality according to AV dysfunction type

	Isolated aortic stenosis[a] (n=669)		Mixed aortic valve disease[a] (n=177)		Isolated aortic regurgitation[a] (n=499)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Univariable analysis						
LV mass index, per 25g/m^2	1.274 (1.105 to 1.468)	0.002	1.186 (1.012 to 1.390	0.036	1.284 (1.115 to 1.480	0.001
LV geometric pattern						
Normal geometry	*Reference*		*Reference*		*Reference*	
Concentric remodeling	3.049 (1.190 to 7.811)	0.020	3.306 (0.207 to 52.903)	0.398	5.779 (0.964 to 34.650)	0.055
Concentric hypertrophy	4.040 (1.672 to 9.758)	0.002	2.615 (0.306 to 22.386)	0.380	3.280 (0.679 to 15.857)	0.140
Eccentric hypertrophy	3.640 (1.295 to 10.232)	0.014	5.207 (0.659 to 41.122)	0.118	2.709 (0.590 to 12.431)	0.200
Multivariable models for LV mass index						
LV mass index, per 25g/m^2	1.143 (0.982 to 1.329)	0.084	1.057 (0.862 to 1.296)	0.592	1.186 (1.004 to 1.400)	0.044
Multivariable models for LV geometric pattern						
LV geometric pattern						
Normal geometry	*Reference*					
Concentric remodeling	2.711 (0.982 to 7.484)	0.054				
Concentric hypertrophy	2.871 (1.093 to 7.541)	0.032				
Eccentric hypertrophy	2.347 (0.749 to 7.356)	0.143				

[a]Multivariable model adjusting for age and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction

Table S3: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Stenosis

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
Age						0.871
	< 50 years	**197**	**Normal**	*Reference*		
			CR	1.738 (1.001 to 3.017)	0.050	
			CH	2.463 (1.437 to 4.220)	0.001	
			ER	1.566 (0.765 to 3.208)	0.220	
	≥ 50 years	**416**	**Normal**	*Reference*		
			CR	2.065 (1.350 to 3.159)	0.001	
			CH	2.481 (1.655 to 3.720)	<0.001	
			ER	2.164 (1.318 to 3.554)	0.002	
Sex						0.612
	Male	**385**	**Normal**	*Reference*		
			CR	2.539 (1.674 to 3.850)	<0.001	
			CH	3.315 (2.206 to 4.982)	<0.001	
			ER	2.704 (1.618 to 4.519)	<0.001	
	Female	**228**	**Normal**	*Reference*		
			CR	1.711 (0.976 to 3.001)	0.061	
			CH	2.478 (1.497 to 4.102)	<0.001	
			ER	1.665 (0.883 to 3.139)	0.115	
Hypertension						0.844
	Yes	**265**	**Normal**	*Reference*		
			CR	2.166 (1.318 to 3.561)	0.002	
			CH	2.584 (1.611 to 4.144)	<0.001	
			ER	1.941 (1.051 to 3.583)	0.034	
	No	**332**	**Normal**	*Reference*		
			CR	2.166 (1.384 to 3.388)	0.001	
			CH	3.128 (2.040 to 4.797)	<0.001	
			ER	2.305 (1.354 to 3.923)	0.002	
Diabetes						0.347
	Yes	**100**	**Normal**	*Reference*		
			CR	1.137 (0.517 to 2.504)	0.749	
			CH	1.621 (0.766 to 3.430)	0.206	
			ER	1.066 (0.430 to 2.640)	0.890	
	No	**453**	**Normal**	*Reference*		
			CR	2.233 (1.520 to 3.280)	<0.001	
			CH	2.980 (2.086 to 4.257)	<0.001	
			ER	2.222 (1.402 to 3.524)	0.001	
CAD						0.416
	Yes	**62**	**Normal**	*Reference*		

Table S3: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Stenosis (*continued*)

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
			CR	2.464 (0.856 to 7.094)	0.095	
			CH	5.467 (1.956 to 15.276)	0.001	
			ER	6.343 (1.738 to 23.149)	0.005	
	No	**525**	**Normal**	*Reference*		
			CR	2.231 (1.558 to 3.196)	<0.001	
			CH	2.870 (2.037 to 4.043)	<0.001	
			ER	2.123 (1.381 to 3.264)	0.001	

ER = eccentric remodelling; CAD = coronary artery disease; CH = concentric hypertrophy; CR = concentric remodelling; LV = left ventricular; Normal = normal geometry

Table S4: Subgroup analysis and interaction for event-free survival for LV Mass Index (per 25g/m^2) in Isolated Aortic Stenosis

Subgroup		Number	Hazard Ratio (95% CI)	P-value	P-value for interaction
Age					0.231
	< 50 years	**197**	1.290 (1.106 to 1.504)	0.001	
	≥ 50 years	**416**	1.161 (1.084 to 1.243)	<0.001	
Sex					0.698
	Male	**385**	1.245 (1.159 to 1.338)	<0.001	
	Female	**228**	1.211 (1.083 to 1.355)	0.001	
Hypertension					0.142
	Yes	**265**	1.171 (1.073 to 1.278)	<0.001	
	No	**332**	1.278 (1.169 to 1.398)	<0.001	
Diabetes					0.105
	Yes	**100**	1.097 (0.951 to 1.265)	0.203	
	No	**453**	1.256 (1.169 to 1.349)	<0.001	
CAD					0.228
	Yes	**62**	1.166 (1.038 to 1.310)	0.010	
	No	**525**	1.243 (1.156 to 1.338)	<0.001	

CAD = coronary artery disease; LV = left ventricular

Table S5: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Regurgitation

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
Age						0.695
	< 50 years	**277**	**Normal**	*Reference*		
			CR	1.201 (0.259 to 5.566)	0.815	
			CH	4.050 (1.904 to 8.615)	<0.001	
			ER	4.433 (2.195 to 8.951)	<0.001	
	≥ 50 years	**138**	**Normal**	*Reference*		
			CR	0.973 (0.249 to 3.792)	0.968	
			CH	2.122 (0.895 to 5.038)	0.088	
			ER	3.012 (1.338 to 6.779)	0.008	
Sex						0.331
	Male	**347**	**Normal**	*Reference*		
			CR	1.409 (0.512 to 3.882)	0.507	
			CH	3.339 (1.855 to 6.012)	<0.001	
			ER	3.497 (2.008 to 6.089)	<0.001	
	Female	**68**	**Normal**	*Reference*		
			CR	-		
			CH	3.936 (0.439 to 35.322)	0.221	
			ER	9.475 (1.269 to 70.731)	0.028	
Hypertension						0.407
	Yes	**126**	**Normal**	*Reference*		
			CR	0.474 (0.057 to 3.941)	0.489	
			CH	1.825 (0.705 to 4.722)	0.215	
			ER	2.446 (1.027 to 5.829)	0.043	
	No	**275**	**Normal**	*Reference*		
			CR	1.726 (0.540 to 5.514)	0.357	
			CH	4.319 (2.122 to 8.790)	<0.001	
			ER	4.221 (2.152 to 8.279)	<0.001	
Diabetes						0.679
	Yes	**19**	**Normal**	*Reference*		
			CR	-		
			CH	1.271 (0.177 to 9.138)	0.812	
			ER	0.775 (0.070 to 8.599)	0.836	
	No	**389**	**Normal**	*Reference*		
			CR	1.463 (0.527 to 4.067)	0.465	
			CH	3.424 (1.876 to 6.249)	<0.001	
			ER	4.262 (2.430 to 7.477)	<0.001	
CAD						0.806
	Yes	**30**	**Normal**	*Reference*		

Table S5: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Regurgitation (*continued*)

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
			CR	-		
			CH	1.728 (0.323 to 9.248)	0.523	
			ER	1.755 (0.351 to 8.762)	0.493	
	No	**363**	**Normal**	*Reference*		
			CR	1.633 (0.582 to 4.586)	0.352	
			CH	3.598 (1.931 to 6.704)	<0.001	
			ER	4.024 (2.241 to 7.226)	<0.001	

ER = eccentric remodelling; CAD = coronary artery disease; CH = concentric hypertrophy; CR = concentric remodelling; LV = left ventricular; Normal = normal geometry

Table S6: Subgroup analysis and interaction for event-free survival for LV Mass Index (per 25g/m^2) in Isolated Aortic Regurgitation

Subgroup		Number	Hazard Ratio (95% CI)	P-value	P-value for interaction
Age					0.011
	< 50 years	**277**	1.345 (1.252 to 1.446)	<0.001	
	≥ 50 years	**138**	1.187 (1.092 to 1.292)	<0.001	
Sex					0.085
	Male	**347**	1.270 (1.199 to 1.345)	<0.001	
	Female	**68**	1.485 (1.225 to 1.801)	<0.001	
Hypertension					0.639
	Yes	**126**	1.263 (1.133 to 1.407)	<0.001	
	No	**275**	1.279 (1.200 to 1.363)	<0.001	
Diabetes					0.567
	Yes	**19**	1.235 (0.818 to 1.863)	0.315	
	No	**389**	1.286 (1.219 to 1.357)	<0.001	
CAD					0.029
	Yes	**30**	2.225 (1.397 to 3.544)	0.001	
	No	**363**	1.275 (1.205 to 1.348)	<0.001	

CAD = coronary artery disease; LV = left ventricular

Table S7: Subgroup analysis and interactions for all-cause mortality for LV Remodelling in Isolated Aortic Stenosis

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
Age						0.928
	< 50 years	**197**	**Normal**	*Reference*		
			CR	3.363 (0.304 to 37.195)	0.323	
			CH	3.734 (0.387 to 36.060)	0.255	
			ER	6.014 (0.544 to 66.498)	0.143	
	≥ 50 years	**416**	**Normal**	*Reference*		
			CR	2.184 (0.784 to 6.089)	0.135	
			CH	2.610 (0.995 to 6.850)	0.051	
			ER	2.617 (0.829 to 8.262)	0.101	
Sex						0.580
	Male	**385**	**Normal**	*Reference*		
			CR	2.341 (0.885 to 6.191)	0.086	
			CH	2.528 (0.985 to 6.489)	0.054	
			ER	3.113 (1.044 to 9.279)	0.042	
	Female	**228**	**Normal**	*Reference*		
			CR	-*		
			CH	-		
			ER	-		
Hypertension						0.093
	Yes	**265**	**Normal**	*Reference*		
			CR	1.429 (0.450 to 4.540)	0.545	
			CH	3.356 (1.261 to 8.930)	0.015	
			ER	3.032 (0.922 to 9.968)	0.068	
	No	**332**	**Normal**	*Reference*		
			CR	10.508 (1.330 to 83.050)	0.026	
			CH	5.400 (0.649 to 44.906)	0.119	
			ER	4.947 (0.448 to 54.671)	0.192	
Diabetes						0.087
	Yes	**100**	**Normal**	*Reference*		
			CR	1.852 (0.359 to 9.562)	0.462	
			CH	2.623 (0.565 to 12.174)	0.218	
			ER	2.560 (0.467 to 14.037)	0.279	
	No	**453**	**Normal**	*Reference*		
			CR	3.250 (0.995 to 10.614)	0.051	
			CH	3.661 (1.223 to 10.955)	0.020	
			ER	3.372 (0.905 to 12.570)	0.070	
CAD						0.321
	Yes	**62**	**Normal**	*Reference*		

Table S7: Subgroup analysis and interactions for all-cause mortality for LV Remodelling in Isolated Aortic Stenosis (*continued*)

Subgroup	Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
		CR	-		
		CH	3.028 (0.338 to 27.116)	0.322	
		ER	-		
No	**525**	**Normal**	*Reference*		
		CR	3.650 (1.323 to 10.070)	0.012	
		CH	4.021 (1.528 to 10.578)	0.005	
		ER	3.849 (1.259 to 11.772)	0.018	

*Coefficients did not converge
ER = eccentric remodelling; CAD = coronary artery disease; CH = concentric hypertrophy; CR = concentric remodelling; LV = left ventricular; Normal = normal geometry

Table S8: Subgroup analysis and interactions for all-cause mortality for LV Mass Index (per 25g/m^2) in Isolated Aortic Regurgitation

Subgroup		Number	Hazard Ratio (95% CI)	P-value	P-value for interaction
Age					0.807
	< 50 years	**277**	1.203 (0.916 to 1.579)	0.184	
	≥ 50 years	**138**	1.298 (1.087 to 1.551)	0.004	
Sex					0.726
	Male	**347**	1.298 (1.123 to 1.502)	<0.001	
	Female	**68**	0.970 (0.448 to 2.099)	0.938	
Hypertension					0.794
	Yes	**126**	1.247 (0.908 to 1.713)	0.173	
	No	**275**	1.250 (1.046 to 1.494)	0.014	
Diabetes					0.741
	Yes	**19**	4.027 (0.019 to 856.392)	0.610	
	No	**389**	1.280 (1.107 to 1.480)	0.001	
CAD					0.658
	Yes	**30**	1.425 (0.928 to 2.188)	0.105	
	No	**363**	1.263 (1.051 to 1.517)	0.013	

CAD = coronary artery disease; LV = left ventricular

5

Prognostic implications of left atrial dilation in aortic regurgitation due to bicuspid aortic valve

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ABSTRACT

Aim

The prognostic value of left atrial volume index (LAVI) in patients with moderate to severe aortic regurgitation (AR) and bicuspid aortic valve (BAV) has not been explored. Left atrial (LA) dilation may reflect subclinical left ventricular (LV) fibrosis, chronically impaired LV diastolic function or reduced LV compliance secondary to significant AR.

Methods

A total of 554 individuals (45 [IQR 33-57] years, 80% male) with BAV and moderate or severe AR were selected from an international, multicenter registry of patients with BAV. Cox proportional hazards regression analyses were performed to investigate the association between LAVI and the combined endpoint of all-cause mortality or aortic valve surgery.

Results

Dilated LAVI was observed in 181 (32.7%) patients. The mean indexed aortic annulus, sinus of Valsalva, sinotubular junction and ascending aorta diameters were 13.0 mm/m^2 (±2.0), 19.4 mm/m^2 (±3.7), 16.5 mm/m^2 (±3.8) and 20.4 mm/m^2 (±4.5), respectively. After a median follow-up of 23 (4-82) months, 272 patients underwent aortic valve surgery (89%) or died (11%). When compared to patients with normal LAVI (<35 ml/m^2), those with a dilated LAVI (≥ 35 ml/m^2) had significantly higher rates of aortic valve surgery or mortality (43% and 60% vs 23% and 36%, at 1- and 5-years of follow-up respectively, p<0.001). Dilated LAVI was independently associated with reduced event-free survival (HR=1.450, 95% CI 1.085-1.938, p=0.012) after adjustment for LV ejection fraction, aortic root diameter, LV end-diastolic diameter and LV end-systolic diameter.

Conclusions

In this large, multicenter registry of patients with BAV and moderate to severe AR, LA dilation was independently associated with reduced event-free survival. The role of this parameter for the risk stratification of individuals with significant AR merits further investigation.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common type of congenital heart disease, present in 0.5 to 1.3% of the overall population[1,2]. Compared to the general population, patients with BAV are significantly more likely to be diagnosed with aortic regurgitation (AR) or aortic stenosis, with approximately 13 to 30% demonstrating moderate or severe AR on echocardiography, a complication frequently requiring surgical intervention[3]. Deciding when to intervene is crucial for patients with AR, as inappropriate delays may lead to irreversible left ventricular (LV) remodeling and dysfunction, with poor long-term post-surgical outcome[4-6].

Left atrial (LA) dilation has been demonstrated to be an important marker of prognosis in aortic stenosis [7 8], and may reflect the cumulative effects of subclinical LV fibrosis, chronically impaired LV diastolic function or reduced LV compliance in those with significant AR[9,10]. However, there has been limited investigation of the epidemiology and prognostic significance of LA dilation in the AR population, especially for those with BAV. Although the pathophysiological mechanism has not yet been elucidated, several studies have demonstrated that LV diastolic dysfunction may be more prevalent in those with BAV when compared to those with a tricuspid aortic valve[11,12], and therefore, evaluation of LA size may be particularly pertinent for those with BAV.

LA volume index (LAVI) is the most accurate measurement of the LA size and is recommended by current guidelines[13]. However, most of the previous epidemiological studies on AR have only reported on LA diameter rather than LAVI[7], and did not focus on its prognostic relevance or potential utility for risk stratification. Accordingly, the aim of this study was to (i) determine the prevalence of LA dilation in patients with significant AR due to BAV, and (ii) to investigate the association between LAVI and long-term prognosis.

METHODS

Study population

Patients with BAV and moderate or severe AR referred for echocardiography from June 1, 1991, through February 6, 2017 were selected from a large, international, multicenter registry[14]. Patients with previous aortic valve surgery, infectious endocarditis and incomplete follow-up were excluded. Baseline clinical (dyslipidemia, diabetes, hypertension, and smoking history) and demographic data (including age, sex, height, weight, and body surface area calculated by the Mosteller method[15]) were collected from medical records at the time of transthoracic echocardiography. Data were collected according to regulations approved by the institutional review boards of each center. As this study

involved the retrospective analysis of clinically acquired data, the institutional review board of each center waived the need for written patient informed consent. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Echocardiography

All echocardiographic images were acquired using commercially available ultrasound systems. Experienced observers from each center retrospectively analyzed the acquired images, with the first echocardiographic study confirming a diagnosis of BAV considered as the index study. Standardized parasternal, apical, subcostal and suprasternal views were used to evaluate the morphology of the aortic valve. BAV morphology was defined according to the classification system proposed by Sievers and Schmidtke[16]. AR severity was graded according to contemporary recommendations as none, mild, moderate or severe, using a multiparametric integrative approach according to the AR vena contracta width, pressure half-time of the regurgitant jet and AR jet width[17]. Aortic stenosis severity was graded as none, mild, moderate or severe according to peak aortic jet velocity, mean pressure gradient and aortic valve area[18]. The severity of mitral regurgitation was graded as none, mild, moderate or severe using a multiparametric approach, according to contemporary recommendations[17]. The dimensions of the sinus of Valsalva, sinotubular junction and ascending aorta were measured from leading edge to leading edge on the parasternal long-axis view, perpendicular to the center of the aorta in end-diastole, while the aortic annulus was measured from inner edge to inner edge[13]. LV ejection fraction was calculated using the biplane Simpson method, while LV end-diastolic diameter, LV end-systolic diameter and LV mass were calculated using the standard linear 2-dimensional approach[13]. LA volume was calculated from apical 2 and 4 chamber views using the Simpson method, and was indexed for body surface area[13]. LA dilation was defined as a LAVI of 35 ml/m^2 or greater[13]. LA dilation was further classified as mildly dilated (35-41 ml/m^2), moderately dilated (42-48 ml/m^2) or severely dilated (>48 ml/m^2) according to guideline recommendations[13]. LV hypertrophy was defined by a LV mass index >95 g/m^2 in women and >115 g/m^2 in men. All other standard measurements were performed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines[13].

Follow-up

The primary endpoint of this study was a composite of aortic valve repair or replacement and all-cause mortality. Aortic valve surgery indications were based on contemporary guidelines[19,20]. Patients with symptomatic severe aortic valve dysfunction or asymptomatic severe aortic valve dysfunction with reduced LV ejection fraction (≤50%) or aortic root/aortic dilation were referred for aortic valve surgery. Follow-up began from the

date of the first echocardiogram confirming a diagnosis of BAV and moderate to severe AR, with censoring applied at the time of aortic valve replacement or death (whichever came first). Data of all patients were included up to the last date of follow-up.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

Categorical variables are expressed as numbers and percentages and were compared using the Pearson χ^2 test. Adherence to a normal distribution was verified using visual assessment of histograms. Normally distributed continuous variables are presented as mean ± standard deviation while variables that are non-normally distributed are presented as median and interquartile range. Continuous variables were compared using the Student *t*-test if normally distributed, whereas the Mann-Whitney *U*-test was utilized for non-normally distributed variables. To investigate the hazard ratio (HR) change for the combined endpoint of aortic valve surgery and all-cause mortality across a range of LAVI values (as a continuous variable), a spline curve was fitted. A threshold of LAVI to dichotomize the population was defined from the spline curve (i.e. when the predicted HR was ≥ 1) and existing literature[13]. Cumulative survival rates were estimated by the Kaplan-Meier method for the combined endpoint, and the log-rank test was used to compare groups. Univariable and multivariable Cox proportional hazards regression analyses were performed to investigate the association between clinical and echocardiographic parameters and the combined endpoint of all-cause mortality or aortic valve repair/replacement. Variables with a univariable value of $p < 0.05$ were incorporated into the multivariable models. Two additional sensitivity analyses were performed, to evaluate the relationship between LAVI and the combined endpoint with the exclusion of patients who underwent surgery within 90 days of the index echocardiogram, and to investigate the association between LAVI and all-cause mortality. Finally, to account for missing data, separate sensitivity analyses were conducted using multiple imputations by predictive mean matching (using a chained-equation approach), generating 100 imputed datasets. The HR and 95% confidence intervals (CI) were calculated and reported. The proportional hazards assumption was verified through the evaluation of scaled Schoenfeld residuals. All tests were two-sided and p-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics

A total of 554 patients (80% male) of a median age of 45 years (interquartile range 33 to 57 years) fulfilled the inclusion criteria (Figure 1). Severe AR was present in 196 (35%) patients, while 358 (65%) had moderate AR. Spline curve analysis was performed to evaluate the relationship between LAVI and the combined endpoint of all-cause mortality and aortic valve surgery (Figure 2). Following a plateau and minimal increase in HR, the HR increased markedly with higher values of LAVI (≥35 ml/m^2). Therefore, based on the spline curve analysis and the American Society of Echocardiography recommendations [13], a cut-off value of 35 ml/m^2 for LAVI was used to define a dilated LA and to dichotomize the population. By this definition, a total of 181 patients (32.7%) had a dilated LA, with 79 (43.6%) classified as mildly dilated, 36 (19.9%) classified as moderately dilated, and 66 (36.5%) classified as severely dilated, according to guideline definitions[13]. Those with a dilated LA were older, more likely to be male and more frequently had coronary artery disease. There was no significant difference between BAV morphology when comparing those with a dilated LA to those with a normal LA size. The clinical and demographic characteristics of the overall population and according to LAVI are presented in Table 1.

Table 1: Clinical and demographic characteristics

Variable	Total Population (n=554)	LAVI <35 ml/m^2 (n=373)	LAVI ≥35 ml/m^2 (n=181)	p value
Age, years	45 (33-57)	43 (31-56)	51 (41-61)	<0.001
Male sex (%)	445 (80.3)	286 (76.7)	159 (87.8)	0.002
Hypertension (%)	171 (31.7)	118 (32.3)	53 (30.5)	0.663
Dyslipidemia (%)	118 (21.3)	82 (22.0)	36 (19.9)	0.572
DM (%)	36 (6.5)	24 (6.4)	12 (6.6)	0.930
CAD (%)	45 (8.5)	22 (6.2)	23 (13.2)	0.007
Current smoker (%)	100 (18.1)	72 (19.3)	28 (15.5)	0.271
Atrial fibrillation (%)	25 (4.5)	9 (2.4)	16 (8.9)	0.001
BAV morphology				0.708
No raphe (%)	55 (9.9)	35 (9.4)	20 (11.0)	
Type 1 raphe (L-R), (%)	383 (69.1)	258 (69.2)	125 (69.1)	
Type 1 raphe (R-N), (%)	94 (17.0)	63 (16.9)	31 (17.1)	
Type 1 raphe (L-N), (%)	19 (3.4)	14 (3.8)	5 (2.8)	
Type 2 raphe, (%)	3 (0.5)	3 (0.8)	0 (0.0)	

Values are presented as mean ± SD, median (IQR) or n (%).
CAD = coronary artery disease; DM = diabetes mellitus; LAVI = left atrial volume index; L-N = left – non-coronary; L-R = left – right; R-N = right – non-coronary.

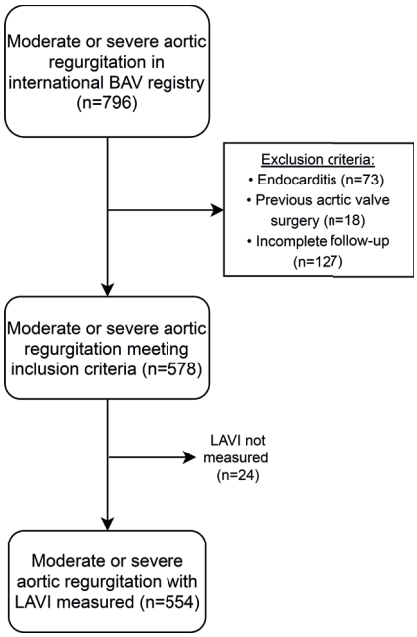

Figure 1: Study flow chart. BAV = bicuspid aortic valve; LAVI = left atrial volume index

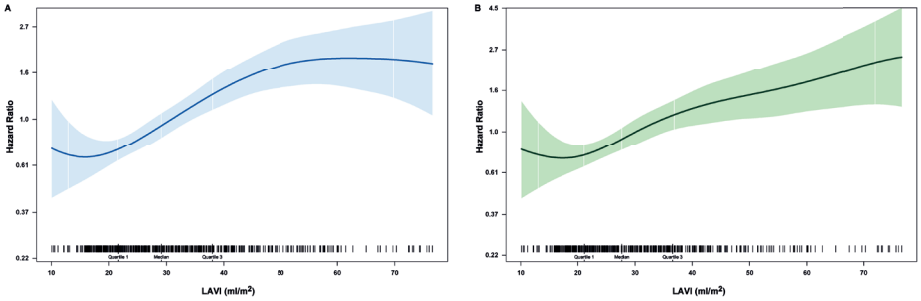

Figure 2: Spline curves for event-free survival according to LAVI for the total population (A, blue) and with those undergoing surgery in the first 90 days excluded (B, green). The curves represent the hazard ratio change for all-cause mortality with overlaid 95% confidence intervals (shaded areas) across a range of LAVI at the time of first echocardiogram. The ticks beneath the curves demonstrate the distribution of the study population according to values of LAVI.
LAVI = left atrial volume index

Echocardiographic characteristics

Patients with a dilated LA had significantly larger LV dimensions and LV mass, lower LV ejection fraction, and more frequently had significant mitral regurgitation when compared to those with normal LAVI. Additionally, those with dilated LA more frequently had concomitant moderate to severe aortic stenosis and a larger AR vena contracta width when compared to the group with normal LAVI. Table 2 summarizes the echocardiographic characteristics of the study population. The variables independently associated with LA dilation are presented in supplemental table S1.

Table 2: Echocardiographic characteristics

Variable	Total Population (n=554)	LAVI <35 ml/m^2 (n=373)	LAVI ≥35 ml/m^2 (n=181)	p value
Left ventricle and atrium				
LV EDD, mm	57 (±9)	56 (±9)	60 (±10)	<0.001
LV ESD, mm	39 (±10)	37 (±9)	42 (± 11)	<0.001
LV EDV, ml	156 (126-199)	148 (120-187)	167 (135-222)	<0.001
LV EF, %	58.9 (±12.9)	60.3 (±11.6)	56.1 (±15.0)	0.001
LV mass indexed, g/m^2	132 (105-170)	124 (99-160)	154 (119-195)	<0.001
LA volume indexed, ml/m^2	29.1 (21.5-38.0)	23.8 (19.6-29.3)	44.5 (38.2-55.0)	<0.001
Mitral inflow E velocity, m/s	0.78 (±0.25)	0.66 (±0.24)	0.80 (±0.29)	0.362
Mitral inflow E/A ratio	1.18 (0.86-1.60)	1.28 (0.88-1.60)	1.33 (±0.72)	0.357
Moderate or severe MR, %	46 (8.3)	17 (4.6)	29 (16.0)	<0.001
Aortic valve and aortic root				
Aortic annulus diameter indexed, mm /m^2	13.0 (±2.0)	13.1 (±2.0)	12.7 (±1.9)	0.031
SOV diameter indexed, mm / m^2	19.4 (±3.7)	19.6 (±3.8)	18.9 (±3.5)	0.293
STJ diameter indexed, mm / m^2	16.5 (±3.8)	16.5 (±3.9)	16.4 (±3.6)	0.853
Ascending aorta diameter indexed, mm / m^2	20.4 (±4.5)	20.6 (±4.5)	20.0 (±4.4)	0.230
Presence of raphe	499 (90.1)	338 (90.6)	161 (89.0)	0.538
No AS (%)	306 (55.2)	209 (56.0)	97 (53.6)	0.084
Mild AS (%)	91 (16.4)	69 (18.5)	22 (12.2)	
Moderate AS (%)	87 (15.7)	54 (14.5)	33 (18.2)	
Severe AS (%)	70 (12.6)	41 (11.0)	29 (16.0)	
Moderate-severe AS (%)	157 (28.3)	95 (25.5)	62 (34.4)	0.031
Pressure-half time, ms	425 (±170)	434 (±170)	407 (±167)	0.100
Vena-contracta width, mm	6.0 (4.6-7.0)	5.5 (4.0-7.0)	6.0 (5.0-8.0)	0.006

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction

Survival Analysis

After a median follow-up of 23 months (interquartile range, 4 to 82 months), 272 (49%) had died or undergone aortic valve surgery. Of the 272 events that were recorded during patient follow-up, 243 (89%) were due to aortic valve surgery, while 29 (11%) were due to all-cause mortality. A total of 138 patients underwent concomitant aortic root surgery. The cumulative 1- and 5- year surgery-free survival rates were 70% and 56% respectively. Patients with a dilated LA (≥35 ml/m^2) had significantly higher rates of aortic valve surgery or mortality when compared to patients with normal LAVI (43% and 60% vs 23% and 36%, at 1- and 5-years of follow-up respectively, p<0.001) (Figure 3A, Figure 3B).

To further evaluate the relationship between LAVI and the combined endpoint of aortic valve surgery and mortality, a multivariable Cox proportional hazards model was

constructed (Table 3). LV end-systolic diameter ≥50 mm, LV end-diastolic diameter ≥70 mm and aortic root/ascending aorta diameter ≥50 mm were introduced as categorical variables, reflecting current guideline indications for surgical intervention in AR [20 21]. Additionally, LAVI was introduced as a categorical variable, utilizing the threshold derived from spline curve analysis (≥35 ml/m^2). Univariable analysis demonstrated that age, hypertension, LV ejection fraction, LV hypertrophy, LV end-systolic diameter, LV end-diastolic diameter, aortic root/ascending aorta diameter, moderate or severe aortic stenosis, mitral inflow E/A ratio, AR pressure half-time, AR vena contracta width and LAVI were significantly associated with the endpoint of aortic valve surgery or mortality. On multivariable Cox regression analysis, LA dilation (≥35 ml/m^2) remained independently associated with the combined endpoint despite adjustment for important confounders and contemporary indications for aortic valve surgery. Furthermore, the following variables also retained an independent association with the combined endpoint: age, LV hypertrophy, aortic root/ascending aorta diameter, moderate or severe aortic stenosis and AR vena contracta width.

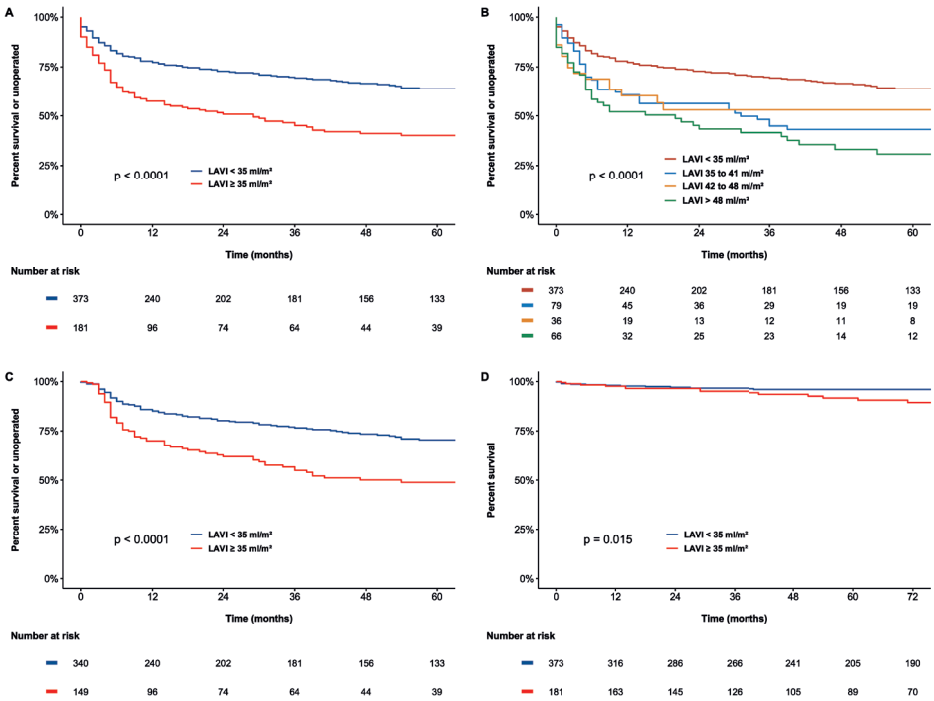

Figure 3: Kaplan-Meier curves for the combined endpoint of event-free survival and for all-cause mortality. Panel A demonstrates the Kaplan Meier curve for the combined endpoint of event-free survival for the total population at a cut-off of LAVI of 35 ml/m^2. Panel B shows the Kaplan Meier curve for the combined endpoint of event-free survival with the population stratified according to normal, mildly, moderately and severely dilated LAVI, while panel C shows the survival curves with those undergoing surgery in the first 90 days excluded. Panel D demonstrates a Kaplan Meier curve for the endpoint of all-cause mortality for the total population at a cut-off of 35 ml/m^2 (D).
LAVI = left atrial volume index

Table 3: Univariable and multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality

	Univariate analysis		Multivariable analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.029 (1.021-1.037)	<0.001	1.029 (1.017-1.040)	<0.001
Male sex	1.140 (0.844-1.541)	0.386		
Current smoker	1.292 (0.959-1.742)	0.093		
Hypertension	1.315 (1.024-1.688)	0.032	0.889 (0.650-1.217)	0.464
Dyslipidemia	1.233 (0.930-1.633)	0.145		
DM	1.119 (0.760-1.892)	0.436		
CAD	1.696 (1.120-2.569)	0.013	1.373 (0.791-2.380)	0.260
Atrial fibrillation	1.375 (0.829-2.280)	0.216		
Echocardiographic characteristics				
LVEF, %	0.977 (0.968-0.987)	<0.001	0.991 (0.978-1.005)	0.214
LVESD > 50 mm	2.502 (1.758-3.560)	<0.001	1.513 (0.793-2.888)	0.209
LVEDD > 70 mm	2.510 (1.716-3.671)	<0.001	1.353 (0.734-2.496)	0.333
Aortic root or ascending aorta > 50 mm	3.567 (2.445-5.203)	<0.001	3.834 (2.422-6.071)	<0.001
LV hypertrophy	2.378 (1.694-3.339)	<0.001	1.499 (1.017-2.208)	0.041
Moderate or severe MR	1.321 (0.897-1.946)	0.159		
Moderate or severe AS	1.771 (1.386-2.262)	<0.001	2.232 (1.650-3.018)	<0.001
Mitral inflow E/A ratio	0.744 (0.585-0.948)	0.017	1.119 (0.853-1.468)	0.415
VC width, mm	1.127 (1.085-1.171)	<0.001	1.113 (1.063-1.165)	<0.001
LAVI ≥ 35 ml / m^2	1.927 (1.514-2.454)	<0.001	1.450 (1.085-1.938)	0.012

*Due to missing data, 450 patients were included in the multivariable analysis. A sensitivity analysis with imputed data can be found in the supplementary material.
AS = aortic stenosis; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

In addition, to reduce the impact of referral bias and to account for the presence of symptoms and LV ejection fraction <50% at the time of first echocardiogram on the decision to perform surgery, all data were reanalyzed following the exclusion of 65 patients who had surgery within 90 days of the index echocardiogram. A spline curve demonstrated a similar relationship between LAVI and the study endpoint in this cohort (Figure 2B). In accordance with the prior analysis, patients with a LAVI ≥35 ml/m^2 had significantly higher rates of aortic valve surgery or mortality when compared to patients with normal LAVI (30% and 51% vs 15% and 30%, at 1- and 5-years of follow-up respectively, p<0.001) over a median follow-up period of 36 months (interquartile range, 7 to 96 months) (Figure 3C). Furthermore, on multivariable Cox regression analysis, LA dilation remained independently associated with the combined endpoint of aortic valve surgery

and mortality, in addition to age, aortic root/ascending aorta diameter, moderate or severe aortic stenosis and AR vena contracta width (Table 4).

Sensitivity analyses were performed to include significant mitral regurgitation (Table S2) and LVEF as dichotomous variable (<50% vs ≥50%; Table S3) as covariates in both multivariable models, demonstrating similar results to the primary analyses. Furthermore, LA dilation was independently associated with mortality after multiple imputation of missing data (Table S4), consistent with the main analyses. In addition, a sensitivity analysis considering only all-cause mortality as the endpoint was performed, and confirmed the prognostic significance of LA dilation (Table S5). After a median follow-up of 65 months (interquartile range, 29 to 128 months), 41 patients died. Patients with LAVI ≥35 ml/m^2 experienced significantly higher rates of mortality compared to those with normal LAVI at 5 years of follow-up (8.3% vs 4.1%, p=0.015) (Figure 3D).

Table 4: Univariable and multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality with exclusion of those undergoing surgery in the first 90 days

	Univariate analysis		Multivariable analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.031 (1.022-1.040)	<0.001	1.031 (1.018-1.044)	<0.001
Male sex	1.164 (0.826-1.640)	0.385		
Current smoker	1.185 (0.829-1.692)	0.352		
Hypertension	1.504 (1.133-1.995)	0.005	1.046 (0.736-1.487)	0.804
Dyslipidemia	1.314 (0.954-1.810)	0.095		
DM	1.479 (0.911-2.403)	0.114		
CAD	1.380 (0.798-2.384)	0.249		
Atrial fibrillation	1.550 (0.883-2.723)	0.127		
LVEF, %	0.978 (0.968-0.989)	<0.001	0.995 (0.979-1.011)	0.525
LVESD > 50 mm	2.527 (1.653-3.862)	<0.001	1.657 (0.796-3.450)	0.177
LVEDD > 70 mm	2.717 (1.735-4.257)	<0.001	1.596 (0.802-3.176)	0.183
Aortic root or ascending aorta > 50 mm	2.406 (1.395-4.419)	0.002	2.134 (1.069-4.258)	0.032
LV hypertrophy	2.283 (1.559-3.344)	<0.001	1.277 (0.832-1.961)	0.263
Moderate or severe MR	1.313 (0.841-2.050)	0.231		
Moderate or severe AS	1.646 (1.238-2.188)	0.001	2.128 (1.507-3.005)	<0.001
Mitral inflow E/A ratio	0.597 (0.443-0.804)	0.001	1.007 (0.720-1.408)	0.967
VC width, mm	1.142 (1.090-1.196)	<0.001	1.138 (1.080-1.201)	<0.001
LAVI ≥ 35 ml / $^{m}2$	1.901 (1.439-2.512)	<0.001	1.534 (1.104-2.131)	0.011

*Due to missing data, 404 patients were included in the multivariable analysis. A sensitivity analysis with imputed data can be found in the supplementary material.

AS = aortic stenosis; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

DISCUSSION

In this large, international multicenter registry of 554 patients with BAV and moderate or severe AR, the prevalence of LA dilation (LAVI ≥35 ml/m^2) was 33%. LA dilation at the time of index echocardiogram was associated with reduced event-free survival following adjustment for contemporary indications for aortic valve surgery and other important confounders. Importantly, this independent association remained after excluding patients who underwent surgery within the first 90 days to avoid referral bias.

Prevalence and pathogenesis of LA dilation in significant AR

This study reveals that LA dilation is common in patients with significant AR and BAV, with one-third demonstrating a LAVI ≥35 ml/m^2. In a study including 372 patients undergoing surgery for aortic regurgitation of a variety of etiologies, LA dilation (defined as an indexed LA diameter ≥23 mm/m^2) was present in 28% of individuals[7], similar to the findings of the present study.

In significant AR, the pathogenesis of LA dilation is highly complex. Initially, the aortic regurgitant jet results in a combination of pressure and volume overload, with higher LV diastolic and systolic wall stress, and dramatic increases in LV volumes and mass[22]. With progressive increases in LV afterload and disturbed coronary flow dynamics, supply-demand mismatch may result, leading to LV myocardial ischemia and potentially, myocardial fibrosis[23,24]. In addition, progressive LV remodeling may result in papillary muscle displacement, tethering of the mitral valve leaflets and a reduction in mitral valve closing forces, leading to secondary mitral regurgitation[25]. Therefore, LA dilation in AR may be the common consequence of several mechanisms, including any one or combination of: secondary mitral regurgitation, chronically impaired LV diastolic function or LV fibrosis and reduced LV compliance[26]. Moreover, compared to other parameters of LV diastolic function (such as mitral inflow E wave velocity and tricuspid regurgitant jet velocity), LA volume may more accurately reflect the cumulative effects of chronically elevated LV filling pressures and LV diastolic dysfunction[9], providing further insight into the pathophysiological status of the LV in individuals with AR. For example, in a study of 54 patients with severe AR, only post-operative LA dilation was independently associated with persistent LV systolic dysfunction at 1 year following surgery in individuals with early postoperative LV systolic dysfunction[27], reflecting the important insight that LA size provides into LV function.

LA dilation as a correlate of event-free survival in significant AR

In the present study, LA dilation was significantly associated with a reduction in event-free survival following adjustment for contemporary indications for aortic valve surgery and clinically important covariates. While previous studies have not investigated the

association of LA dilation and the need for future aortic valve surgery in patients with significant AR, inferences can be made from several studies that have identified an association between LA dilation and the development of symptoms (a class I indication for aortic valve surgery)[19, 28, 29]. The presence of LA dilation may identify individuals who have worse subclinical LV diastolic function and are more likely to develop symptoms, thus requiring surgical intervention. However, this study was not designed to investigate the relationship between LA dilatation and diastolic dysfunction.

Consistent with previous literature, the present study also demonstrated a significant increase in all-cause mortality for those with LA dilation compared to those without LA dilation. Previously, in an unadjusted sub-group analysis of 372 patients with significant AR, Mosquera et al. demonstrated that increasing indexed LA diameter on pre-surgical echocardiography was significantly associated with future cardiovascular mortality[7]. Likewise, in another smaller study, a sub-group analysis of 41 patients with AR demonstrated that a LAVI ≥35 ml/m^2 on pre-surgical echocardiography was associated with long-term adverse cardiovascular outcome[30]. However, thus far, no study has demonstrated the independent prognostic impact of LA dilation. Therefore, the potential usefulness of this parameter for risk stratification in AR has remained unclear. The current study demonstrates that LA dilation is independently associated with reduced event-free survival in patients with significant AR and BAV, likely reflecting subclinical LV dysfunction and an increased propensity for the development of symptoms in the future.

Clinical implications and future directions

The present study has demonstrated that LA dilation is common and is independently associated with event-free survival in those with significant AR and BAV. Indeed, LA dilation probably anticipates the onset of symptoms, which currently represents the main indication for surgery in patients with severe AR[19]. However, symptoms or the reduction of LV ejection fraction may represent late markers of LV damage secondary to AR, and the optimal timing for surgical intervention may have passed[22]. The presence of LA dilation in significant AR may also identify patients at increased risk of persistent LV dysfunction and poorer long-term outcome following surgery[7, 27]. For example, a LAVI ≥35 ml/m^2 may be present in patients prior to significant changes in LV dimensions, and may be used to identify those who would benefit from surgery earlier than current guideline recommendations [20, 21]. Additionally, it is possible that LAVI could be integrated into a scoring system with LV ejection fraction, LV end-systolic diameter and LV end-diastolic diameter to identify patients who would benefit from earlier surgical intervention than contemporary guideline recommendations. Furthermore, because LAVI is simple to measure and is widely reported as a standard parameter, integration into clinical workflow would be effortless.

Limitations

This study is subject to all of the limitations associated with a retrospective, observational design. Consequently, the findings of this study are hypothesis generating only, with randomized clinical trials required to determine if earlier surgery is justified in patients with severe AR and LA dilation. Additionally, guideline indications for surgery have changed over the period of the registry, with more contemporary guidelines incorporating LV dimensions into their recommendations, possibly influencing the results of this study. LA strain was not performed which may have provided additional prognostic information through the evaluation of LA function. Although only present in a small percentage of the population, atrial fibrillation rather than AR may have been the primary cause of a dilated LAVI in some patients. Likewise, the presence of concomitant aortic stenosis may also be a primary cause of LA dilation. Furthermore, despite additional analysis excluding patients who underwent surgery within three months of index echocardiography, it is still possible that referral bias and the presence of symptoms at baseline may have influenced the decision to perform surgery after this time period. In addition, remodeling of the LA and LV frequently occur following aortic valve surgery, and the prognostic significance of baseline values of LAVI may depend on an individual patient's response to future surgery.

CONCLUSION

In this large, multicenter registry of patients with BAV and significant AR, LA dilation was independently associated with reduced event-free survival following adjustment for contemporary indications for aortic valve surgery and other significant confounders. The role of this parameter for the risk stratification of individuals with significant AR merits further investigation.

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SUPPLEMENTARY MATERIAL

Table S1: Univariable and multivariable logistic regression models evaluating clinical and echocardiographic parameters associated LA dilation (LAVI ≥ 35ml/m^2)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Patient demographics and comorbidities				
Age	1.025 (1.014-1.037)	<0.001	1.009 (0.996-1.023)	0.184
Male sex	2.199 (1.325-3.648)	0.002	1.808 (1.032-3.168)	0.038
Current smoker	0.830 (0.550-0.1252)	0.374		
Hypertension	0.917 (0.621-1.355)	0.663		
Dyslipidemia	0.881 (0.568-1.368)	0.572		
DM	1.033 (0.504-2.115)	0.930		
CAD	2.306 (1.246-4.266)	0.008	1.684 (0.801-3.541)	0.169
Atrial fibrillation	3.915 (1.695-9.046)	0.001	1.990 (0.737-5.376)	0.175
Echocardiographic characteristics				
LVEF, %	0.976 (0.962-0.989)	0.001	0.987 (0.971-1.004)	0.123
Aortic root or ascending aorta > 50 mm	0.720 (0.329-1.576)	0.411		
LV hypertrophy	2.920 (1.835-4.646)	<0.001	2.291 (1.358-3.864)	0.002
Moderate or severe MR	3.995 (2.132-7.487)	<0.001	2.756 (1.281-5.930)	0.009
Moderate or severe AS	1.525 (1.037-2.241)	0.032	1.299 (0.811-2.080)	1.299
Mitral inflow E/A ratio	1.175 (0.865-1.596)	0.303		
VC width, mm	1.124 (1.044-1.210)	0.002	1.087 (1.000-1.182)	0.050
LV stroke volume, ml	1.005 (1.000-1.010)	0.066		

AS = aortic stenosis; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S2: Multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality including significant mitral regurgitation as a covariate

	Total Population		Total population excluding those who underwent surgery in first 90 days	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Patient demographics and comorbidities				
Age	1.029 (1.017-1.040)	<0.001	1.031 (1.018-1.044)	<0.001
Hypertension	0.877 (0.641-1.201)	0.414	1.018 (0.715-1.451)	0.919
CAD	1.458 (0.838-2.537)	0.182		
Echocardiographic characteristics				
LVEF, %	0.989 (0.975-1.003)	0.136	0.993 (0.976-1.009)	0.377
LVESD > 50 mm	1.465 (0.766-2.801)	0.248	1.629 (0.779-3.406)	0.195
LVEDD > 70 mm	1.401 (0.756-2.596)	0.285	1.671 (0.829-3.367)	0.151
Aortic root or ascending aorta > 50 mm	3.729 (2.351-5.915)	<0.001	2.024 (1.008-4.062)	0.047
LV hypertrophy	1.508 (1.023-2.221)	0.038	1.291 (0.841-1.982)	0.243
Moderate or severe MR	0.729 (0.427-1.244)	0.247	0.691 (0.376-1.268)	0.232
Moderate or severe AS	2.257 (1.668-3.053)	<0.001	2.161 (1.528-3.056)	<0.001
Mitral inflow E/A ratio	1.096 (0.834-1.442)	0.511	0.981 (0.699-1.376)	0.911
VC width, mm	1.114 (1.065-1.165)	<0.001	1.140 (1.081-1.201)	<0.001
LAVI ≥ 35 ml / m^2	1.467 (1.098-1.962)	0.010	1.566 (1.125-2.178)	0.008

AS = aortic stenosis; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S3: Multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality including LVEF at a cut-off of 50% as a covariate

	Total Population		Total population excluding those who underwent surgery in first 90 days	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Patient demographics and comorbidities				
Age	1.030 (1.018-1.041)	<0.001	1.031 (1.018-1.044)	<0.001
Hypertension	0.889 (0.649-1.217)	0.462	1.039 (0.730-1.479)	0.832
CAD	1.356 (0.781-2.353)	0.280		
Echocardiographic characteristics				
LVEF < 50%	1.172 (0.762-1.803)	0.469	1.203 (0.728-1.987)	0.471
LVESD > 50 mm	1.659 (0.873-3.155)	0.122	1.633 (0.783-3.407)	0.191
LVEDD > 70 mm	1.334 (0.722-2.463)	0.357	1.601 (0.803-3.190)	0.181
Aortic root or ascending aorta > 50 mm	3.740 (2.347-5.960)	<0.001	2.053 (1.019-4.136)	0.044
LV hypertrophy	1.499 (1.018-2.209)	0.040	1.276 (0.832-1.959)	0.265
Moderate or severe AS	2.183 (1.618-2.946)	<0.001	2.110 (1.498-2.972)	<0.001
Mitral inflow E/A ratio	1.141 (0.871-1.495)	0.338	1.008 (0.722-1.408)	0.962
VC width, mm	1.111 (1.062-1.163)	<0.001	1.139 (1.080-1.201)	<0.001
LAVI ≥ 35 ml / m^2	1.464 (1.096-1.956)	0.010	1.545 (1.112-2.147)	0.010

AS = aortic stenosis; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S4: Multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality: sensitivity analysis after multiple imputation of missing data

	Total Population		Total population excluding those who underwent surgery in first 90 days	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.025 (1.015-1.036)	<0.001	1.027 (1.015-1.039)	<0.001
Hypertension	0.899 (0.683-1.184)	0.450	0.993 (0.727-1.355)	0.964
CAD	0.984 (0.619-1.565)	0.946		
Echocardiographic characteristics				
LVEF	0.994 (0.980-1.007)	0.367	0.998 (0.983-1.013)	0.575
LVESD > 50 mm	1.311 (0.696-2.472)	0.402	1.304 (0.610-2.789)	0.494
LVEDD > 70 mm	1.160 (0.649-2.071)	0.617	1.225 (0.604-2.484)	0.575
Aortic root or ascending aorta > 50 mm	3.003 (1.983-4.548)	<0.001	1.542 (0.834-2.851)	0.168
LV hypertrophy	1.523 (1.066-2.178)	0.021	1.397 (0.937-2.083)	0.101
Moderate or severe AS	1.861 (1.429-2.423)	<0.001	1.791 (1.322-2.427)	<0.001
Mitral inflow E/A ratio	1.096 (0.834-1.441)	0.511	0.975 (0.705-1.350)	0.881
VC width, mm	1.101 (1.052-1.153)	<0.001	1.129 (1.069-1.193)	<0.001
LAVI ≥ 35 ml / m^2	1.449 (1.115-1.884)	0.006	1.519 (1.129-2.045)	0.006

AS = aortic stenosis; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S5: Univariable and multivariable Cox proportional hazard models for all-cause mortality.

	Univariable analysis		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities						
Age	1.064 (1.040-1.088)	<0.001	1.054 (1.029-1.079)	<0.001	1.052 (1.027-1.078)	<0.001
Hypertension	2.265 (1.207-4.250)	0.011			1.374 (0.713-2.648)	0.342
DM	3.596 (1.633-7.919)	0.001	2.896 (1.270-6.601)	0.011		
CAD	4.386 (1.994-9.646)	<0.001			2.117 (0.916-4.895)	0.079
LVEF, %	0.952 (0.933-0.973)	<0.001	0.971 (0.950-0.992)	0.007		
Category of LA dilation						
LAVI <35ml/m^2	*Reference group*		*Reference group*		*Reference group*	
LAVI 35 to 48 ml/m^2	1.188 (0.504-2.802)	0.694	1.073 (0.452-2.551)	0.873	0.925 (0.386-2.216)	0.861
LAVI >48 ml/m^2	3.765 (1.854-7.649)	<0.001	2.315 (1.039-5.159)	0.040	2.718 (1.293-5.710)	0.008

*Clinically important, pre-specified variables were included in univariable and multivariable analyses, with a maximum of 4 variables included per model to avoid overfitting.
DM = diabetes mellitus; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction

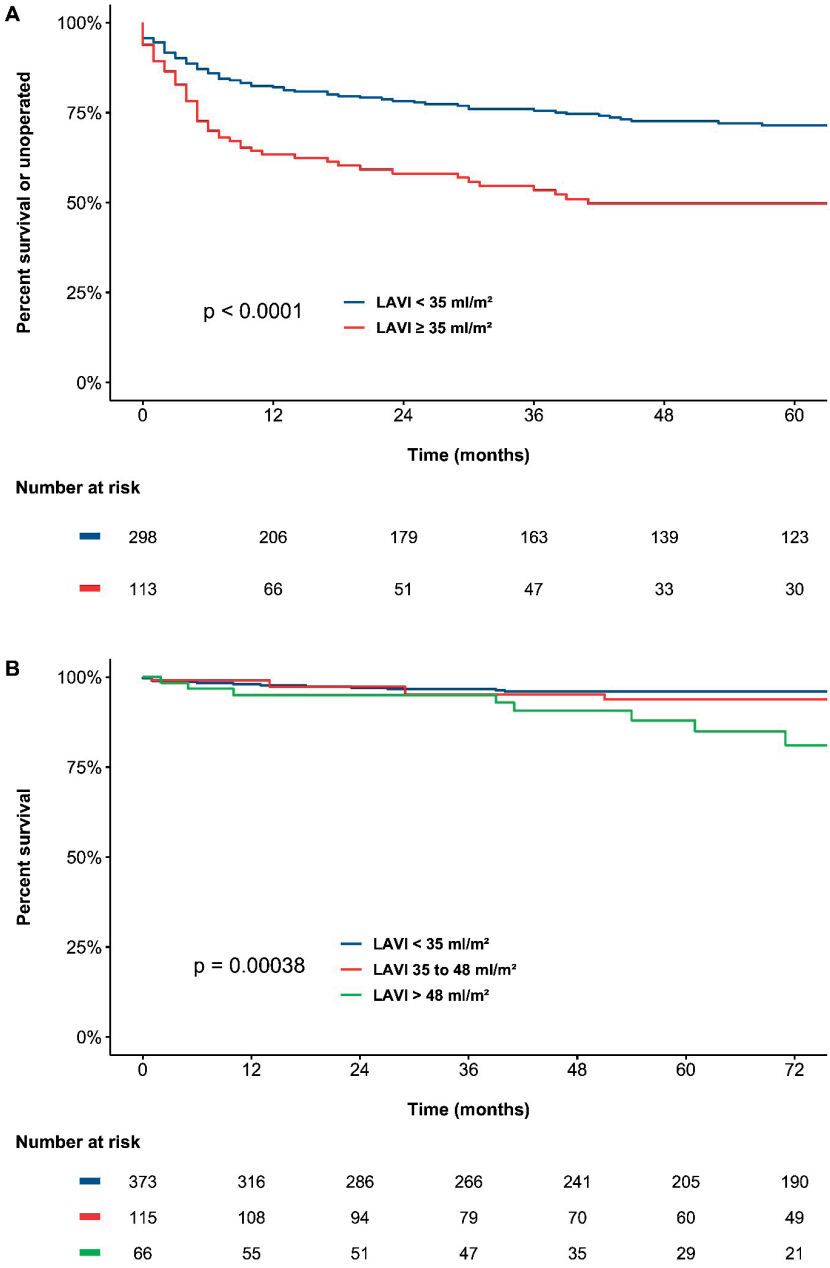

Figure S1: Kaplan-Meier curves for the combined endpoint of event-free survival for patients not meeting contemporary criteria for surgical intervention (A), for all-cause mortality stratified according to normal LAVI, mild to moderately dilated LAVI and severely dilated LAVI (B). The Kaplan-Meier curve in panel A demonstrates the higher event-free survival rates and survival rates of patients with normal LAVI (≥35 ml/m^2, blue line) compared to those with LA dilation (<35 ml/m^2, red line) in the patient subgroup with an LVEF≥50%, LVEDD < 70mm and LVESD < 50mm. The curve in panel B demonstrates the increased rates of all-cause mortality for patients with a LAVI > 48 ml/m^2.
LAVI = left atrial volume index

6

Prevalence and Prognostic Implications of Moderate or Severe Mitral Regurgitation in Patients with Bicuspid Aortic Valve

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ABSTRACT

Background

Significant (≥ moderate) mitral regurgitation (MR) could augment the hemodynamic effects of aortic valvular disease in patients with bicuspid aortic valve (BAV), imposing a greater hemodynamic burden on the left ventricle and atrium, possibly culminating in a faster onset of left ventricular (LV) dilation and/or symptoms. The aim of this study was to determine the prevalence and prognostic implications of significant MR in patients with BAV.

Methods

In this large, multicenter, international registry, a total of 2,932 patients (48±18 years, 71% male) with BAV were identified. All patients were evaluated for the presence of significant primary or secondary MR by transthoracic echocardiography and were followed-up for the endpoints of all-cause mortality and event-free survival.

Results

Overall, 147 patients (5.0%) had significant primary (1.5%) or secondary (3.5%) MR. Significant MR was associated with all-cause mortality (HR 2.80, 95% CI 1.91 to 4.11, p<0.001) and reduced event-free survival (HR 1.97, 95% CI 1.58 to 2.46, p<0.001) on univariable analysis. MR was not associated with all-cause mortality (adjusted HR 1.33, 95% CI 0.85 to 2.07, p=0.21) or event-free survival (adjusted HR 1.10, 95% CI 0.85 to 1.42, p=0.49) after multivariable adjustment. However, sensitivity analyses demonstrated that significant MR not due to aortic valve disease retained an independent association with mortality (adjusted HR 1.81, 95% CI 1.04 to 3.15, P=0.037). Subgroup analyses demonstrated an independent association between significant MR and all-cause mortality for individuals with significant aortic regurgitation (HR 2.037, 95% CI 1.025 to 4.049, p=0.042), although this association was not observed for subgroups with significant aortic stenosis or without significant aortic valve dysfunction.

Conclusions

Significant MR is uncommon in patients with BAV. Following adjustment for important confounding variables, significant MR was not associated with adverse prognosis in this large study of patients with BAV, except for the patient subgroup with moderate to severe aortic regurgitation. In addition, significant MR not due to aortic valve disease demonstrated an independent association with all-cause mortality.

INTRODUCTION

Bicuspid aortic valve (BAV) is frequently associated with other congenital cardiac abnormalities, such as aortic coarctation, hypoplastic left heart syndrome, Shone's syndrome or reversal of coronary artery dominance[1-5]. In addition, several studies have suggested an association between BAV and primary mitral regurgitation (MR), although further research is required to confirm this relationship[6-9]. Severe aortic stenosis or regurgitation due to BAV may also be associated with left ventricular (LV) remodeling and dysfunction, which can lead to secondary MR.

In patients with BAV, significant (≥moderate) MR could augment the hemodynamic effects of coexistent aortic valvular disease[10, 11], imposing a greater hemodynamic burden on left ventricle and atrium, conceivably culminating in a faster onset of LV dilation or symptoms, or a poorer long-term outcome[12]. Although previous studies have demonstrated that significant MR is independently associated with an adverse prognosis in the general population[13, 14], until now, the prognostic importance of significant MR in patients with BAV had not been investigated.

In this context, the aims of this study were i) to determine the prevalence of significant primary and secondary MR in patients with BAV, and ii) to investigate the association of significant MR with overall survival and event-free survival in individuals with BAV.

METHODS

Study population

From an international, multicenter registry of patients with BAV, patients with MR were identified[15]. Individuals with previous aortic or mitral valve surgery, endocarditis of the mitral valve or complex congenital heart disease were excluded. Demographic (including age, sex and body surface area calculated by the Mosteller method[16]), clinical data and cardiovascular risk factors (hypertension, dyslipidemia, diabetes and smoking history[17-19]) were collected from medical records at the time of the first diagnosis of BAV by transthoracic echocardiography. Coronary artery disease was defined as a history of previous myocardial infarction or revascularization, or coronary artery stenosis ≥50% on coronary angiography. Data were collected according to the regulations approved by institutional review boards of each research center and retrospectively analysed. Due to the retrospective study design and anonymous handling of clinical data, the ethical committees of participating centers waived the need for written informed consent. This investigation conforms to the principles outlined in the *Declaration of Helsinki*. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Echocardiography

All echocardiograms were performed using commercially available equipment and were retrospectively analyzed by experienced investigators in each centre. The first transthoracic echocardiogram confirming a diagnosis of BAV was considered as the index study. The phenotype of BAV was defined according to the classification proposed by Sievers and Schmidtke[20]: type 0, valve without raphe; type 1, valve with one raphe (which is further sub-classified according to the orientation of the raphe in relation to the coronary sinuses); and type 2, valves with two raphes. The presence of either aortic valve stenosis and/or regurgitation was assessed and graded as none, mild, moderate, and severe according to current guidelines, where moderate or severe grading was considered as significant[21, 22]. MR was assessed and classified according to the mechanism: primary (organic/structural intrinsic mitral valve disease) or secondary (without evident structural abnormality of the mitral valve). The severity of MR was graded as none, mild, moderate, and severe according to guideline recommendations, integrating qualitative, semiquantitative and quantitative parameters[23]. Vena contracta (VC) width was measured from an apical four-chamber view at the narrowest portion of the regurgitant flow at the regurgitant orifice. The effective regurgitation orifice area (EROA) and regurgitant volume were calculated using the proximal isovelocity surface area method[23]. Mitral valve prolapse was evaluated in the parasternal long-axis window and was defined as systolic displacement of the mitral leaflet/s into the left atrium of at least 2 mm from the mitral annular plane[23]. A mixed aetiology of significant MR was defined as including components of both primary and secondary MR[23]. The diameter of the aortic root and ascending aorta (4 to 5 cm distal to the sinotubular junction) were measured by two-dimensional (2D) echocardiography on the parasternal long-axis view using the leading edge-to-leading edge convention in an end-diastolic frame[24]. The aortic dilatation configurations were reported following the classification by Fazel and colleagues: aortic root dilatation only, ascending aorta dilatation only and diffuse involvement of both aortic root and ascending aorta[25]. LV end-diastolic diameter and LV end-systolic diameter were calculated using the linear 2D approach. LV ejection fraction (LVEF) and LV end-diastolic volume were calculated using the biplane Simpson method[24]. All other standard measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines[24].

Follow-up

The primary endpoint of the study was all-cause mortality. Follow-up started at the time of the index echocardiogram confirming the diagnosis of BAV. The secondary endpoint was a composite of aortic valve repair/replacement and all-cause mortality (event-free survival). Indications for aortic valve surgery were based on contemporary guidelines[26, 27]. Data of all patients were included up to the last date of follow-up.

Statistical analysis

Categorical variables are presented as counts and percentages and were compared using the Pearson χ^2 test. Adherence to a normal distribution was evaluated by comparing histograms to overlaid normal probability curves. Normally distributed continuous variables are presented as mean ± standard deviation and were compared using the Student *t*-test or one-way ANOVA, while non-normally distributed parameters are presented as median and interquartile range (IQR) and were compared with the Mann-Whitney *U* or Kruskal-Wallis test. Multiple comparisons were tested using Bonferroni's correction. The association between BAV morphology and significant primary MR with prolapse of the anterior mitral valve leaflet was evaluated with logistic regression.

Cumulative 1- and 5- year survival rates were estimated using the Kaplan Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was performed to investigate the association of significant MR with all-cause mortality and event-free survival. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. Prespecified clinical and echocardiographic variables known to be associated with all-cause mortality or event-free survival were entered into the respective multivariable models, with additional adjustment for aortic root/ascending aorta dilation in the model evaluating the combined endpoint. Aortic root/ascending aorta diameter ≥50 mm was defined as aortic root/ascending aorta dilation, to reflect current guideline indications for surgical intervention[28]. Sensitivity analyses incorporating aortic valve surgery as a time-dependent covariate were performed for each multivariable Cox regression model that evaluated all-cause mortality as the endpoint. In addition, further sensitivity analyses evaluating the prognostic implications of significant MR stratified according to etiology (due to aortic valve disease or not) were performed. The proportional-hazards assumption was verified with the evaluation of scaled Schoenfeld residuals.

In addition, subgroup analyses of BAV patients with significant aortic regurgitation, significant aortic stenosis and without significant aortic valvular disease were performed. The relationship of significant MR with all-cause mortality and event-free survival were examined for each subgroup in univariable and multivariable Cox regression models. Multivariable subgroup analyses were limited to adjustment of four prespecified variables (age, diabetes mellitus, LV end-diastolic volume and LVEF) due to the risk of model overfitting[29]. All tests were two-sided and *P* values <0.05 were considered statistically significant. The statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient population

A total of 2932 patients with BAV (mean age 48±18 years, 71% male) met the study inclusion criteria (Figure 1). Significant MR was identified in 148 patients (5%), with primary MR observed in 44 (1.5%) patients and secondary MR in 104 (3.5%) patients. Individuals with significant MR were older and more likely to have diabetes mellitus. Overall, the most frequently encountered BAV morphology was type 1 with raphe fusion between the right and left coronary cusps (Table 1). Patients with significant primary MR were more likely to have a type 1 raphe with left and non-coronary cusp fusion compared to patients without significant primary MR (19.0% vs 4.6%, p<0.001) (Figure 2). Furthermore, the presence of a type 1 raphe with left and non-coronary cusp fusion was associated with a significantly higher prevalence of significant MR due to prolapse of the anterior mitral valve leaflet compared to patients with other BAV morphologies (OR 6.76, 95% CI 2.42 to 18.90, p<0.001). Etiologies of significant primary MR included mitral valve prolapse (57%), leaflet calcification (18%), rheumatic heart disease (5%), leaflet billowing (5%), mitral valve cleft (2%), parachute mitral valve (2%), and mixed (11%). Of those with secondary MR, the etiology was aortic valve disease in 76 (73%), non-ischemic cardiomyopathy in 11 (11%), ischemic cardiomyopathy in 8 (8%), hypertensive cardiomyopathy in 3 (3%), atrial functional MR in 2 (2%) and unclear aetiology in 4 (4%). The clinical and demographic characteristics of the total population are summarised in Table 1.

Table 1: Clinical and BAV characteristics of patients divided according to mitral regurgitation mechanism.

	Total population (n=2932)	No significant MR (n=2784)	Significant MR (n=148)	*P* value
Clinical characteristics				
Age (years)	47.9 (±17.7)	47.3 (±17.5)	59.0 (±17.5)	<0.001
Male (%)	2065 (70.5%)	1961 (70.5%)	104 (70.3%)	0.960
Prior CAD (%)	216 (8.0%)	198 (7.8%)	18 (12.6%)	0.040
BSA, m^2	1.90 (±0.26)	1.90 (±0.27)	1.87 (±0.22)	0.27
Hypertension (%)	950 (34.7%)	891 (34.4%)	59 (41.3%)	0.092
Dyslipidemia (%)	741 (26.2%)	695 (25.9%)	46 (31.1%)	0.162
Diabetes mellitus (%)	285 (10.5%)	262 (10.2%)	23 (15.9%)	0.032
Current smoker (%)	447 (16.5%)	421 (16.4%)	26 (17.9%)	0.638
BAV characteristics				
No raphe (%)	397 (14.6%)	386 (15.0%)	11 (7.5%)	<0.001
Type 1 raphe (L-R), (%)	1759 (64.6%)	1657 (64.3%)	102 (69.9%)	
Type 1 raphe (R-N), (%)	422 (15.5%)	405 (15.7%)	17 (11.6%)	
Type 1 raphe (L-N), (%)	132 (4.8%)	116 (4.5%)	16 (11.0%)	
Type 2 raphe, (%)	13 (0.5%)	13 (0.5%)	0 (0.0%)	

Values are mean ± SD and n (%). Percentages are calculated based on data availability.
AA = ascending aorta; CAD = coronary artery disease; LA = left atrium; LVEDd = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESd = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; SD = standard deviation.

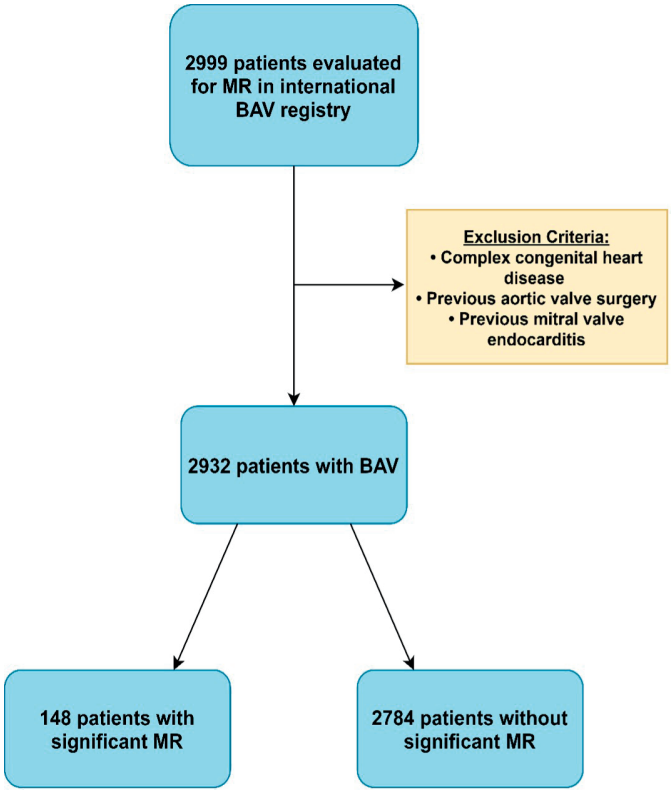

Figure 1: Study flow chart
BAV = bicuspid aortic valve; MR = mitral regurgitation.

Echocardiographic characteristics

The echocardiographic characteristics of the population are presented in Table 2. The mean LVEF for the total population was 60.8±11.8% and the median LV end-diastolic volume was 122 (IQR 94 to 154) ml. Patients with significant secondary MR had lower LVEF and larger LV dimensions compared to those with significant primary MR and those without significant MR (Supplementary Table 1 and Supplementary Table 2). In addition, a higher proportion of patients with significant secondary MR had moderate or severe aortic regurgitation (45.2% vs 27.3%, p<0.001) and aortic stenosis (54.8% vs 35.4%, p<0.001) compared to those without significant MR. Individuals with significant secondary MR had larger ascending aorta (39.0±8.0 vs 36.4±7.3 mm, p=0.001) and sinus of Valsalva diameters (37.2±7.2 vs 34.6±6.2 mm, p<0.001) compared to those without significant MR, while aortic annulus and sinotubular junction diameters were similar between the two groups.

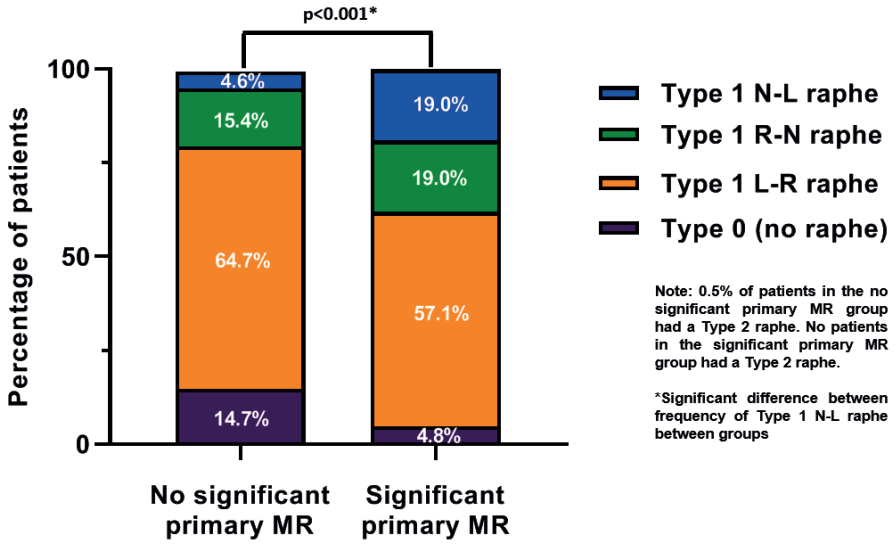

Figure 2: **Distribution of BAV raphe phenotype according to the presence or absence of significant primary MR.**
BAV = bicuspid aortic valve; MR = mitral regurgitation.

Table 2: Echocardiographic characteristics

Variable	Total population (n=2932)	No significant MR (n=2784)	Significant MR (n=148)	*P* value
Left ventricle				
LV EDD, mm	51.7 (±8.7)	51.3 (±8.3)	57.9 (±12.3)	<0.001
LV ESD, mm	34.4 (±9.1)	33.8 (±8.4)	43.6 (±14.1)	<0.001
LV EDV, ml	122 (94 to 154)	120 (93 to 153)	154 (110 to 211)	<0.001
LV EF, %	60.8 (±11.8)	61.5 (±11.0)	48.3 (±17.8)	<0.001
Mitral inflow E velocity, m/s	0.8 (±0.3)	0.8 (±0.3)	1.0 (0.4)	<0.001
Aortic Valve and Aortic Root				
Aortic annulus diameter, mm	23.0 (±3.2)	23.0 (±3.2)	23.5 (±3.1)	0.081
SOV diameter, mm	34.7 (±6.3)	34.6 (±6.2)	36.4 (±6.9)	0.001
STJ diameter, mm	30.5 (±6.5)	30.5 (±6.4)	31.0 (±7.4)	0.321
Ascending aorta diameter, mm	36.5 (±7.4)	36.4 (±7.3)	38.0 (±8.1)	0.014
Dilated aortic root or tubular aorta (≥ 40mm), %	1125 (39.1%)	1058 (38.8%)	67 (45.6%)	0.099
Dilated aortic root or tubular aorta (≥ 50mm), %	140 (4.9%)	130 (4.8%)	10 (6.8%)	0.255
Moderate or severe AS, %	1054 (36.0%)	984 (35.4%)	70 (47.3%)	0.003
Moderate or severe AR, %	822 (28.1%)	760 (27.3%)	62 (41.9%)	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; AR = aortic regurgitation; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LV = left ventricle; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction

Survival analysis

Over a median follow-up time of 51 months (IQR 18 to 95 months), 223 (7.6%) patients died. In total, 84 (38%) patients had a cardiovascular cause of death, 67 (30%) patients had a non-cardiovascular cause of death, while 72 (32%) patients had an unknown cause of death. One- and five- year cumulative survival rates were 97% and 93%, respectively. Analysis with the Kaplan-Meier method demonstrated a reduction in survival for patients with significant MR compared to their counterparts (91% and 81% vs 97% and 93%, at 1- and 5-years of follow-up, respectively, χ^2=29.95, p<0.001). To further evaluate the association between significant MR and all-cause mortality, univariable and multivariable Cox regression analyses were performed (Table S3). In the unadjusted model, significant MR was associated with all-cause mortality (HR 2.80, 95% CI 1.91 to 4.11, p<0.001). However, following adjustment for age, smoking, hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, LV end-diastolic volume and LVEF, significant MR was not associated with the primary outcome (HR 1.33, 95% CI 0.85 to 2.07, p=0.21) (Figure 3). When stratified by etiology of MR, significant secondary MR due to aortic valve disease was not associated with all-cause mortality (adjusted HR 0.99, 95% CI 0.54 to 1.83, P=0.98), whereas significant MR not due to aortic valve disease was independently associated with worse survival (adjusted HR 1.81, 95% CI 1.04 to 3.15, P=0.037) (Table S4). For the analysis of the secondary endpoint of event-free survival, after a median follow-up of 23 months (IQR 3 to 67 months), 996 (34.0%) patients died (n=161, 5.5%) or underwent aortic valve surgery (n=835, 28.5%). Univariable analysis demonstrated that significant MR was associated with a reduction in event-free survival (Table S3), although this association was not observed following adjustment (adjusted HR 1.10, 95% CI 0.85 to 1.42, p=0.49).

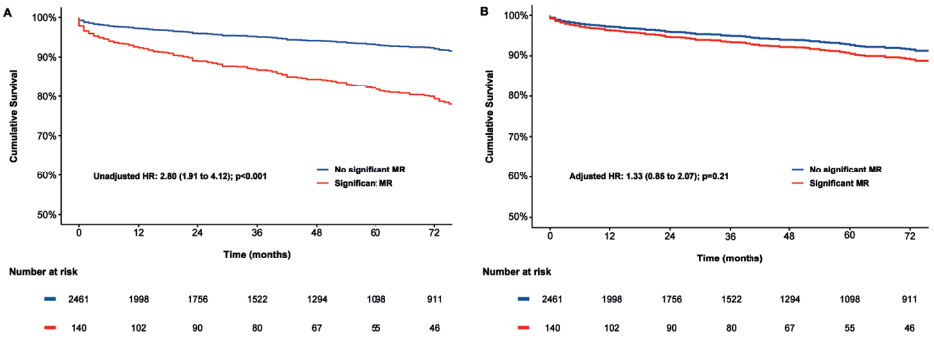

Figure 3: Cumulative survival estimates for all-cause mortality according to the presence or absence of significant MR in the overall population.

Panel A demonstrates that significant MR is associated with all-cause mortality in an unadjusted model in patients with BAV. However, panel B demonstrates that significant MR was not associated with all-cause mortality in a model adjusted for important confounding variables. The model in panel B is adjusted based on the average covariate values of the study population for age, diabetes mellitus, hypertension, smoking, dyslipidemia, coronary artery disease, LV ejection fraction and LV end-diastolic volume.

BAV = bicuspid aortic valve; LV = left ventricle; MR = mitral regurgitation

Subgroup analyses were performed to investigate the association between significant MR and outcomes for patients with significant aortic regurgitation, significant aortic stenosis and for those without significant aortic valvular disease (Figure 4). Significant MR was independently associated with all-cause mortality in the subgroup with moderate or severe aortic regurgitation (adjusted HR 2.037, 95% CI 1.025 to 4.049, p=0.042). However, no independent association with all-cause mortality was observed in patients with significant aortic stenosis or without significant aortic valvular disease. Moreover, there was no independent association between significant MR and the endpoint of event-free survival in any subgroup.

In addition, sensitivity analyses incorporating aortic valve surgery as a time-dependent covariate were performed for all multivariable Cox regression models utilising all-cause mortality as the endpoint. The results of all sensitivity analyses were consistent with the main analysis (Table S5).

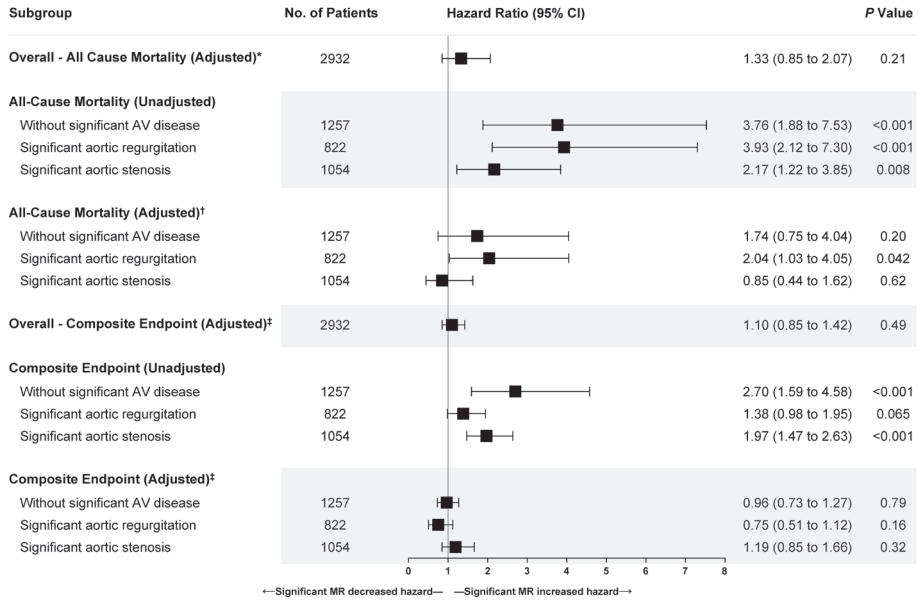

Figure 4: Forest plot of Cox regression models investigating the association between significant MR for the endpoints of all-cause mortality and event-free survival in patient subgroups

* Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

† Multivariable model adjusting for age, diabetes mellitus, LVEDV and LVEF.

‡ Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation ≥50 mm, LVEDV and LVEF.

AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

DISCUSSION

In this large, international BAV registry, significant primary and secondary MR were uncommon, with a prevalence of 1.5% and 3.5%, respectively. Significant MR was not independently associated with either all-cause mortality or event-free survival on multivariable analysis. However, when stratified by the etiology of MR, significant MR not due to aortic valve disease was independently associated with worse survival. Subgroup analyses suggested an independent association between significant MR and all-cause mortality for individuals with significant aortic regurgitation, although not for subgroups with significant aortic stenosis or without significant aortic valve disease.

Prevalence of primary and secondary MR in BAV

The association between BAV and primary MR remains somewhat contentious[6, 7, 9]. Previously, in a retrospective study of 1820 patients referred for surgery for significant BAV disease, Lad et al. [6] demonstrated a prevalence of significant primary MR of 1.6%, similar to that observed in the present study. In another smaller study of 191 patients with BAV, the prevalence of significant primary MR was 2.0%[7]. In comparison, in a large community cohort study of the general adult population, the prevalence of significant primary MR was approximately 0.26%[13]. However, despite evidence suggesting a higher prevalence of primary MR in individuals with BAV compared to the general population, a large study of approximately 360,000 patients did not observe an increased prevalence of mitral valve prolapse in individuals with BAV[9]. However, the authors did not report on the frequency of significant MR due to mitral valve prolapse, which may explain this discrepancy. Interestingly, an association between mitral valve prolapse and BAV has previously been described by several authors, who reported an increased prevalence of a large and myxomatous anterior mitral valve leaflet in those with BAV[6-9]. In the present study, the prevalence of significant primary MR due to mitral valve prolapse was 0.9%. Although a prevalence of significant secondary MR of 3.5% was observed in the current study, this could be an overestimation and not representative of the general BAV population, due to referral center bias and the associated higher rate of significant aortic valve disease, which may influence LV remodeling that leads to secondary MR.

Association of MR with BAV morphology and aortic root dimensions

In the present study, an association between primary MR with prolapse of the anterior mitral valve leaflet and the type 1 left-non coronary cusp fusion BAV raphe phenotype was observed. In contrast to the findings of our study, Schaefer et al. [7] observed an association between primary MR due to mitral valve prolapse and a type 1 raphe with right-non coronary cusp fusion, although in a limited number of patients. Several mechanisms may explain the association between primary MR and BAV. Individuals with

BAV may have an extension of the degenerative process that results in dilation of the aortic root to the anterior mitral valve leaflet, either mediated anatomically through the fibrous aortic-mitral continuity or because of a common embryological origin[6, 30, 31]. This could potentially manifest as an enlarged, myxomatous anterior mitral valve leaflet, as described earlier.

In addition, we also observed an association between secondary MR and larger sinus of Valsalva and ascending aorta dimensions. This may be explained by the common relationship between significant aortic regurgitation, secondary MR and aortic root dilation in BAV disease, or alternatively, could represent altered motion of the anterior mitral valve leaflet, owing to changes in biomechanical forces transmitted through the aortic-mitral continuity in the presence of aortic root dilation.

Prognostic implications of MR in patients with BAV

In this large cohort of patients with BAV, no independent association between significant MR and all-cause mortality was observed. This contrasts with several large community studies of the general population that reported an independent association between significant MR and increased all-cause mortality[13, 14]. However, in those studies, limited adjustment for important confounding variables were performed, notably for LV end-diastolic volume and LV ejection fraction. Moreover, the patients with significant MR in those studies were nearly 20 years older, and it is likely that the etiology of secondary MR differed dramatically from the BAV population in our study. Indeed, a substantial proportion of secondary MR in the present study was due to significant aortic valve disease, which typically has a more favorable prognosis than secondary MR due to LV systolic dysfunction or ischemic heart disease, particularly in the context of timely aortic valve intervention. Following aortic valve surgery, approximately 55% of patients with aortic stenosis and 70% of those with aortic regurgitation will have improvement in the grade of secondary MR, likely due to a combination of reverse LV remodeling and alterations in mitral valve hemodynamics[32-34]. In accordance with this hypothesis, when stratifying by the etiology of MR, we observed an independent association between significant MR not due to aortic valve disease and all-cause mortality, findings consistent with prior literature. In contrast, no association between significant secondary MR due to aortic valve disease was observed. This suggests that consideration of the etiology of significant MR is essential in the setting of treatable AV disease.

In the present study, the absence of a relationship between the composite endpoint of aortic valve repair/replacement and all-cause mortality with significant MR was unexpected, given the greater hemodynamic burden on the left ventricle in multiple left-sided valvular disease[10]. The combination of significant MR and aortic stenosis and/or aortic regurgitation, may have been expected to culminate in additional LV and LA remodeling, an earlier onset of symptoms, and therefore, an earlier indication for aortic

valve surgery[10]. However, there are several explanations for these findings. Significant MR may mask reductions in LVEF[35], an important indication for intervention in aortic regurgitation and aortic stenosis, leading to a delay in referral. In addition, significant MR may lead to low-flow low-gradient aortic stenosis and an underestimation of the hemodynamic severity of disease[36], potentially delaying referral for surgery or intervention.

The subgroup analysis suggested an independent association between significant MR and all-cause mortality in patients with moderate to severe aortic regurgitation. This finding is consistent with a previous study of 756 patients with severe aortic regurgitation due to a variety of etiologies, which also demonstrated an independent association between all-cause mortality and significant MR[12]. The relationship between mortality and significant MR in aortic regurgitation is probably mediated by increased LV dilation and eccentric hypertrophy, with poorer long-term LV functional recovery[10]. In addition, due to the absence of the premature mitral valve closure usually seen in severe aortic regurgitation, the combination of significant MR and aortic regurgitation may lead to elevated left atrial and pulmonary capillary wedge pressures and poor clinical tolerability[10]. In an additional subgroup analysis of patients with moderate or severe aortic stenosis, we did not observe an independent association between significant MR and all-cause mortality. Indeed, the association of significant MR with mortality in severe aortic stenosis remains contentious in the context of both surgical and transcatheter aortic valve interventions[32, 37]. As discussed previously, the BAV population is typically much younger, with fewer comorbidities, and it is likely that the absence of an association with all-cause mortality in the aortic stenosis subgroup can be attributed to patients with BAV having etiologies of secondary MR with a more favorable prognosis. In addition, it is also conceivable that the concentric remodeling induced by severe pressure overload in aortic stenosis is fundamentally different and not additive to the severity of eccentric remodeling that is typically observed in significant MR (and vice-versa). In contrast, volume overload secondary to both aortic regurgitation and MR may be additive, causing a greater degree of eccentric remodeling and severe LV dilatation, which could induce an earlier onset of LV systolic dysfunction and ultimately, a poorer prognosis[38, 39].

Limitations

This study is subject to the inherent limitations of any observational, retrospective registry. Furthermore, due to the registry study design, clinical outcomes could be under reported if a patient left the registry or was lost to follow-up, and although all centers followed guideline recommendations, assessment and treatment criteria may vary across countries and centers. In addition, many of the participating international centers act as referral centers for their respective regions, resulting in increased complexity

in the interpretation of epidemiological data, due to a higher prevalence of clinically significant aortic valve disease than in the general BAV population. Furthermore, data pertaining to the specific indication for aortic valve surgery were not available.

CONCLUSION

Significant MR is uncommon in patients with BAV. Following adjustment for important confounding variables, significant MR was not associated with adverse prognosis in this large study of patients with BAV, except for the patient subgroup with moderate to severe aortic regurgitation. In addition, significant MR not due to aortic valve disease demonstrated an independent association with all-cause mortality.

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SUPPLEMENTARY MATERIAL

Table S1: Echocardiographic characteristics divided according to mitral regurgitation mechanism.

Variable	No significant MR (n=2784)	Significant primary MR (n=44)	Significant secondary MR (n=104)	*P* value
Left ventricle				
LV EDD, mm	51.3 (±8.3)	54.0 (±10.2)	59.1 (±12.7)*†	<0.001
LV ESD, mm	33.8 (±8.4)	36.5 (±8.7)	45.7 (±14.8)*†	<0.001
LV EDV, ml	120 (93 to 153)	135 (98 to 186)	163 (121 to 232)*	<0.001
LV EF, %	61.5 (±11.0)	59.4 (±13.5)	44.3 (±17.5)*†	<0.001
Mitral inflow E velocity, m/s	0.8 (±0.25)	1.1 (±0.4)*	0.95 (±0.3) *†	<0.001
Aortic Valve and Aortic Root				
Aortic annulus diameter, mm	23.0 (±3.2)	23.3 (±2.8)	23.7 (±3.3)	0.179
SOV diameter, mm	34.6 (±6.2)	34.5 (±5.7)	37.2 (±7.2)*	<0.001
STJ diameter, mm	30.5 (±6.4)	30.2 (±5.6)	31.4 (±8.1)	0.366
Ascending aorta diameter, mm	36.4 (±7.3)	35.4 (±7.8)	39.0 (±8.0)*†	0.001
Dilated aortic root or tubular aorta (> 50mm), %	130 (4.8%)	3 (7.1%)	7 (6.7%)	0.520
Moderate or severe AS, %	984 (35.4%)	13 (29.5%)	57 (54.8%)*†	<0.001
Moderate or severe AR, %	760 (27.3%)	15 (34.1%)	47 (45.2%)*	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; AR = aortic regurgitation; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LV = left ventricle; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction
*p<0.05 vs Group I;†p<0.05 vs Group II

Table S2: Clinical and BAV characteristics divided according to mitral regurgitation mechanism.

	No significant MR (n=2784)	Significant primary MR (n=44)	Significant secondary MR (n=104)	*P* value
Clinical characteristics				
Age (years)	47.3 (±17.5)	58.6 (**±20.1**)*	59.1 (**±16.4**)*	<0.001
Male (%)	1961 (70.5%)	29 (65.9%)	75 (72.1%)	0.750
Prior CAD (%)	198 (7.8%)	4 (9.3%)	14 (14.0%)	0.077
Hypertension (%)	891 (34.4%)	15 (34.9%)	44 (44.0%)	0.140
Dyslipidemia (%)	695 (25.9%)	13 (29.5%)	33 (31.7%)	0.362
Diabetes mellitus (%)	262 (10.2%)	4 (9.5%)	19 (18.4%)*	0.028
Current smoker (%)	421 (16.4%)	6 (14.3%)	20 (19.4%)	0.673
BAV characteristics				
No raphe (%)	386 (15.0%)	2 (4.8%)	9 (8.7%)	<0.001
Type 1 raphe (L-R), (%)	1657 (64.3%)	24 (57.1%)	78 (75.0%)*†	
Type 1 raphe (R-N), (%)	405 (15.7%)	8 (19.0%)	9 (8.7%)	
Type 1 raphe (L-N), (%)	116 (4.5%)	8 (19.0%)*	8 (7.7%)†	
Type 2 raphe, (%)	13 (0.5%)	0 (0.0%)	0 (0.0%)	

Values are mean ± SD, median (interquartile range) and n (%). Percentages are calculated based on data availability.
AA = ascending aorta; CAD = coronary artery disease; LA = left atrium; LVEDd = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESd = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; SD = standard deviation.
*p<0.05 vs Group I;†p<0.05 vs Group II

Table S3: Cox regression models investigating the association between significant MR for the endpoints of all-cause mortality and a composite of aortic valve surgery and all-cause mortality

Total Population (n=2932)	**All-cause mortality[a]**		**Composite endpoint of aortic valve surgery and all-cause mortality[b]**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Univariable analysis				
No significant MR	*Reference*		*Reference*	
Significant MR	2.801 (1.907 to 4.115)	<0.001	1.971 (1.581 to 2.459)	<0.001
Multivariable analysis				
No significant MR	*Reference*		*Reference*	
Significant MR	1.330 (0.854 to 2.071)	0.207	1.095 (0.847 to 1.417)	0.49

[a] Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.
[b] Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, aortic root or ascending aorta dilation, LVEDV and LVEF.
AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

Table S4: Cox regression models investigating the association between significant MR stratified according to MR etiology for the endpoints of all-cause mortality and a composite of aortic valve surgery and all-cause mortality

Total Population (n=2932)	All-cause mortality[a]		Composite endpoint of aortic valve surgery and all-cause mortality[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariable analysis				
No significant MR (N=-2784; 192 and 909 events)	*Reference*		*Reference*	
Secondary MR due to AV disease (N=76; 13 and 50 events)	2.32 (1.32 to 4.09)	0.004	2.91 (2.19 to 3.87)	<0.001
Significant MR not due to AV disease (N=72; 18 and 37 events)	3.30 (2.03 to 5.37)	<0.001	1.40 (1.01 to 1.95)	0.045
Multivariable analysis				
No significant MR	*Reference*		*Reference*	
Secondary MR due to AV disease	0.99 (0.54 to 1.83)	0.98	1.17 (0.85 to 1.62)	0.33
Significant MR not due to AV disease	1.81 (1.04 to 3.15)	0.037	0.85 (0.59 to 1.24)	0.41
Univariable analysis				
No significant MR	*Reference*		*Reference*	
Secondary MR due to AV disease	2.31 (1.31 to 4.08)	0.004	2.91 (2.19 to 3.87)	<0.001
Secondary MR not due to AV disease	5.17 (2.74 to 9.78)	<0.001	1.77 (1.09 to 2.86)	0.02
Primary MR	2.25 (1.10 to 4.60)	0.026	1.19 (0.76 to 1.86)	0.45
Multivariable analysis				
No significant MR	*Reference*		*Reference*	
Secondary MR due to AV disease	1.00 (0.54 to 1.84)	1.00	1.16 (0.84 to 1.60)	0.38
Secondary MR not due to AV disease	2.04 (0.98 to 4.25)	0.055	0.67 (0.39 to 1.17)	0.16
Primary MR	1.57 (0.69 to 3.59)	0.29	1.06 (0.66 to 1.70)	0.82

[a] Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

[b] Multivariable model adjusting for age, smoking, hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, aortic root or ascending aorta dilation, ≥moderate AS, ≥moderate AR, LVEDV and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

Table S5: Cox regression models investigating the association between significant MR and all-cause mortality adjusted for aortic valve surgery as a time-dependent covariate

	Total population[a] (n=2932, 223 events)		**Individuals without significant AV disease[b] (n=1257, 83 events)**		**Individuals with significant AR[b] (n=822, 54 events)**		**Individuals with significant AS[b] (n=1054, 106 events)**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Multivariable analysis								
No significant MR	*Reference*		*Reference*		*Reference*		*Reference*	
Significant MR	1.278 (0.818 to 2.00)	0.281	1.691 (0.727 to 3.931)	0.223	2.015 (1.012 to 4.015	0.046	0.814 (0.420 to 1.578)	0.541

[a] Multivariable model adjusting for aortic valve surgery (as a time dependent covariate), age, smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, LVEDV and LVEF.

[b] Multivariable model adjusting for aortic valve surgery (as a time dependent covariate), age, diabetes mellitus, LVEDV and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

7

Impact of Left Ventricular Ejection Fraction on Clinical Outcomes in Bicuspid Aortic Valve Disease

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ABSTRACT

Background

The prognostic impact of left ventricular ejection fraction (LVEF) in patients with bicuspid aortic valve (BAV) disease has not been previously studied.

Objectives

The objective of this study was to determine the prognostic impact of LVEF in BAV patients according to the type of aortic valve dysfunction.

Methods

We retrospectively analyzed the data collected in 2,672 patients included in an international registry of patients with BAV. Patients were classified according to the type of aortic valve dysfunction: isolated aortic stenosis (AS) (n=749), isolated aortic regurgitation (AR) (n=554), mixed aortic valve disease (MAVD) (n=190), or no significant aortic valve dysfunction (n=1179; excluded from this analysis). The study population was divided according to LVEF strata to investigate its impact on clinical outcomes.

Results

The risk of all-cause mortality and the composite endpoint of aortic valve replacement or repair (AVR) and all-cause mortality increased when LVEF was <60% in the whole cohort as well as in the AS and AR groups, and <55% in MAVD group. In multivariable analysis, LVEF strata were significantly associated with increased rate of mortality (LVEF 50-59%: HR [95%CI]: 1.83 [1.09-3.07], p=0.022; LVEF 30-49%: HR [95%CI]: 1.97 [1.13-3.41], p=0.016; LVEF<30%: HR [95%CI]: 4.20 [2.01-8.75], p<0.001; versus LVEF 60-70%, reference group).

Conclusion

In BAV patients, the risk of adverse clinical outcomes increases significantly when the LVEF is <60%. These findings suggest that LVEF cut-off values proposed in the guidelines to indicate intervention should be raised from 50 to 60% in AS or AR and 55% in MAVD.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease with a prevalence of 1-2% in the general population[1]. This congenital cardiac defect is known as a strong risk factor for the development of aortic valve diseases such as aortic stenosis (AS), aortic regurgitation (AR), and mixed aortic valve disease (MAVD)[2-5]. Patients with BAV often develop AS and AR earlier and more frequently than patients with tricuspid aortic valve (TAV) and they have ~50% risk of requiring aortic valve replacement (AVR) during their lifetime[6].

In patients with asymptomatic severe AS (both in BAV and TAV), left ventricular (LV) systolic dysfunction, defined as left ventricular ejection fraction (LVEF) ≤50%, is a major criterion (Class I) to recommend AVR[7-10]. However, LVEF may underestimate the degree of LV systolic dysfunction and several studies conducted in patients with AS suggested that the cut-off value of LVEF to define LV systolic dysfunction and eventually trigger intervention should be raised to 55% or 60%[11]. Accordingly, the recent editions of the American and European guidelines included new recommendations for AVR in asymptomatic patients with severe AS if LVEF is <60% (American guidelines) or 55% (European guidelines). In asymptomatic patients with chronic severe aortic regurgitation, surgery is recommended when LVEF is < 50% (Class I in ESC guidelines) or <55% (Class I in American guidelines and IIb in European guidelines). The prognostic impact of LVEF however, has not been explored in BAV disease.

The objectives of this study were: i) to determine the prognostic impact (AVR and/or all-cause mortality) of LVEF in patients with BAV disease; ii) to determine the cut-off value of LVEF below which the risk of adverse outcomes (AVR and/or all-cause mortality) becomes significant in BAV patients with AS, AR, or MAVD.

METHODS

Population

We retrospectively analyzed the data of 2,672 patients from an international BAV registry.[12] Patients with complex congenital heart disease, previous endocarditis, or AV surgery, or without significant (<moderate) aortic valve disease, were excluded. First, the study population was divided according to LVEF strata (LVEF>70%, n=269; 60-70%, n=679; 50-59%, n=316; 30-49%, n=182; <30%, n=47) in order to investigate the impact of LVEF on clinical outcomes. Then, to investigate the impact of LVEF on clinical outcomes in each type of aortic valve dysfunction, the BAV cohort was divided in 4 groups: whole cohort (BAV patients with significant aortic valve dysfunction, n=1493), isolated AS (significant AS [≥ moderate] and less than moderate AR, n=749), isolated AR (significant

AR [≥ moderate] and less than moderate AS, n=554), mixed AV disease (both AS and AR ≥ moderate, n=190) (Figure 1). Demographic and clinical data were collected at the time of the first diagnosis of BAV on transthoracic echocardiography. The study was approved by the institutional review board of each center, and because of its retrospective nature, written informed consent was not required.

Echocardiographic Data

All echocardiographic exams were conducted using commercially available ultrasound systems. Measurements were retrospectively performed by experienced investigators from each center, using the first transthoracic echocardiography that allowed to diagnose BAV according to the system proposed by Sievers and Schmidtke[13]. AS severity was classified according to the actual guideline recommendations[14]. AR severity was assessed using a multiparametric approach as previously described[15]. MAVD was defined as the coexistence of moderate AS and moderate AR. MAVD was considered being severe if AS and / or AS was equal or greater than moderate. The diameters of the sinus of Valsalva, sinotubular junction and ascending aorta were measured on a parasternal long-axis view from leading-edge to leading-edge, perpendicular to the centerline of the aorta in end-diastole[16]. The aortic annulus was conventionally measured in mid-systole from inner-edge to inner-edge on a parasternal long-axis view[16]. LVEF was estimated using the biplane Simpson method. LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were measured using the 2D linear method, as per guideline recommendations[16]. LV mass was calculated by the modified American Society of Echocardiography formula and subsequently indexed to body surface area [16]. All other measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines and as previously described[16].

Follow-up

Follow-up started at the time of the first echocardiogram that confirmed a diagnosis of BAV. The primary endpoint of the study was all-cause mortality occurring prior or after AVR, and the secondary endpoint was the composite of AVR and all-cause mortality. Indications for AVR were according to recommendations of contemporary guidelines, including patients with symptomatic severe aortic valve dysfunction, asymptomatic severe aortic valve dysfunction with reduced LVEF (≤50%), or patients with aortopathy, irrespective of the severity of aortic valve dysfunction[7,8]. The occurrence of surgical aortic valve repair or replacement was recorded with data collected by medical record review. The end-of-study follow-up date was September 31st, 2019. Follow-up data were available for 1334 (89.3%) patients: 693 (92.5%) of patients with isolated AS, 176 (92.6%)

patients with MAVD and 465 (83.9%) patients with isolated AR. Data for all patients were included up to the last date of follow-up.

Statistical Analyses

Continuous variables were expressed as median and interquartile range (IQR) and Kruskal-Wallis tests were performed to evaluate for differences according to the type of AV dysfunction. Multiple comparisons were tested using Bonferroni's correction. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate, and are expressed in number of patients with percentages. To account for missing data, analyses were conducted using multiple imputations by predictive mean matching using a chained-equation approach and generating 100 imputed datasets[17]. The results of the survival analyses were obtained by averaging the parameter estimates across the multiple datasets using Rubin's rules to combine the standard errors[18]. Cumulative incidence of 1- and 5- year all-cause mortality and the composite endpoint of all-cause mortality and AVR were calculated using the Kaplan Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was used to evaluate the associations between LVEF strata with the endpoint of all-cause mortality and the composite endpoint of all-cause mortality and AVR. Multivariable Cox proportional hazards regression analyses were performed adjusting for pre-specified clinical and echocardiographic variables associated with event-free survival specific to each patient group (isolated AS, MAVD, isolated AR). Hazard ratio (HR) and 95% confidence intervals (CI) were reported for each model. The proportional hazards assumption was confirmed through the evaluation of scaled Schoenfeld residuals. In addition, to further investigate the relationship between LVEF strata and the HR change for the primary and secondary endpoints, a spline curve was fitted for each type of AV disease (isolated AS, isolated AR and MAVD). The incremental predictive value on the multivariable models including LVEF versus the baseline model was assessed by the C-index. Likelihood ratio (LR) tests and the rank correlation U-statistic for paired censored data were used to evaluate the prognostic value of LVEF by comparing model fit and the concordance of models with and without LVEF, respectively. All tests were two-sided and P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical and echocardiographic characteristics

Baseline characteristics of the study population according to LVEF are shown in Table 1. Among the 1493 patients with BAV disease, 269 (18.0%) had LVEF >70%, 679 (45.5%) had LVEF between 60-70%, 316 (21.2%) had LVEF between 50-59%, 182 (12.2%) had LVEF between 30-49% and 47 (3.1%) had LVEF <30%. In the total cohort, the median age was 51 (37-63) years and 70% were male. Overall, patients with reduced LVEF (<50%) were older, more frequently male and had worse cardiovascular profiles. Echocardiographic data are presented in Table 2. Patients with LVEF >70% had smaller LV, aorta and sinus of Valsalva dimensions as compared to the other groups ($p<0.05$). On the other hand, patients with LVEF <30% had more extensive cardiac damage. The proportion of AS ≥ moderate was similar across all groups, but moderate aortic and mitral regurgitation were more prevalent in groups with reduced LVEF (<50%) (Table 2). Echocardiographic characteristics of the whole cohort according to aortic valve dysfunction are presented in Table S1.

Prognostic value of LVEF in overall cohort

In the whole cohort, the primary endpoint of all-cause mortality occurred in 117 (8.8%) patients over a median follow-up of 56 (22-102) months. The secondary endpoint occurred in 675 (51%) patients: i.e. 602 (45%) patients underwent AVR and 73 (5.5%) died over a median follow-up of 21 (3-67) months. Of those who underwent AVR, 334 (55%), had a biological AVR, 178 (30%) had a mechanical AVR, 13 (2.2%) had a homograft or autograft, 13 (2.2%) underwent valvulotomy, 18 (3.0%) underwent TAVI, 18 (3.0%) underwent aortic valve repair, while data pertaining to the specifics of the other 28 (4.6%) surgeries were not available. In addition, 268 (44.5%) patients also underwent aortic root repair.

On Kaplan-Meier analysis, LVEF stratum <50% was significantly associated with higher rates of all-cause mortality (Figure 2A) and the composite endpoint of AVR and mortality (Figure 3A), and there was also a trend toward association with events for patients with a LVEF 50-59%. Using spline curve analysis, a LVEF <60% was found to be associated with increased risk of mortality (Figure S1A) and of the composite endpoint of mortality and AVR (Figure S2A).

In univariate Cox regression analysis, using LVEF 60-70% stratum as a reference group, there was a significant increase in the risk of all-cause mortality and of the composite endpoint for each decrease in LVEF stratum except for the LVEF 50-59% stratum where a strong trend was noted (Table 3). In multivariable analysis, when compared to the LVEF 60-70% stratum as a reference group, each decrease in LVEF strata was significantly associated with incremental increase in the rate of mortality (LVEF 50-59%: HR

Table 1: Patient Characteristics According to LVEF Strata

Variable	Overall N = 1,493	LVEF >70% N = 269	LVEF 60-70% N = 679	LVEF 50-59% N = 316	LVEF 30-49% N = 182	LVEF <30% N = 47	P-value
Age, years	51 (37 – 63)	50 (36 – 63)	50 (35 – 62)	51 (37 – 61)	60 (47 – 69) *†‡	57 (46 – 64)	**<0.001**
Male Sex	1,049 (70%)	178 (66%)	458 (67%)	232 (73%)	145 (80%)*†	36 (77%)	**0.005**
Hypertension	531 (38%)	90 (38%)	237 (37%)	109 (36%)	77 (44%)	18 (41%)	0.47
Dyslipidemia	427 (30%)	58 (24%)	198 (30%)	83 (27%)	75 (42%)*†‡	13 (28%)	**0.002**
Current smoker	226 (16%)	38 (16%)	95 (16%)	52 (17%)	34 (19%)	7 (15%)	0.87
Diabetes mellitus	161 (12%)	27 (11%)	62 (10%)	36 (12%)	26 (15%)	10 (22%)	0.13
Coronary artery disease	119 (8.7%)	19 (8.1%)	49 (7.8%)	24 (8.2%)	19 (11%)	8 (18%)	0.15
BAV morphology							0.07
No raphe	132 (9.6%)	17 (7.1%)	56 (9.3%)	31 (10%)	21 (12%)	7 (15%)	
Type 1 raphe (L-R)	935 (68%)	159 (67%)	404 (67%)	210 (69%)	128 (72%)	34 (74%)	
Type 1 raphe (R-N)	229 (17%)	46 (19%)	115 (19%)	45 (15%)	19 (11%)	4 (8.7%)	
Type 1 raphe (L-N)	63 (4.6%)	14 (5.9%)	19 (3.2%)	18 (5.9%)	11 (6.1%)	1 (2.2%)	
Type 2 raphe	12 (0.9%)	3 (1.3%)	8 (1.3%)	1 (0.3%)	0 (0%)	0 (0%)	

Legends: Continuous data are expressed by median (IQR). Categorical data are expressed by number (percent). P-values refer to comparison between LVEF groups. BAV, bicuspid aortic valve; LVEF, left ventricular ejection fraction.
*p<0.05 vs Group I; †p<0.05 vs Group II; ‡p<0.05 vs Group III; §p<0.05 vs Group IV.

Table 2: Echocardiographic Characteristics According to LVEF Strata

Variable	Overall N = 1,493	LVEF >70% N = 269	LVEF 60-70% N = 679	LVEF 50-59% N = 316	LVEF 30-49% N = 182	LVEF <30% N = 47	P-value
LV end-diastolic diameter, cm	5.20 (4.60 – 5.80)	4.90 (4.40 – 5.40)	5.04 (4.50 – 5.60)*	5.20 (4.80 – 5.80)*†	5.80 (5.20 – 6.40)*†‡	6.80 (5.60 – 7.60)*†‡	**<0.001**
LV end-systolic diameter, cm	3.40 (2.90 – 4.00)	2.70 (2.40 – 3.00)	3.30 (2.90 – 3.70)*	3.70 (3.30 – 4.10)*†	4.60 (4.00 – 5.20)*†‡	6.20 (5.20 – 6.70)*†‡	**<0.001**
LV end diastolic volume, ml	127 (97 – 166)	108 (86 – 137)	122 (95 – 154)*	129 (103 – 167)*	163 (129 – 211)*†‡	227 (172 – 294)*†‡§	**<0.001**
LV end systolic volume, ml	47 (32 – 69)	27 (20 – 35)	42 (32 – 56)*	58 (47 – 74)*†	97 (71 – 130)*†‡	174 (130 – 228)*†‡§	**<0.001**
LVEF, %	63 (55 – 69)	75 (73 – 79)	65 (62 – 67)*	55 (53 – 58)*†	42 (36 – 46)*†‡	23 (20 – 26)*†‡	-
LV mass index, g/m^2	117 (93 – 150)	111 (90 – 143)	111 (88 – 138)	119 (93 – 150)	145 (116 – 188)*†‡	167 (144 – 221)*†‡	**<0.001**
Left atrial volume index, ml/m^2	28 (21 – 37)	24 (20 – 34)	27 (21 – 36)	27 (20 – 36)	32 (23 – 48)*†‡	37 (26 – 56)*†‡	**<0.001**
Mitral inflow E wave velocity, m/s	0.80 (0.60 – 0.91)	0.80 (0.62 – 0.96)	0.80 (0.63 – 0.90)	0.80 (0.60 – 0.90)	0.78 (0.60 – 0.95)	0.80 (0.65 – 1.00)	0.22
Mitral inflow E/A ratio	1.14 (0.82 – 1.55)	1.11 (0.85 – 1.43)	1.14 (0.83 – 1.50)	1.14 (0.79 – 1.60)	1.00 (0.75 – 1.60)	1.67 (0.99 – 2.02)*†‡§	**0.014**
MR							
Moderate MR	82 (5.5%)	5 (1.9%)	22 (3.2%)	12 (3.8%)	27 (15%)*†‡	15 (32%)*†‡§	**<0.001**
Severe MR	25 (1.7%)	5 (1.9%)	3 (0.4%)	5 (1.6%)	5 (2.7%)*†‡	7 (15%)*†‡§	**<0.001**
AS							
Moderate AS	458 (31%)	87 (32%)	221 (32%)*	95 (30%)*	48 (26%)	7 (15%)‡	**<0.001**
Severe AS	481 (32%)	113 (42%)	208 (31%)*	81 (26%)*	57 (31%)	22 (47%)‡	**<0.001**
AR							
Moderate AR	487 (33%)	87 (32%)	209 (31%)	122 (39%)	56 (31%)*†	13 (28%)*‡	**<0.001**
Severe AR	257 (17%)	31 (12%)	105 (15%)	59 (19%)	48 (26%)*†	14 (30%)*†	**<0.001**
Severe MAVD	190 (13%)	49 (18%)	64 (9%)*	41 (13%)	27 (15%)	9 (19%)	**0.002**
Mean pressure gradient, mmHg	20 (10 – 35)	27 (15 – 41)	20 (10 – 34)*	17 (8 – 30)*†	16 (9 – 29)*	19 (8 – 34)*	**<0.001**
Peak aortic velocity, m/s	2.97 (2.12 – 3.80)	3.48 (2.67 – 4.20)	2.99 (2.20 – 3.80)*	2.68 (2.00 – 3.55)*†	2.66 (2.05 – 3.52)*	2.80 (1.84 – 3.62)*	**<0.001**
Aortic valve area, cm	1.30 (1.00 – 2.10)	1.10 (0.90 – 1.50)	1.30 (1.00 – 2.10)*	1.36 (1.00 – 2.50)*	1.30 (1.00 – 2.20)	1.15 (0.75 – 1.98)	**<0.001**
SOV diameter indexed, mm/m^2	18.3 (16.3 – 20.5)	17.1 (15.3 – 19.3)	18.4 (16.3 – 20.5)*	18.7 (16.6 – 20.7)*	19.4 (17.1 – 21.8)*†	18.8 (16.8 – 20.9)*	**<0.001**
STJ diameter indexed, mm/m^2	15.8 (13.8 – 17.9)	15.3 (13.5 – 17.1)	15.7 (14.0 – 17.6)	16.1 (13.7 – 18.4)*	16.7 (14.6 – 19.0)*†	16.2 (13.7 – 18.5)	**<0.001**
Ascending aorta diameter indexed, mm/m^2	19.7 (17.2 – 22.5)	19.7 (17.0 – 22.5)	19.9 (17.3 – 22.5)*	19.3 (16.9 – 22.3)*†	20.1 (17.5 – 23.5)*†‡	19.8 (17.8 – 22.4)*†‡§	0.41

Legends: As Table 1. AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; BAV, bicuspid aortic valve; LV, left ventricle; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease; MR, mitral regurgitation; SOV, sinus of Valsalva; STJ, sinotubular junction.
*p<0.05 vs Group I; †p<0.05 vs Group II; ‡p<0.05 vs Group III; §p<0.05 vs Group IV.

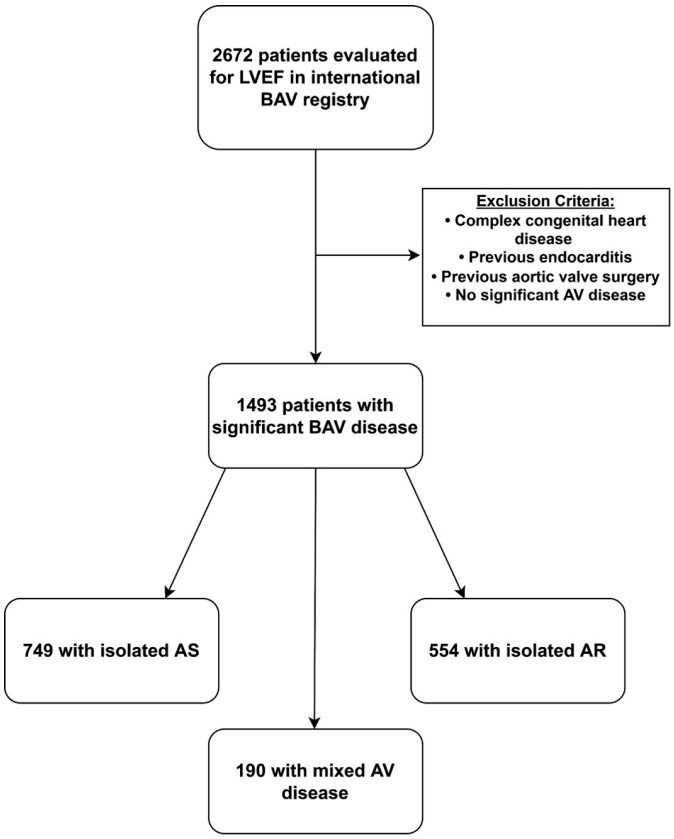

Figure 1:. Study Flow Chart. AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; BAV, bicuspid aortic valve; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease.

[95% CI]: 1.83 [1.09-3.07], p=0.022; LVEF 30-49%: HR [95% CI]: 1.97 [1.13-3.41], p=0.016; LVEF<30%: HR [95% CI]: 4.20 [2.01-8.75], p<0.001) and of the composite endpoint of AVR and mortality (LVEF 60-70% vs. LVEF 50-59%, HR [95% CI]: 1.35 [1.09-1.67], p=0.007; vs. LVEF 30-49%, HR [95% CI]: 1.69 [1.33-2.16], p<0.001; vs. LVEF <30%, HR [95% CI]: 1.82 [1.17-2.81], p=0.007). On the other hand, the >70% LVEF stratum was not associated with all-cause mortality or the composite endpoint in either univariate or multivariate analyses. The adjustment for AVR as a time dependent covariate provided similar results (Table S2).

Moreover, the addition of LVEF to the baseline model improved the predictive value of the model for the primary endpoint of all-cause mortality: C-Index increased from 0.766±0.024 to 0.789±0.023 (p=0.006) and χ^2 from 135.2 to 152.7, change 17.47, p=0.0016. The addition of LVEF to the baseline model improved the predictive value of the model for the composite of AVR and mortality: C-Index from 0.718±0.011 to 0.732±0.01 (p<0.0001) and χ^2 from 350.6 to 380.6, change 29.99, p<0.0001).

There was no significant interaction between LVEF and peak aortic jet velocity with regards to the impact on mortality (p=0.34). However, there was a significant interaction between LVEF and peak aortic velocity with regards to the combined endpoint (p=0.004) (Figure S3). For the LVEF strata > 30% the rate of the composite endpoint was higher in the patients with severe peak aortic velocity (4 m/s) versus mild velocity (2.5 m/s), and this was essentially driven by the higher rate of AVR in the former group, as expected. However, in the LVEF <30% stratum, the rates of the composite endpoint for patients with severe vs. those with mild peak aortic velocity tended to converge due to the mortality excess in this stratum.

In a sub-group analysis of asymptomatic patients (NYHA Class I), there was a trend toward higher risk of all-cause mortality in the LVEF 50-59% group (HR [95% CI]: 2.36 [0.68 to 8.17], p=0.17

Prognostic value of LVEF in isolated AS

Among the patients with isolated AS, 71 (10%) patients died during a median follow-up of 51 (21-83) months and 381 (55%) met the composite endpoint: 340 (49%) patients underwent AVR and 41 (5.9%) died over a median follow-up of 19 (2-57) months. On Kaplan-Meier analyses, the rate of mortality increased in patients with LVEF <50% (p=0.005, Figure 2B). However, there was only a trend between LVEF strata and the composite endpoint of all-cause mortality and AVR (p=0.075, Figure 3B). On spline curve analyses, the risk of mortality and of the composite of mortality and AVR increased when LVEF becomes <55-60% (Figures S1B and S2B).

Prognostic value of LVEF in isolated AR

For those with AR, during a median follow-up of 57 (20-119) months, 27 (5.8%) patients died and 181 (39%) met the composite endpoint: 162 (35%) patients underwent AVR and 19 (4.1%) died over a median follow-up of 25 (4-79) months. On Kaplan-Meier analyses, there was a significant increased risk of all-cause mortality (p=0.028, Figure 2C) and of the composite of AVR and mortality (p<0.001, Figure 3C) in patients with LVEF <60%. On spline curve analyses, the risk of mortality and of the composite of AVR and mortality increased when LVEF fell below a threshold of ~60% (Figures S1C and S2C).

Prognostic value of LVEF in MAVD

Of the patients with MAVD, 19 (11%) patients died during a median follow-up of 69 (29-120) months and 113 (64%) met the composite endpoint: 100 (57%) AVR and 13 (7.4%) deaths over a median follow-up of 18 (2-76) months. On Kaplan-Meier analyses, there was a significant increase (p<0.001) in the risk of mortality (Figure 2D) and of the composite of AVR and mortality (Figure 3D) with LVEF <50%. On spline curve analyses, the threshold of LVEF below which the risk of mortality and of the composite endpoint appeared to be around 55% (Figures S1D and S2D).

Table 3: Association of LVEF Strata with All-cause Mortality and with the Composite Endpoint (AVR and Mortality)

Variable	LVEF >70% N = 269	LVEF 60-70% N = 679	LVEF 50-59% N = 316	LVEF 30-49% N = 182	LVEF <30% N = 47	LVEF (continuous), %
All-cause mortality						
Events/person-years	21/1631	36/3761	26/1697	22/775	12/169	
Incidence rate, per 1000-person years (95% CI)	12.88 (7.97 to 19.68)	9.57 (6.70 to 13.25)	15.32 (10.01 to 22.44)	28.41 (17.80 to 43.01)	71.18 (36.78 to 124.34)	
Hazard ratio (95% CI)	1.45 (0.84 to 2.48)	*Reference*	1.62 (0.98 to 2.69)	2.80 (1.64 to 4.76)	7.17 (3.71 to 13.85)	0.97 (0.96 to 0.98)
P-value for hazard ratio	0.18		0.06	**<0.001**	**<0.001**	**<0.001**
Adjusted hazard ratio (95% CI)[a]	1.68 (0.97 to 2.92)	*Reference*	1.83 (1.09 to 3.07)	1.97 (1.13 to 3.41)	4.20 (2.01 to 8.75)	0.98 (0.97 to 0.99)
P-value for adjusted hazard ratio	0.064		**0.022**	**0.016**	**<0.001**	**0.003**
Composite of AVR and mortality						
Events/person-years	125/1034	276/2440	141/1002	105/421	28/70	
Incidence rate, per 1000-person years (95% CI)	120.90 (100.64 to 144.05)	113.11 (100.16 to 127.28)	140.74 (118.47 to 165.98)	249.60 (204.15 to 302.16)	401.43 (266.75 to 580.18)	
Hazard ratio (95% CI)	1.13 (0.91 to 1.39)	*Reference*	1.219 (0.99 to 1.49)	1.877 (1.50 to 2.35)	2.491 (1.69 to 3.68)	0.983 (0.98 to 0.99)
P-value for hazard ratio	0.27		0.06	**<0.001**	**<0.001**	**<0.001**
Adjusted hazard ratio (95% CI)[b]	0.95 (0.76 to 1.18)	*Reference*	1.35 (1.09 to 1.67)	1.69 (1.33 to 2.16)	1.82 (1.17 to 2.81)	0.985 (0.98 to 0.99)
P-value for adjusted hazard ratio	0.63		**0.007**	**<0.001**	**0.007**	**<0.001**

Legends: [a] Multivariable model adjusting for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, symptoms and coronary artery disease.
[b] Multivariable model adjusting for age, sex smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation, peak aortic velocity and symptoms.
AVR, aortic valve replacement; CI, confidence interval; LVEF, left ventricular ejection fraction.

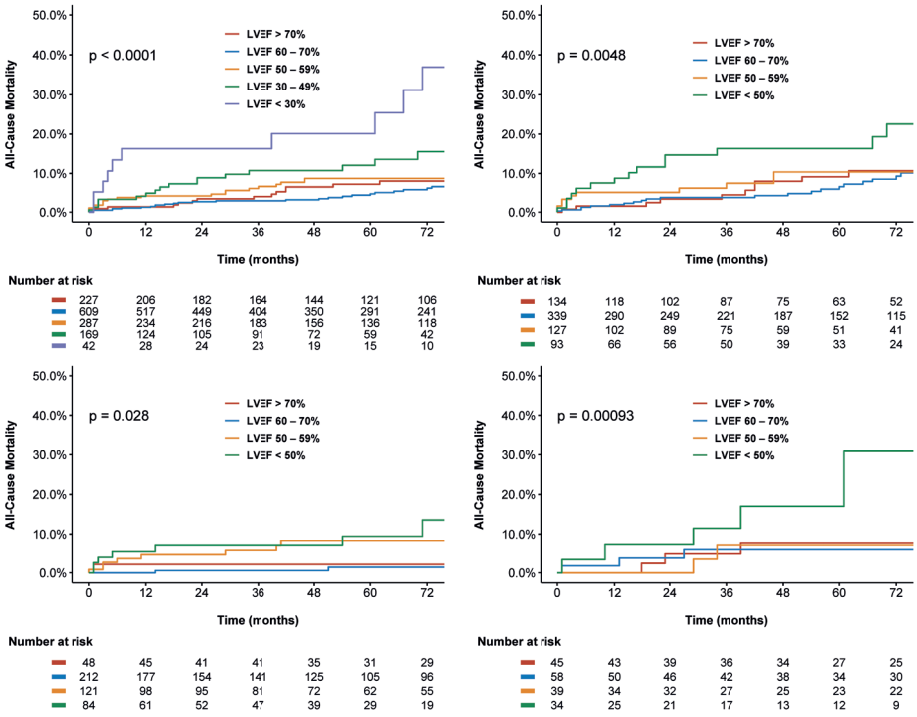

Figure 2: Event (AVR or death)-Free Survival According to the Type of aortic valve dysfunction and LVEF strata
Legends: Panel A shows the Kaplan-Meier survival estimates according to LVEF strata in the whole BAV population. Panel B, C, D demonstrate Kaplan-Meier survival estimates according to LVEF strata and isolated AS, isolated AR and MAVD, respectively. In the whole cohort, 5 strata of LVEF were analyzed, whereas the AS, AR, and MAVD subgroups, 4 strata were analyzed: i.e. the <30% and 30-49% strata were indeed merged together because of too small number of patients in the <30% stratum. AV, aortic valve; LVEF, left ventricular ejection fraction; AVR, aortic valve replacement; BAV, bicuspid aortic valve; AS, aortic stenosis; AR, aortic regurgitation; MAVD, mixed aortic valve disease.

DISCUSSION

The main findings of this study are: i) There is a stepwise increase in the risk of all-cause mortality with decreasing strata of LVEF in patients with BAV disease; ii) This increase in the risk of adverse outcomes appears to become significant with LVEF ≤60% rather than ≤50%, which is the traditional cut-off value of LVEF generally recommended in the guidelines and used in practice to identify LV systolic dysfunction and consider intervention in patients with AS and/or AR.

In aortic valve disease, the LVEF measured by 2D TTE is commonly used to assess LV systolic dysfunction and indicate intervention since its deterioration is associated with poor short- and long-term outcomes[19,20]. LV systolic dysfunction has been traditionally defined in the guidelines as LVEF <50% when AVR is then recommended (Class I) in patients with severe aortic valve disease who present with symptoms and/or LVEF <50%. However, the deterioration of LVEF generally occurs late in the course of the disease and

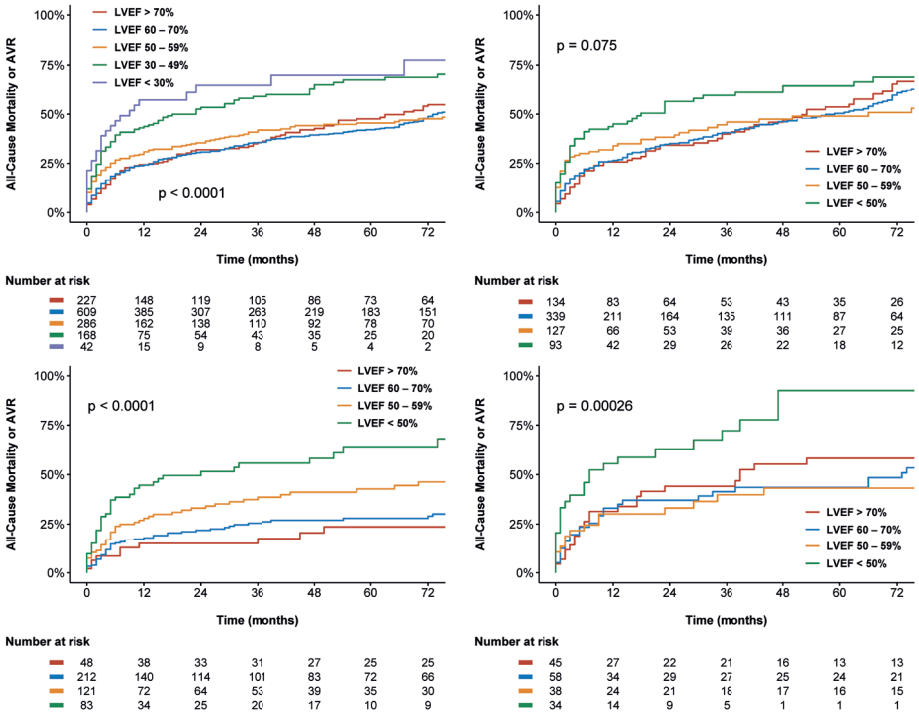

Figure 3: Survival Analysis According to the Type of aortic valve dysfunction and LVEF strata

Legends: Panel A shows the Kaplan-Meier survival estimates according to LVEF strata in the whole BAV population. Panels B, C, D demonstrate Kaplan-Meier survival estimates according to LVEF strata and isolated AS, isolated AR and MAVD, respectively. AV, aortic valve; LVEF, left ventricular ejection fraction; BAV, bicuspid aortic valve; AS, aortic stenosis; AR, aortic regurgitation; MAVD, mixed aortic valve disease.

an LVEF <50% may represent an advanced stage of LV systolic dysfunction in patients with aortic valve disease. Recent studies in AS suggested that a large proportion of patients with LVEF >50% have subclinical LV systolic dysfunction and are at higher risk for adverse events[11,21-24]. Indeed, LVEF markedly underestimates the extent of myocardial systolic dysfunction in the presence of LV concentric remodeling or hypertrophy, which is generally present in most patients with AS or MAVD. Several studies also reported that the cut-off value of LVEF associated with increased risk of adverse outcomes in AR is closer to <55% rather than <50%[25-32]. These findings underline the lack of sensitivity of an LVEF <50% to identify patients with subclinical LV systolic dysfunction who may be at higher risk of adverse events in the short-term and who may thus benefit from earlier intervention. These findings have led to some changes or addition of recommendations in the recent editions of guidelines for the management of aortic valve disease. The 2020 American guidelines state that AVR may be considered (Class IIb) in patients with severe AS if LVEF is <60% on at least 3 serial imaging studies[9], whereas in the 2021 European guidelines, AVR should be considered (Class IIa) when LVEF is <55%[10]. In patients with

severe AR, AVR is recommended (Class I) when LVEF is ≤55%, and may be considered (Class IIb) when there is a progressive decline in LVEF on at least 3 serial studies to the low–normal range (LVEF 55-60%)[9]. In contrast, the European guidelines recommend AVR (Class I) when LVEF is ≤50% and suggest that AVR may be considered (Class IIb) if LVEF is ≤55% and surgery is at low risk[10]. In asymptomatic patients with severe MAVD, AVR is indicated if LVEF is <50%[9].

The findings of the present study provide support and reinforce these changes of these recommendations with regard to the LVEF threshold to consider intervention in aortic valve disease. Our findings strongly suggest that an LVEF <60% should be applied to trigger intervention in patients with bicuspid aortic valve disease, regardless of the type of valve dysfunction: AS, AR or MAVD. Furthermore, our study extends the previously reported results from series predominantly composed of patients with tricuspid aortic valve to patients with BAV disease.

Our findings further support and expand the concept that LVEF lacks sensitivity to detect subclinical LV dysfunction in patients with aortic valve disease. One option to overcome this limitation is to raise the cut-off value of LVEF to identify LV systolic dysfunction from 50% to 60%. Another but more complex option is to use other echocardiographic parameters that are more sensitive to assess myocardial systolic dysfunction, such as global longitudinal strain. A previous meta-analysis reported that a global longitudinal strain <14.7% is associated with higher risk of rapid progression to symptoms and worse outcomes in asymptomatic patients with severe AS[33]. Inter-vendor differences in the measurements as well as the afterload dependence of global longitudinal strain remain limitations to widespread use of this parameter in clinical practice. Nonetheless, a report from the EACVI-ASE strain standardization task force nevertheless reported a good reproducibility of LV global longitudinal strain[34].

Egbe et al. reported that patients with MAVD had similar clinical outcomes compared to those with severe AS[35]. Furthermore, MAVD is associated with larger LV mass index compared to isolated AS or AR, and smaller LV end diastolic/systolic diameters compared to isolated AR but larger diameters compared to AS[35,36]. This hybrid concentric / eccentric LV remodeling pattern associated with MAVD may increase the tolerance of the LV to the hemodynamic burden related to the valve dysfunction. In particular, the LV hypertrophy induced by the AS component of MAVD may protect the LV against excessive LV dilatation and ensuing dysfunction caused by the AR component. These findings may explain, at least in part, that the impact of LVEF on clinical outcomes occurs at a slightly lower threshold (<55% vs. 60%) in MAVD vs. isolated AS or AR. This difference could also be related to the limited statistical power in the MAVD subset.

Finally, our results suggest a “U-shape” relationship between LVEF and mortality hazard, where both lower LVEF (<60%) and elevated LVEF (>70%) are associated with

worse outcomes. High LVEF may be a marker for "hyperdynamic" LV, which may be at higher risk for earlier decompensation.

Study Limitations

This is a retrospective, observational and non-randomized study and it is thus subject to inherent limitations associated with this type of study. The echocardiography data were reported by the participating sites and were not centrally adjudicated by an echocardiographic core laboratory. In addition, the diagnosis of BAV was ascertained primarily using echocardiography, and was not systematically confirmed by CT or surgical inspection in all patients. Although the LVEF data was available for the whole cohort at baseline, it was not systematically collected at the time of AVR. It was thus not possible to determine whether the LVEF had declined prior to AVR compared to baseline. Given that this was a retrospective study, the indications and criteria for valvular intervention, whilst broadly following contemporary guidelines, may have varied across each center, and the specific reason for AVR was not available. Another limitation was the small number of events in some subsets of patients, especially in patients with MAVD, therefore limiting the statistical power and accuracy for some analyses in these subsets.

CONCLUSION

This study shows that there is a progressive increase in the risk of mortality with decreasing LVEF in patients with BAV disease. A significant increase in the risk of mortality was observed at a LVEF threshold of <60% in AS and AR and <55% in MAVD. These results suggest that the current guidelines thresholds to define LV dysfunction may need to be re-evaluated in patients with BAV disease and should be raised from 50 to 60% in isolated AS or AR and 55% in MAVD. Ideally, randomized strategy trials would be necessary to determine if asymptomatic patients with severe BAV disease and LVEF <60% benefit of early AVR.

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SUPPLEMENTARY MATERIAL

Table S1: Echocardiographic Characteristics According to Aortic Valve Dysfunction

Variable	Overall N = 1,493	Isolated Significant AS N = 749	Significant MAVD N = 190	Isolated Significant AR N = 554	P-value
LV end-diastolic diameter, cm	5.20 (4.60 – 5.80)	4.80 (4.30 – 5.20)	5.38 (4.97 – 5.82)*	5.70 (5.20 – 6.30)*†	**<0.001**
LV end-systolic diameter, cm	3.40 (2.90 – 4.00)	3.00 (2.60 – 3.50)	3.50 (3.00 – 4.00)*	3.80 (3.30 – 4.40)*†	**<0.001**
LV end diastolic volume, ml	127 (97 – 166)	104 (83 – 129)	136 (113 – 173)*	157 (128 – 207)*†	**<0.001**
LV end systolic volume, ml	47 (32 – 69)	36 (26 – 51)	52 (36 – 71)*	60 (45 – 88)*†	**<0.001**
LVEF, %	63 (55 – 69)	64 (57 – 70)	61 (53 – 71)	61 (54 – 66)*	**<0.001**
LV mass index, g/m^2	117 (93 – 150)	107 (85 – 134)	132 (102 – 168)*	127 (102 – 169)*	**<0.001**
Left atrial volume index, ml/m^2	28 (21 – 37)	28 (21 – 37)	31 (22 – 42)	26 (20 – 36)*†	**0.003**
Mitral inflow E wave velocity, m/s	0.80 (0.60 – 0.91)	0.80 (0.60 – 0.95)	0.80 (0.67 – 1.00)	0.78 (0.60 – 0.90)*†	**0.005**
Mitral inflow E/A ratio	1.14 (0.82 – 1.55)	1.00 (0.78 – 1.46)	1.15 (0.82 – 1.71)*	1.22 (0.87 – 1.60)*	**<0.001**
MR ≥ moderate	107 (7.2%)	48 (6.4%)	18 (9.5%)	41 (7.4%)	0.33
Severe AR	257 (17%)	0 (0%)	55 (29%)*	202 (36%)*	**<0.001**
Severe AS	481 (32%)	401 (54%)	80 (42%)*	0 (0%)*†	**<0.001**
Mean pressure gradient, mmHg	20 (10 – 35)	29 (18 – 44)	30 (21 – 41)	9 (6 – 13)*†	**<0.001**
Peak aortic velocity, m/s	2.97 (2.12 – 3.80)	3.50 (2.80 – 4.20)	3.60 (3.00 – 4.23)	2.00 (1.70 – 2.53)*†	**<0.001**
Aortic valve area, cm	1.30 (1.00 – 2.10)	1.00 (0.80 – 1.23)	1.10 (0.85 – 1.30)	2.50 (2.00 – 3.15)*†	**<0.001**
SOV diameter indexed, mm/m^2	18.3 (16.3 – 20.5)	17.7 (15.9 – 19.8)	18.4 (16.5 – 20.2)	19.2 (17.0 – 21.3)*†	**<0.001**
STJ diameter indexed, mm/m^2	15.8 (13.8 – 17.9)	15.6 (13.7 – 17.7)	15.6 (13.9 – 17.3)	16.3 (14.1 – 18.5)*†	**0.001**
Ascending aorta diameter indexed, mm/m^2	19.7 (17.2 – 22.5)	20.0 (17.3 – 22.7)	19.8 (17.6 – 22.4)	19.2 (16.9 – 22.3)*	**0.041**

Legends: AR, aortic regurgitation; AS, aortic stenosis; LV, left ventricle; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease; MR, mitral regurgitation; SOV, sinus of Valsalva; STJ, sinotubular junction.

*p<0.05 vs Group I; †p<0.05 vs Group II

Table S2: Sensitivity Analysis with AVR As Time-dependent Covariate

Total Population (n=1493)	All-cause mortality[a]		Composite endpoint of AVR and all-cause mortality[b]	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariable analysis				
LVEF > 70%	1.45 (0.84 to 2.48)	0.180	1.13 (0.91 to 1.39)	0.268
LVEF 60-70%	*Reference*		*Reference*	
LVEF 50-59%	1.62 (0.98 to 2.68)	0.062	1.22 (0.99 to 1.49)	0.057
LVEF 30-49%	2.80 (1.64 to 4.76)	**<0.001**	1.88 (1.50 to 2.35)	**<0.001**
LVEF <30%	7.17 (3.71 to 13.85)	**<0.001**	2.49 (1.69 to 3.68)	**<0.001**
LVEF (continuous), %	0.97 (0.96 to 0.98)	**<0.001**	0.98 (0.98 to 0.99)	**<0.001**
Multivariable analysis				
LVEF > 70%	1.66 (0.96 to 2.86)	0.068	0.95 (0.76 to 1.18)	0.63
LVEF 60-70%	*Reference*		*Reference*	
LVEF 50-59%	1.80 (1.08 to 3.01)	**0.025**	1.35 (1.09 to 1.67)	**0.007**
LVEF 30-49%	1.97 (1.14 to 3.38)	**0.014**	1.69 (1.33 to 2.16)	**<0.001**
LVEF <30%	4.73 (2.34 to 9.54)	**<0.001**	1.82 (1.17 to 2.81)	**0.007**
LVEF (continuous), %	0.98 (0.97 to 0.99)	**<0.001**	0.98 (0.98 to 0.99)	**<0.001**

Legends: [a] Multivariable model adjusting for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, symptoms and coronary artery disease and AVR as a time-dependent covariate.
[b] Multivariable model adjusting for age, sex smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation, peak aortic velocity and symptoms. AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

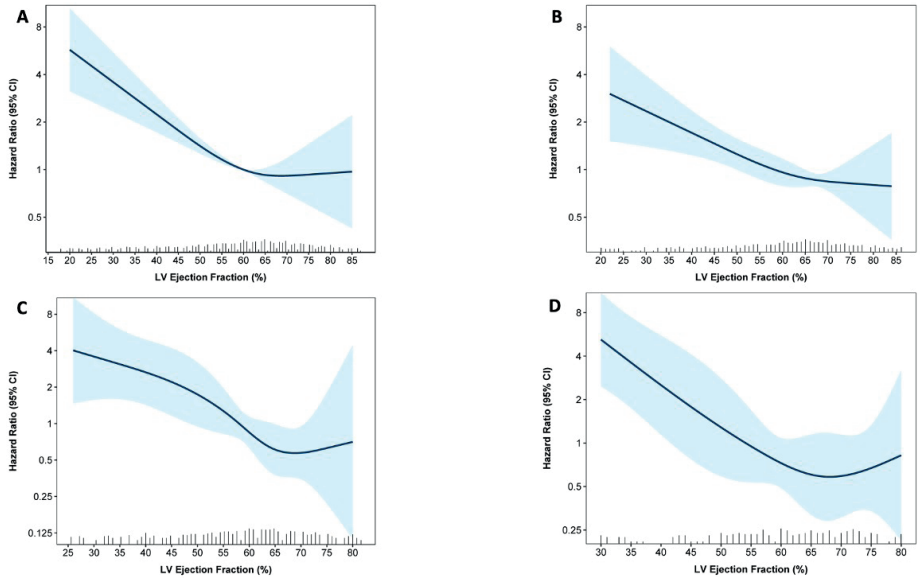

Figure S1: Spline Curves Analysis of All-cause Mortality According to AV Disease and LVEF

Legends: Spline curves analysis of all-cause mortality according to the type of aortic valve disease and LVEF. Panel A: whole BAV cohort. Panel B, C, D demonstrate spline curve survival estimates according to aortic valve disease: isolated AS, isolated AR and MAVD, respectively. AV, aortic valve; CI, confidence interval; LV, left ventricle; LVEF, left ventricular ejection fraction.

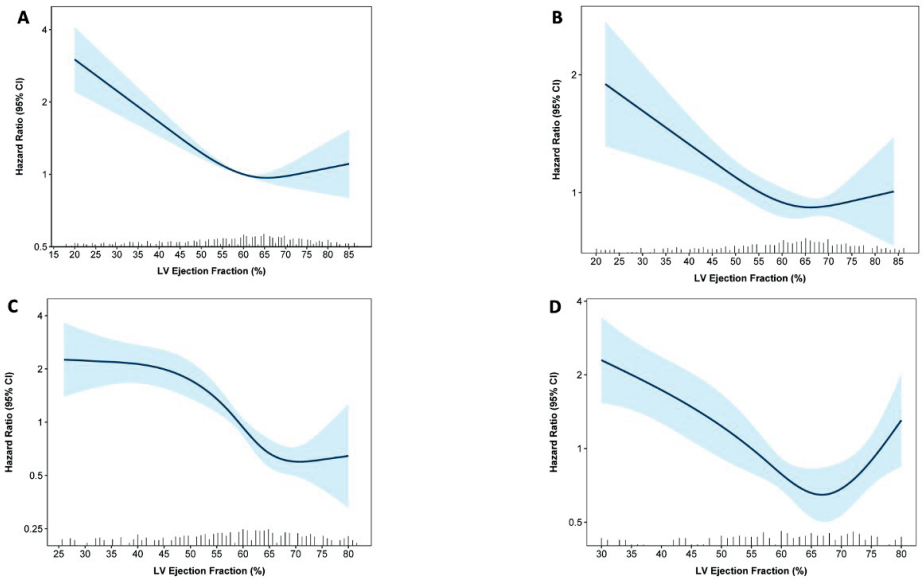

Figure S2: Spline Curves Analysis of the Composite Endpoint According to AV Disease and LVEF

Legends: Spline curves analysis of the composite endpoint of AVR and all-cause mortality according to the type of AV disease and LVEF. Panel A: whole BAV cohort. Panel B, C, D demonstrate spline curve event-free survival estimates according to aortic valve disease: isolated AS, isolated AR and MAVD, respectively. Legends as Online Figure 1. AVR, aortic valve replacement or repair.

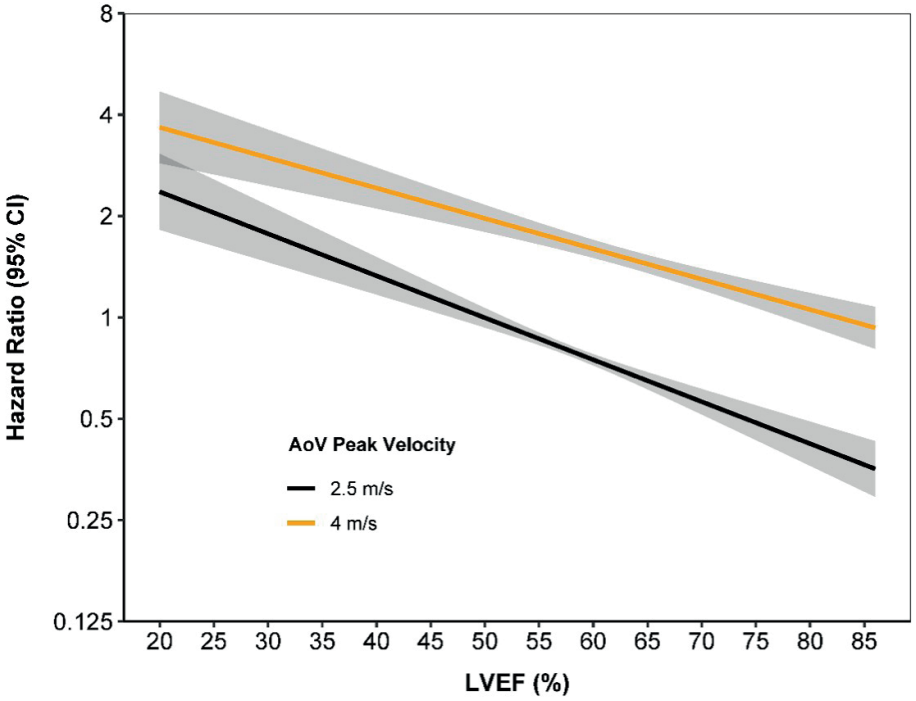

Figure S3: Interaction Analysis Between LVEF, Vmax and the Composite Endpoint of AVR and mortality.
Legends: Interaction analysis between LVEF, peak aortic jet velocity, and the composite endpoint of AVR and mortality. AVR, aortic valve replacement or repair; CI, confidence interval; LVEF, left ventricular ejection fraction; Vmax, peak aortic jet velocity.

8

Renal function in patients with significant tricuspid regurgitation: pathophysiological mechanisms and prognostic implications

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ABSTRACT

Background

The pathophysiological mechanisms linking tricuspid regurgitation (TR) and chronic kidney disease (CKD) remain unknown. This study aimed to determine which pathophysiological mechanisms related to TR are independently associated with renal dysfunction and to evaluate the impact of renal impairment on long-term prognosis in patients with significant (≥ moderate) secondary TR.

Methods

A total of 1,234 individuals (72 [IQR 63-78] years, 50% male) with significant secondary TR were followed up for the occurrence of all-cause mortality and the presence of significant renal impairment (eGFR of less than 60 mL/min/1.73m^2) at the time of baseline echocardiography.

Results

Multivariable analysis demonstrated that severe right ventricular (RV) dysfunction (TAPSE <14 mm) was independently associated with the presence of significant renal impairment (OR 1.49, 95% CI 1.11 to 1.99, p=0.008). Worse renal function was associated with a significant reduction in survival at 1- and 5 years (85% vs 87% vs 68% vs 58% at 1 year, and 72% vs 64% vs 39% vs 19% at 5 years, for stage 1, 2, 3 and 4-5 CKD groups respectively, p<0.001). The presence of severe RV dysfunction was associated with reduced overall survival in stage 1-3 CKD groups, but not for those with stage 4-5 CKD.

Conclusions

Of the pathophysiological mechanisms identified by echocardiography that are associated with significant secondary TR, only severe RV dysfunction was independently associated with the presence of significant renal impairment. In addition, worse renal function according to CKD group was associated with a significant reduction in survival.

INTRODUCTION

Secondary tricuspid regurgitation (TR), the principal mechanism of TR, is common, with a complex and often multifactorial etiology including left-sided valvular heart disease, pulmonary hypertension and left ventricular (LV) dysfunction[1]. Contemporary epidemiological studies have demonstrated that significant (≥ moderate) secondary TR is independently associated with poor long-term prognosis[2, 3], which has led to significant interest in the development of tricuspid valve interventions that may modify this unfavorable natural history[4].

However, how TR contributes to increased mortality remains ill-defined. Possibilities include acute or chronic right ventricular (RV) failure, acceleration of LV failure, or reduced physiological reserve secondary to renal or hepatic impairment from chronically elevated central venous pressure. Indeed, several studies have demonstrated that worsening TR grade (ranging from none to severe) in individuals with heart failure is independently associated with renal dysfunction[2, 5], which could theoretically lead to increased rates of cardiovascular and non-cardiovascular mortality as a consequence of chronic kidney disease (CKD)[6]. However, the pathophysiological mechanisms underlying the association between significant renal impairment and secondary TR remain unknown. In addition, the prognostic implications of renal impairment in a patient cohort with significant secondary TR have not yet been elucidated.

Therefore, the aim of this study was to i) investigate the prevalence of renal impairment in individuals with significant secondary TR, ii) determine the pathophysiological mechanisms identified by echocardiography that are associated with significant renal impairment in secondary TR and iii) to investigate the prognostic implications of renal impairment in significant secondary TR.

MATERIALS AND METHODS

Study population

Patients diagnosed with moderate or severe secondary TR between June 1995 and September 2016 were selected from the departmental echocardiographic database at Leiden University Medical Center (Leiden, The Netherlands). Patients with congenital heart disease and those who underwent tricuspid valve repair were excluded. Additionally, patients with incomplete data to assess TR severity or without renal function recorded were excluded. Patient demographic and clinical data were obtained from the departmental electronic medical record (EPD-vision; Leiden University Medical Center, Leiden, The Netherlands). As this study involved the retrospective analysis of clinically acquired data, the institutional review board of the Leiden University Medical Center

waived the need for written patient informed consent. This investigation conforms with the principles outlined in the *Declaration of Helsinki*.

Clinical and echocardiographic parameters

Clinical, demographic and laboratory variables were recorded from the time of first diagnosis of moderate or severe secondary TR by transthoracic echocardiography. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease formula[7]. Patients were subsequently divided into four categories according to eGFR, as per the recommendations of contemporary guidelines[7]. These groups were defined as normal renal function (Stage 1 CKD, eGFR ≥90 ml/min/1.73 m^2), mildly impaired renal function (Stage 2 CKD, eGFR 60 to 89 ml/min/1.73 m^2), moderately impaired renal function (Stage 3 CKD, eGFR 30 to 59 ml/min/1.73 m^2) and severely impaired renal function (Stage 4 and 5 CKD, eGFR <30 ml/min/1.73 m^2). Patients with an eGFR of less than 60 mL/min per 1.73 m^2 were defined as having significant renal impairment[7].

Comprehensive transthoracic echocardiography was performed with patients at rest in the left lateral decubitus position, using Vivid 7, E9 and E95 ultrasound systems (General Electric Vingmed Ultrasound, Milwaukee, WI) equipped with 3.5 MHz or M5S transducers. All echocardiographic data were stored digitally in a cine-loop format for offline analysis with EchoPac software (EchoPAC version 113.0.3, 202, and 203; GE-Vingmed). Apical, parasternal and subcostal views were used to acquire M-mode, 2-dimensional and color-, continuous- and pulsed-wave Doppler data according to contemporary guideline recommendations[8]. LV end-diastolic and end-systolic volumes were calculated using the biplane Simpson method and used to derive the LV ejection fraction. LV mass was calculated using the 2-dimensional linear approach[9]. Significant (moderate or severe) mitral regurgitation and aortic stenosis were defined according to contemporary guidelines[8]. TR grade was evaluated using a multiparametric approach according to guideline recommendations, integrating qualitative, semiquantitative and quantitative parameters[10]. Pacemaker or implantable cardioverter defibrillator lead-related TR was only classified as primary TR in the absence of significant left-sided valvular heart disease (defined as ≥ moderate mitral regurgitation/stenosis or aortic stenosis/regurgitation) or LV myocardial disease (defined as LV ejection fraction < 50%). RV dimensions, RV end-systolic and RV end-diastolic areas were acquired using an RV-focused apical view. Tricuspid annular plane systolic excursion (TAPSE) was used to quantify RV systolic function, derived from M-mode recordings of the lateral tricuspid annulus in an RV-focused apical view. Severe RV dysfunction was defined by a TAPSE less than 14 mm[11]. Pulmonary artery systolic pressure was estimated by applying the modified Bernoulli equation to the TR jet peak velocity, and adding mean right atrial (RA) pressure. Estimated RA pressure was calculated from the inferior vena cava diam-

eter and its collapsibility. All other standard echocardiographic measurements were performed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines[9].

Follow-up

All patients were followed up for the endpoint of all-cause mortality. Survival data were collected through the Social Security Death Index or by medical record review, and were complete for all patients. Follow-up began from the date of first diagnosis of moderate or severe TR by transthoracic echocardiography.

Statistical analysis

Categorical variables are expressed as numbers and percentages and were compared using the Pearson χ^2 test. Assessment of the distribution of continuous variables were performed by comparing a histogram of the sample data to a superimposed normal probability curve. Normally distributed continuous variables are presented as mean ± standard deviation, while variables that are non-normally distributed are displayed as median and interquartile range. Differences between the four renal function groups were analyzed using one-way ANOVA for continuous variables that were normally distributed, while the Kruskal-Wallis test was used to compare continuous variables that did not adhere to a normal distribution. Multiple comparisons for continuous and categorical variables were tested using the Bonferroni's correction.

To investigate the association between clinical and echocardiographic parameters with the presence of significant renal impairment, univariable and multivariable logistic regression analyses were performed. Clinically important variables known or postulated to be associated with significant renal impairment[12-14] and with a p-value < 0.05 on univariable analysis were included in the multivariable model. A minimum tolerance level of 0.5 was established to avoid multicollinearity between covariates. To further characterize the relationship of RV systolic function (i.e. TAPSE) and the probability of significant renal impairment, a spline curve was fitted in unadjusted and adjusted models. A sensitivity analysis using multivariable logistic regression was performed to investigate the relationship between clinical and echocardiographic parameters and severely impaired renal function. An additional sensitivity analysis using univariable and multivariable linear regression was performed to examine the association between clinical and echocardiographic parameters with eGFR as a continuous variable. Cumulative 1- and 5- year survival rates were calculated using the Kaplan-Meier method and differences between groups were analyzed using the log-rank test.

All tests were two-sided and p-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical and echocardiographic characteristics

A total of 1,234 patients with moderate to severe secondary TR were included. The median age of the population was 72 (interquartile range 63 to 78) years, 50% were male and 23% had severe TR. The potential contributing etiologies of secondary TR in the overall population included: LV ejection fraction < 40% (41.1%), atrial fibrillation (49.5%), significant mitral regurgitation (27.4%), significant aortic stenosis (21.2%), chronic obstructive pulmonary disease (14.4%) and pulmonary hypertension (defined as a pulmonary artery systolic pressure > 40 mmHg) (53.9%). The population was divided into four groups based on renal function: 230 (18.6%) had normal renal function, 451 (36.6%) had mildly impaired renal function, 439 (35.6%) had moderately impaired renal function, while 114 (9.2%) had severely impaired renal function. Those with renal impairment were older and more frequently hypertensive when compared to those with normal renal function. When compared to those with normal or mildly impaired renal function, patients with moderately or severely impaired renal function had more diabetes mellitus, known coronary artery disease and peripheral edema, were more often prescribed diuretics and presented with New York Heart Association III or IV heart failure symptoms. The baseline clinical characteristics of the population are summarized in Table 1.

The echocardiographic characteristics of the overall population are presented in Table 2. Patients with moderately or severely impaired renal function had larger LV, RV and left atrial dimensions, lower LV ejection fraction, more impaired RV systolic function and higher pulmonary arterial pressures than those with normal or mildly impaired renal function. In addition, patients with moderate or severe renal impairment had a larger tricuspid vena contracta width, tricuspid regurgitant volume and more frequently had significant mitral regurgitation when compared to individuals with normal or mildly impaired renal function.

Association of echocardiographic parameters of TR severity with significant renal impairment

To investigate the association between the pathophysiological mechanisms identified by echocardiography and significant renal impairment, univariable logistic regression analysis was performed, including clinical and echocardiographic variables known or postulated to be associated with significant renal impairment in patients with secondary TR[12-14]. On univariable analysis, age, diabetes mellitus, hypertension, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker use, diuretic use, aldosterone antagonist use, LV ejection fraction and LV end-diastolic volume were associated with significant renal impairment (Table S1). Of the parameters associated with TR severity,

Table 1: Clinical and demographic characteristics

Variable	Total Population (n=1234)	Group 1: GFR ≥ 90 ml/min/1.73 m^2 (n=230)	Group 2: GFR 60-89 ml/min/1.73 m^2 (n=451)	Group 3: GFR 30-59 ml/min/1.73 m^2 (n=439)	Group 4: GFR <30 ml/min/1.73 m^2 (n=114)	*P* value
Age (years)	72 (63 to 78)	65 (55 to 75)	72 (63 to 79)*	74 (67 to 80)*	71 (64 to 78)*	<0.001
Male sex (%)	612 (49.6%)	124 (53.9%)	217 (48.1%)	218 (49.7%)	53 (46.5%)	0.466
Body mass index (kg/m^2)	25.6 (±4.3)	25.1 (±4.3)	25.7 (±4.2)	25.6 (±4.2)	26.4 (±4.6)	0.129
Hypertension (%)	929 (80.2%)	147 (66.8%)	336 (80.6%)*	353 (84.7%)*	93 (88.6%)*	<0.001
Dyslipidemia (%)	550 (47.6%)	88 (40.4%)[a]	180 (43.3%)	225 (54.0%)*†	57 (54.3%)	0.001
Diabetes mellitus (%)	238 (20.5%)	32 (14.6%)	55 (13.2%)	100 (23.9%)*†	51 (48.1%)*†§	<0.001
Coronary artery disease (%)	498 (40.4%)	62 (27.0%)	154 (34.1%)	215 (49.1%)*†	67 (58.8%)*†	<0.001
Chronic obstructive pulmonary disease (%)	168 (14.4%)	24 (10.9%)	54 (12.8%)	70 (16.7%)	20 (18.7%)	0.086
Current or former smoker (%)	365 (31.6%)	73 (33.5%)	138 (33.3%)	127 (30.6%	27 (25.5%)	0.405
Atrial fibrillation (%)	586 (49.5%)	94 (42.0%)	221 (51.5%)	222 (52.4%)	49 (45.4%)	0.048
NYHA class III-IV (%)	534 (47.3%)	82 (40.6%)	168 (40.7%)	211 (51.8%)†	73 (68.2%)*†§	<0.001
Peripheral edema (%)	284 (23.6%)	36 (16.3%)	86 (19.5%)	120 (27.9%)*†	42 (37.2%)*†	<0.001
Diuretic use (%)	714 (58.9%)	87 (38.7%)	220 (49.9%)*	322 (74.2%)*†	85 (75.9%)*†	<0.001
Pacemaker/ICD (%)	401 (33.0%)	58 (25.7%)	131 (29.2%)	170 (39.4%)*†	42 (38.5%)	<0.001
ACEi/ARB use (%)	702 (61.4%)	109 (50.9%)	251 (60.9%)	287 (69.2%)*	55 (53.9%)§	<0.001
Beta-blocker use (%)	685 (59.8%)	120 (55.8%)	244 (59.1%)	255 (61.4%)	66 (64.1%)	0.430
Aldosterone receptor antagonist use (%)	243 (21.3%)	28 (13.1%)	68 (16.6%)	123 (29.6%)*†	24 (23.5%)	<0.001
Heart failure classification						
LVEF ≥ 50%	461 (37.7%)	106 (46.3%)	101 (42.8%)	123 (28.3%)*	41 (36.3%)	<0.001
LVEF = 41-49%	259 (21.2%)	61 (26.6%)	92 (20.6%)	88 (20.2%)	18 (15.9%)	
LVEF ≤ 40%	503 (41.1%)	62 (27.1%)	163 (36.5%)	224 (51.5%)*†	54 (47.8%)*	

Values are presented as mean ± SD, median (IQR) or n (%).

ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RV = right ventricular.

*p<0.05 vs Group I; †p<0.05 vs Group II; §p<0.05 vs Group III

Table 2: Echocardiographic characteristics

Variable	Total Population (n=1234)	Group 1: GFR ≥ 90 ml/min/1.73 m^2 (n=230)	Group 2: GFR 60-89 ml/min/1.73 m^2 (n=451)	Group 3: GFR 30-59 ml/min/1.73 m^2 (n=439)	Group 4: GFR <30 ml/min/1.73 m^2 (n=114)	*P* value
Left ventricle and atrium						
LV EDD (mm)	48.9 (±11.7)	46.3 (±10.5)	47.2 (±11.2)	51.3 (±12.3)*†	51.2 (±10.7)*†	<0.001
LV ESD (mm)	39.0 (±13.4)	35.8 (±11.7)	37.8 (±12.3)	41.4 (±14.9)*†	40.9 (±12.9)*	<0.001
LV EDV (ml/m^2)	114 (82 to 169)	104 (75 to 151)	104 (77 to 144)	128 (87 to 209)*†	136 (103 to 192) *†	<0.001
LVEF (%)	43.9 (±15.8)	48.7 (±15.5)	45.4 (±15.6)	40.2 (±15.0)*†	42.5 (±16.5)*	<0.001
LA volume (ml)	92 (61 to 126)	74 (51 to 109)	89 (59 to 123)*	101 (66 to 131)*	98 (69 to 132)*	<0.001
Significant AS (%)	251 (21.2%)	35 (16.4%)	92 (21.2%)	98 (23.0%)	26 (24.1%)	0.225
Significant MR (%)	336 (27.4%)	42 (18.3%)	108 (24.2%)	144 (32.9%)*†	42 (37.2%)*†	<0.001
Right Heart						
RV basal diameter, mm	45.6 (±8.6)	44.4 (±8.8)	44.9 (±8.1)	46.8 (±9.0)*†	46.2 (±7.8)	0.001
RV mid diameter, mm	35.3 (±9.0)	33.9 (±8.9)	34.6 (±8.9)	36.4 (±9.2)*†	36.5 (±8.4)	0.001
RV EDA, cm^2	23.6 (18.5 to 29.8)	21.6 (17.7 to 28.4)	22.7 (18.1 to 28.2)	24.8 (19.2 to 31.5)*†	26.9 (20.5 to 31.3) *†	<0.001
RA area, cm^2	25.7 (20.2 to 33.2)	23.5 (18.4 to 30.8)	25.8 (20.2 to 33.2)*	26.6 (20.8 to 34.9)*	26.5 (21.3 to 32.3)	0.010
TAPSE, mm	15.3 (±5.1)	16.1 (±5.2)	15.9 (±5.1)	14.6 (±4.9)*†	13.9 (±4.6)*†	<0.001
PASP, mmHg	43.0 (±16.9)	40.4 (±18.1)	41.9 (±16.4)	44.7 (±16.2)*	46.6 (±17.8)*	0.001
PASP > 40 mmHg (%)	618 (53.9%)	89 (42.6%)	212 (50.1%)	248 (60.3%)*†	69 (66.3%)*†	<0.001
eRAP, mm Hg	9.0 (±4.9)	9.2 (±4.7)	8.4 (±5.0)	9.2 (±4.9)†	10.1 (±4.8)	0.006
Tricuspid Valve						
Moderate TR (%)	948 (76.9%)	178 (77.7%)	363 (80.5%)	328 (74.7%)	79 (69.9%)	0.054
Severe TR (%)	284 (23.1%)	51 (22.3%)	88 (19.5%)	111 (25.3%)	34 (30.1%)	0.054
TA diameter, mm	41.7 (±8.0)	40.1 (±7.9)	41.6 (±8.0)	42.5 (±8.1)*	42.5 (±7.8)	0.003
Vena contracta, mm	10.4 (±4.03)	9.7 (±4.2)	10.5 (±4.0)	10.6 (±3.9)*	11.2 (±4.2)*	0.006
EROA, mm^2	64 (40 to 101)	56 (34 to 100)	64 (42 to 96)	67 (42 to 107)	64 (42 to 100)	0.536
RVol, ml/beat	60 (36 to 100)	52 (28 to 90)	60 (36 to 96)	66 (37 to 105)*	64 (42 to 114)*	0.007

Values are presented as mean ± SD, median (IQR) or n (%).

AS = aortic stenosis; EDA = end-diastolic area; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; eRAP = estimated right atrial pressure; EROA = effective regurgitant orifice area; ESD = end-systolic diameter; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; RA = right atrial; RV = right ventricular; RVol = regurgitant volume; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

*p<0.05 vs Group I; †p<0.05 vs Group II; §p<0.05 vs Group III

decreasing TAPSE, increasing TR vena contracta width, TR regurgitant volume, tricuspid annulus diameter, RV end-diastolic area, estimated RA pressure and pulmonary artery systolic pressure were associated with the presence of significant renal impairment on univariable analysis. On multivariable logistic regression, following adjustment for important covariates, age, diabetes mellitus, diuretic use and LV end-diastolic volume remained associated with significant renal impairment at the time of baseline echocardiography (Table 3). Of all the echocardiographic parameters related to TR severity, only TAPSE was associated with significant renal impairment in the multivariable model. Subsequently, spline curve analysis was performed to investigate the nature of the association between TAPSE and the probability of significant renal impairment at the time of echocardiography (Figure 1). In the adjusted model (Figure 1, Panel B), following a long plateau phase and no evidence of an association, there was a significant increase in the probability of significant renal impairment with values of TAPSE less than 14 mm. Values of TAPSE less than 14 mm were associated with the presence of significant renal impairment in the adjusted model (OR 1.49, 95% CI 1.11 to 1.99, p=0.008).

Table 3: Multivariable logistic regression for parameters associated with significant renal impairment (eGFR <60 ml/min/1.73 m^2) and severely impaired renal function (eGFR <30 ml/min/1.73 m^2)

	Multivariable analysis for significant renal impairment (<60 ml/min/1.73 m^2)		Multivariable analysis for severe renal impairment (<30 ml/min/1.73 m^2)	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Patient demographics and comorbidities				
Age, years	1.034 (1.021-1.047)	<0.001	1.001 (0.981-1.022)	0.914
Diabetes mellitus	1.922 (1.342-2.752)	<0.001	3.860 (2.352-6.336)	<0.001
Hypertension	1.372 (0.913-2.063)	0.128	2.518 (1.114-5.691)	0.026
ACEi/ARB use	0.917 (0.664-1.265)	0.597	0.412 (0.245-0.691)	<0.001
Diuretic use	2.339 (1.696-3.226)	<0.001	2.157 (1.164-3.997)	0.015
Aldosterone antagonist	1.266 (0.875-1.831)	0.211	0.656 (0.361-1.191)	0.166
Echocardiographic variables				
LV EDV, ml	1.004 (1.002-1.006)	0.001	1.004 (1.000-1.007)	0.028
LVEF, %	0.994 (0.984-1.005)	0.288	1.016 (0.998-1.034)	0.075
Significant MR	1.137 (0.827-1.564)	0.428	1.390 (0.834-2.317)	0.206
RV EDA, mm^2	1.009 (0.995-1.024)	0.189	0.997 (0.969-1.025)	0.811
TA diameter, mm	0.997 (0.976-1.017)	0.739	0.985 (0.950-1.022)	0.433
TR RVol, ml	1.000 (0.997-1.003)	0.998	1.002 (0.998-1.007)	0.271
TAPSE, mm	0.963 (0.935-0.992)	0.012	0.944 (0.893-0.997)	0.038
Estimated RAP, mmHg	0.978 (0.947-1.010)	0.174	1.014 (0.961-1.070)	0.605
PASP, mmHg	1.006 (0.997-1.015)	0.217	1.001 (0.987-1.016)	0.854

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; EDA = end-diastolic area; EDV = end-diastolic volume; EF = ejection fraction; eRAP = estimated right atrial pressure; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; RV = right ventricular; RVol = regurgitant volume; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

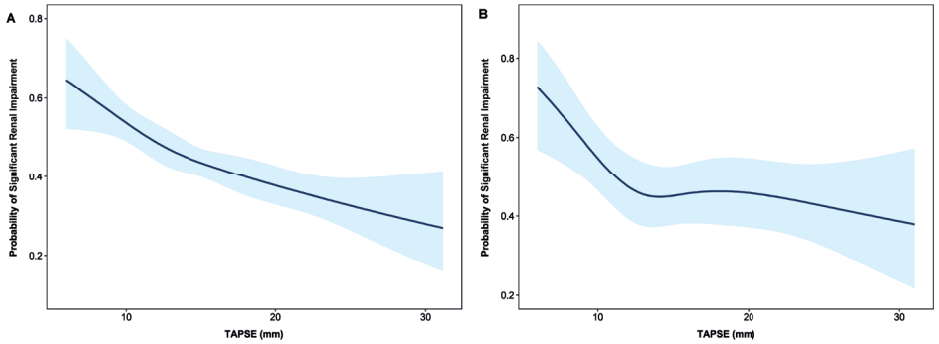

Figure 1: Spline curves demonstrating the probability of significant renal impairment (eGFR <60 ml/min/1.73 m^2) according to TAPSE in unadjusted (A) and adjusted models (B).

The curve in panel A demonstrates the probability of significant renal impairment according to TAPSE measured at the time of index echocardiogram, with overlaid 95% confidence intervals displayed (shaded blue areas). The curve in panel B demonstrates the probability of significant renal impairment according to values of TAPSE, adjusted for age, diabetes mellitus, hypertension, ACEi/ARB use, diuretic use, aldosterone antagonist use, LV end-diastolic volume, LV ejection fraction, the presence of significant MR, RV end-diastolic area, tricuspid annulus diameter, TR regurgitant volume, estimated RAP and PASP.

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; LV = left ventricle; PASP = pulmonary artery systolic pressure; RAP = right atrial pressure; RV = right ventricle; MR = mitral regurgitation; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

In a sensitivity multivariable logistic regression analysis, of the echocardiographic parameters associated with TR, only TAPSE was related to the probability of presenting with severe renal impairment (eGFR <30 ml/min/1.73m^2) (Table 3). A further sensitivity analysis utilizing uni- and multi-variable linear regression was performed to investigate the association between parameters related to TR severity and eGFR as a continuous variable (Table S2). Results consistent with those of the previous analyses were observed, with TAPSE being the only pathophysiological mechanism identifiable by echocardiography that was associated with eGFR after adjusting for potential confounders.

Survival Analysis

Over a median follow-up of 53 (interquartile range, 16 to 89) months, 692 patients (56%) died. The 1- and 5- year cumulative survival rates were 77% and 53% respectively, for the total population. Kaplan-Meier analysis for all-cause mortality demonstrated a significant reduction in survival for patients with worse renal function at 1- and 5 years (85% vs 87% vs 68% vs 58% at 1 year, and 72% vs 64% vs 39% vs 19% at 5 years, for stage 1, 2, 3 and 4-5 CKD groups respectively, p<0.001) (Figure 2A). In addition, the Kaplan-Meier survival analysis demonstrated that the presence of severe RV dysfunction was associated with a reduction in overall survival in the stage 1-3 CKD groups, but not for those with stage 4-5 CKD (Figure 2B-E).

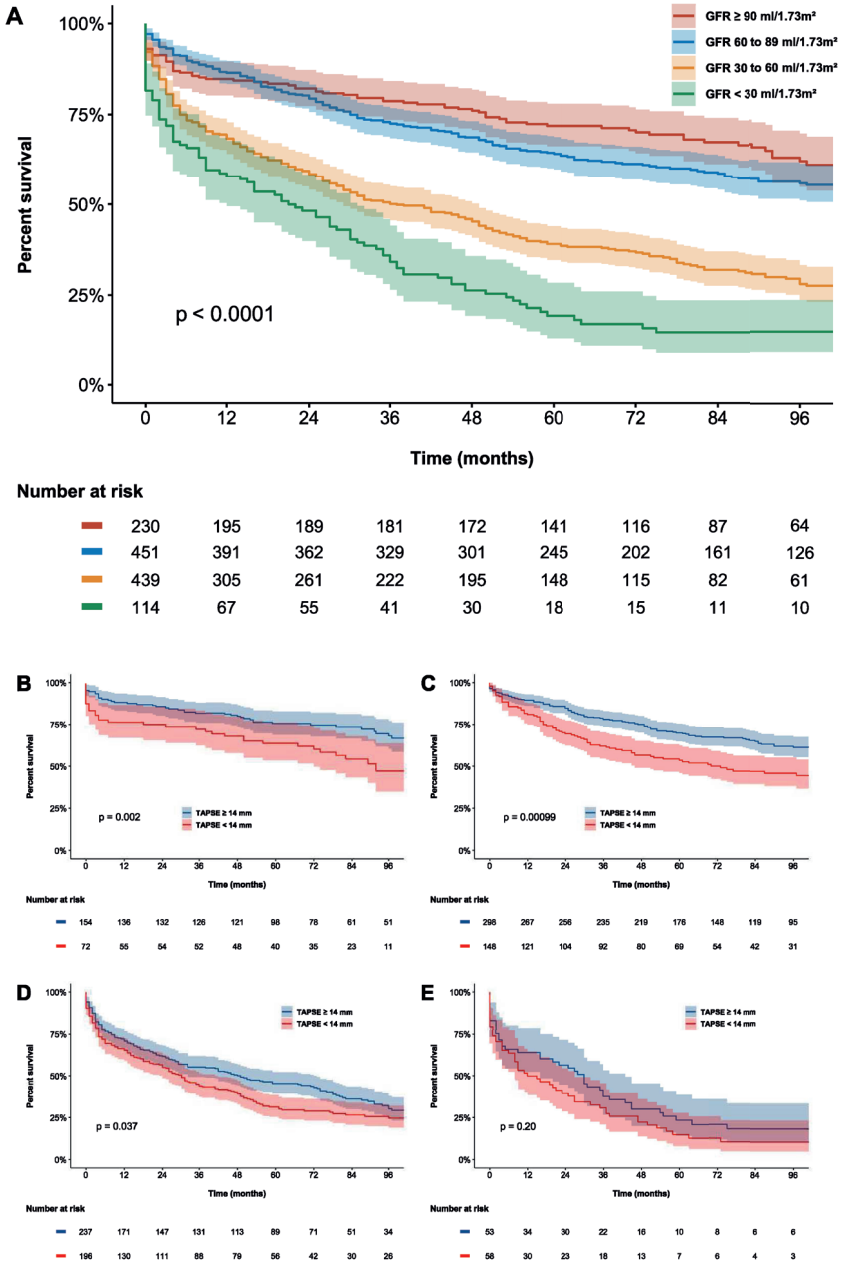

Figure 2: Kaplan-Meier estimates for all-cause mortality stratified by renal function group and according to the presence of severe RV dysfunction (TAPSE < 14 mm). The Kaplan-Meier curves demonstrate reduced survival with worsening renal function (panel A) and the improved survival rates of patients with TAPSE ≥ 14 mm (blue line) compared to those with TAPSE < 14 mm (red line) in renal function stage 1 (panel B), 2 (panel C) and 3 (panel D) CKD. For patients with severe renal impairment (Stage 4 and 5 CKD, eGFR <30 ml/min/1.73 m^2), the presence of severe RV dysfunction did not portend a worse prognosis (panel E).

CKD = chronic kidney disease; GFR = glomerular filtration rate; TAPSE = tricuspid annular plane systolic excursion

DISCUSSION

In this study of 1,234 patients with significant secondary TR, the prevalence of significant renal impairment (eGFR <60 ml/min/1.73 m^2) was 45%. On multivariable analysis, age, diabetes mellitus, diuretic use and LV end-diastolic volume were associated with significant renal impairment. Of all the pathophysiological mechanisms identified by echocardiography that are related to TR, only severe RV dysfunction (TAPSE <14 mm) was independently associated with the presence of significant renal impairment. In addition, worsening renal function was associated with a significant reduction in survival at long-term follow-up. Severe RV dysfunction was associated with reduced overall survival in stage 1-3 CKD groups, although not in those with stage 4-5 CKD.

Prevalence of renal dysfunction in moderate to severe TR

The prevalence of significant renal impairment (eGFR <60 ml/min/1.73 m^2) in patients with significant secondary TR and heart failure with reduced ejection fraction (HFrEF) has previously been reported as 45-50%, in agreement with the results of the present study,[2] which evaluated patients with significant secondary TR due to a variety of etiologies. This is in contrast to a recent study of 2,380 patients with significant secondary TR of various etiologies, where the reported prevalence of significant renal impairment was only 14%, although a specific definition of renal impairment was not provided[15].

Association of echocardiographic parameters of TR severity and CKD

Although previous studies[2, 5] have clearly demonstrated an independent association between worse renal function and increasing grade of TR in patients with HFrEF, there has been minimal investigation into the possible mechanisms linking significant secondary TR and significant renal impairment. From a theoretical perspective, numerous echocardiographic parameters associated with the presence of significant TR could be directly related to increased central venous pressure and venous congestion, and consequently, renal impairment (i.e. increased TR volume, estimated RA pressure or RV dysfunction). In the present study of over 1,200 patients with significant secondary TR of various etiologies, of the echocardiographic parameters associated with TR, we observed that only TAPSE was independently associated with significant renal impairment (eGFR <60 ml/min/1.73 m^2) and severe renal impairment (eGFR <30 ml/min/1.73 m^2). Moreover, in an adjusted non-linear model, this relationship was only evident at values of TAPSE <14 mm (i.e. severe RV dysfunction), further strengthening the notion of a biologically plausible association. It is possible that previous associations observed between significant renal impairment and the grade of TR were actually indicative of the increased incidence of RV dysfunction observed with increasing TR severity. In addition, these findings are consistent with a previous study of 373 patients with HFrEF, where TAPSE ≤14 mm was

independently associated with the presence of significant renal impairment[16]. However, the authors did not have access to important echocardiographic data pertaining to the severity of TR, so were unable to adjust for vital confounding variables in their analysis.

Pathophysiological interactions between the right ventricle and kidney in significant secondary TR

Numerous pathophysiological interactions between the kidney and the volume-overloaded right ventricle may explain the independent association observed between RV dysfunction and renal impairment in the present study (Figure 3). Essentially, any hemodynamic change contributing to a reduction in trans-renal perfusion pressure (determined by the difference between mean arterial pressure and central venous pressure) may lead to a reduction in eGFR[17]. In individuals with RV dysfunction, LV cardiac output may be reduced as a direct result of decreased RV cardiac output (as a series interaction)[18] and/or due to a reduction in ventricular systolic interdependence[19]. In addition, RV dysfunction may lead to RV remodeling and increased volume as a compensatory response to maintain adequate RV stroke volume (heterometric adaptation)[20]. Increased RV volume may then impair LV filling secondary to increased ventricular diastolic interdependence and/or paradoxical diastolic septal motion[19], further decreasing LV cardiac output and therefore, mean arterial pressure.

In addition to these important interactions with LV function, adequate RV function is also necessary for maintaining a low central venous pressure[21]. In the presence of severe RV dysfunction, the central venous pressure may rise, resulting in a further reduction in renal perfusion pressure[21]. Indeed, in an experimental study of 17 normal human subjects, artificially increasing intra-abdominal venous pressure to 20 mmHg resulted in a reduction in GFR of approximately 30% and of renal plasma flow by almost 25%[22]. Numerous additional animal and human studies have since confirmed the close relationship between elevated central venous pressure and significant renal impairment[17, 23], with several studies demonstrating that central venous pressure may be more important than forward cardiac output in modulating renal function[24, 25]. Interestingly, in the present study, no independent association between significant renal impairment and estimated RA pressure was observed, suggesting that the association with RV dysfunction may not be mediated by increase central venous pressure. However, the estimation of right atrial pressure on echocardiography through the evaluation of the inferior vena cava diameter and collapsibility may correlate less closely with invasively-derived right atrial pressure in patients with significant TR[26]. Furthermore, estimated RA pressure may change acutely with alterations in volume or clinical status, whereas RV dysfunction may more accurately identify patients who are exposed to the cumulative effects of chronically elevated central venous pressure. In addition, estimated RA

pressure may rise with even minimal exertion, which may not be captured on resting echocardiogram.

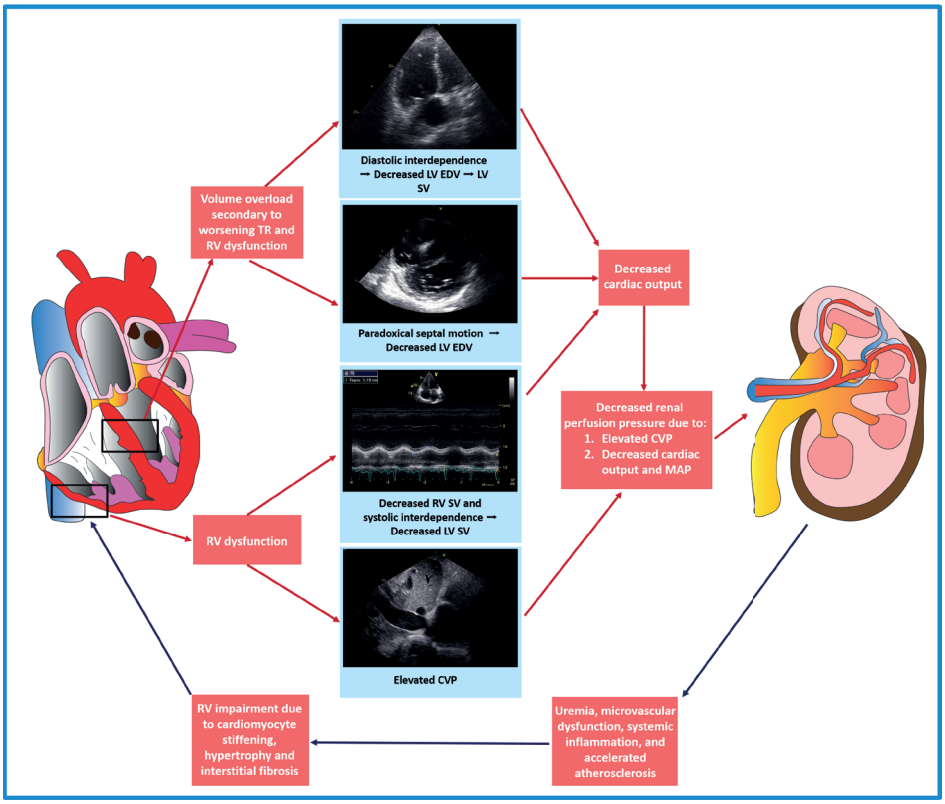

Figure 3: Pathophysiological interactions between the right ventricle and kidney in significant tricuspid regurgitation.
CVP = central venous pressure; EDV = end-diastolic volume; LV = left ventricle; MAP = mean arterial pressure; RV = right ventricle; SV = stroke volume; TR = tricuspid regurgitation.

Importantly, pathophysiological consequences of renal impairment, including uremia, microvascular dysfunction, inflammation, cytokine release and accelerated atherosclerosis, could directly result in progressive cardiomyocyte stiffening, hypertrophy and interstitial fibrosis, manifesting as worsening RV function[27, 28]. Indeed, these cardiorenal interactions may also potentially explain some of the association observed between RV dysfunction and renal impairment in the present study.

Prognostic and clinical implications of renal impairment in secondary TR

Significant TR induces RV remodeling, characterized by progressive RV dilation and dysfunction[29]. In our study, we demonstrated that lower values of TAPSE are associated with worse renal function, which in turn, may exacerbate the volume overload on the

right ventricle and induce a vicious circle of progressive RV remodeling through a variety of mechanisms[30].

Interventions and therapies aiming to reduce the impact of potential causes of secondary TR may halt RV remodeling and also improve renal function. Significant left-sided valvular heart disease and the consequent increase in pulmonary pressures are among the major determinants of secondary TR [31] and targeted interventions have shown a beneficial effect on renal function[32]. However, these beneficial effects on renal function have yet to be specifically linked with changes in TR or RV function.

Tricuspid valve interventions have the potential to reduce central venous pressure[33], halt the remodeling of the right ventricle, increase stroke volume[34], improve peripheral perfusion and theoretically, permit the recovery of renal function. However, although Karam et al. demonstrated a positive impact of transcatheter tricuspid valve interventions on liver function in a cohort of 126 patients, no improvement in renal function was recorded during 6 months of follow-up[35]. Nevertheless, they did not stratify their results according to pre-procedural renal function and RV remodeling, factors which could logically impact on the likelihood of renal function recovery. Severe renal impairment (eGFR <30 ml/min/1.73 m^2) may represent a degree of organ dysfunction that is too advanced to derive significant survival benefit from tricuspid valve interventions and the consequent RV reverse remodeling that may arise from the unloading of the right ventricle. Our results and the study by Karam et al.[35] may underline the importance of adequate risk stratification, screening and patient selection for tricuspid valve interventions, an assessment that should probably also include an evaluation of renal function.

Limitations

This study is subject to the inherent limitations of a single center, observational, retrospective design. While an independent association between RV dysfunction and significant renal impairment was observed, causality could not be established due to study design. The effects of tricuspid valve interventions on RV remodeling, renal function and the potential relationship with patient outcomes requires further investigation.

CONCLUSION

Of the pathophysiological mechanisms identified by echocardiography that are associated with significant secondary TR, only severe RV dysfunction (TAPSE < 14 mm) was independently associated with the presence of significant renal impairment. In addition, worse renal function according to CKD group was associated with a significant reduction in survival at long-term follow-up.

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SUPPLEMENTARY MATERIAL

Table S1: Univariable logistic regression for parameters associated with significant renal impairment (eGFR <60 ml/min/1.73 m^2)

	Univariable analysis	
	OR (95% CI)	***P* value**
Patient demographics and comorbidities		
Age, years	1.027 (1.017 to 1.036)	<0.001
BMI, kg/m^2	1.016 (0.986 to 1.047)	0.299
Male sex	0.958 (0.766 to 1.199)	0.709
Diabetes mellitus	2.559 (1.906 to 3.437)	<0.001
Hypertension	1.871 (1.381 to 2.534)	<0.001
ACEi/ARB use	1.444 (1.134 to 1.838)	0.003
Diuretic use	3.424 (2.679 to 4.377)	<0.001
Beta blocker use	1.182 (0.932 to 1.499)	0.169
Aldosterone antagonist use	2.185 (1.636 to 2.919)	<0.001
Current smoking	0.839 (0.653 to 1.078)	0.170
Heart Failure Category		
LVEF ≥ 50%	**Reference**	
LVEF = 41-49%	1.255 (0.918 to 1.715)	0.155
LVEF ≤ 40%	2.238 (1.726 to 2.900)	<0.001
Echocardiographic variables		
LV EDV, ml	1.005 (1.003 to 1.007)	<0.001
LV EF, %	0.976 (0.969 to 0.983)	<0.001
Stroke volume, ml	1.000 (0.999 to 1.001)	0.764
Significant MR	1.784 (1.385 to 2.297)	<0.001
Significant AS	1.241 (0.938 to 1.640)	0.130
RV EDA, mm^2	1.020 (1.008 to 1.032)	0.001
TA diameter, mm	1.022 (1.008 to 1.036)	0.003
TR EROA, mm^2	1.001 (0.999 to 1.002)	0.340
TR RVol, ml	1.003 (1.001 to 1.005)	0.004
TAPSE, mm	0.940 (0.919 to 0.963)	<0.001
Estimated RAP, mmHg	1.030 (1.006 to 1.055)	0.013
PASP, mmHg	1.013 (1.006 to 1.020)	<0.001

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AS = aortic stenosis; BMI = body mass index; EDA = end-diastolic area; EDV = end-diastolic volume; EF = ejection fraction; eRAP = estimated right atrial pressure; EROA = effective regurgitant orifice area; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; RA = right atrial; RV = right ventricular; RVol = regurgitant volume; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

Table S2: Univariable and multivariable linear regression for estimated GFR

	Univariable analysis		Multivariable analysis	
	B (95% CI)	***P* value**	**B (95% CI)**	***P* value**
Patient demographics and comorbidities				
Age	-0.541 (-0.669 to -0.414)	<0.001	-0.609 (-0.750 to -0.467)	<0.001
Obesity	-3.526 (-9.182 to 2.130)	0.221		
Male sex	0.392 (-2.998 to 3.782)	0.821		
Diabetes mellitus	-13.269 (-17.559 to -8.979)	<0.001	-8.580 (-13.121 to -4.039)	<0.001
Hypertension	-10.994 (-15.369 to -6.620)	<0.001	-6.173 (-11.225 to -1.120)	0.017
ACEi/ARB use	-7.337 (-10.947 to -3.726)	<0.001	-0.268 (-4.337 to 3.802)	0.897
Diuretic use	-17.084 (-20.433 to -13.734)	<0.001	-9.462 (-13.579 to -5.346)	<0.001
Beta blocker use	-3.152 (-6.753 to 0.448)	0.086		
Aldosterone antagonist use	-9.753 (-14.045 to -5.461)	<0.001	-1.748 (-6.499 to 3.004)	0.471
LV EDV, ml	-0.069 (-0.093 to -0.045)	<0.001	-0.052 (-0.080 to -0.025)	<0.001
LVEF, %	0.345 (0.238 to 0.452)	<0.001	0.044 (-0.087 to 0.175)	0.511
Significant MR	-8.455 (-12.766 to -4.144)	<0.001	-4.147 (-8.187 to -0.107)	0.044
RV EDA, mm^2	-0.193 (-0.31 to -0.072)	0.002	-0.112 (-0.265 to 0.042)	0.154
TA diameter, mm	-0.323 (-0.534 to -0.113)	0.003	0.077 (-0.178 to 0.332)	0.554
TR vena contracta, mm	-0.655 (-1.084 to -0.227)	0.003		
TR EROA, mm^2	-0.002 (-0.028 to 0.023)	0.852		
TR RVol, ml	-0.048 (-0.081 to -0.016)	0.003	0.002 (-0.032 to 0.036)	0.910
TAPSE, mm	0.982 (0.651 to 1.314)	<0.001	0.566 (0.211 to 0.921)	0.002
eRAP, mmHg	-0.255 (-0.612-0.103)	0.162		
PASP, mmHg	-0.221 (-0.325 to -0.117)	<0.001	-0.072 (-0.181 to 0.037)	0.194

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; EDA = end-diastolic area; EDV = end-diastolic volume; eRAP = estimated right atrial pressure; EROA = effective regurgitant orifice area; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; RV = right ventricular; RVol = regurgitant volume; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

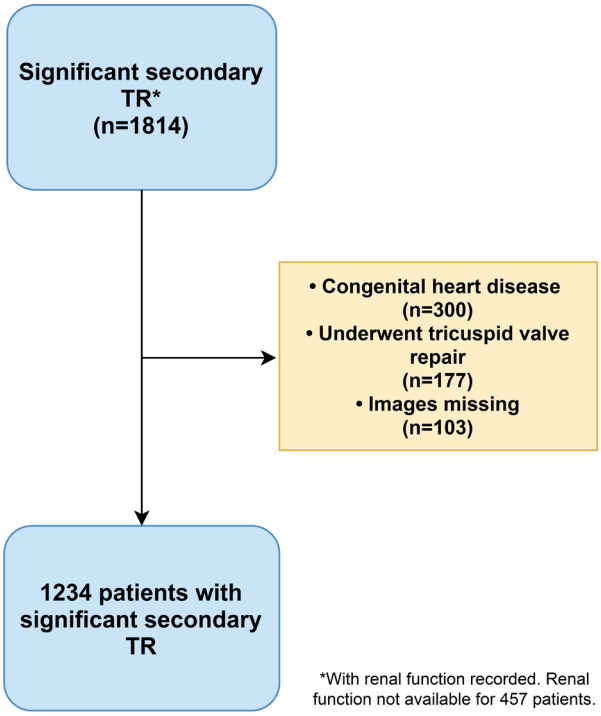

Figure S1: Study Flow Chart

9

Factors influencing post-surgical survival in degenerative mitral regurgitation

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ABSTRACT

Aims

Indications for surgery in patients with degenerative mitral regurgitation (DMR) are increasingly liberal in all clinical guidelines but the role of secondary outcome determinants (left atrial volume index [LAVI] ≥60ml/m^2, atrial fibrillation [AF], pulmonary artery systolic pressure [PASP] ≥50mmHg and moderate to severe tricuspid regurgitation [TR]) and their impact on postoperative outcome remain disputed. Whether these secondary outcome markers are just reflective of the DMR severity or intrinsically affect survival after DMR surgery is uncertain and may have critical importance in the management of patients with DMR. To address these gaps of knowledge the present study gathered a large cohort of patients with quantified DMR, accounted for the number of secondary outcome markers and examined their independent impact on survival after surgical correction of the DMR.

Methods and Results

The Mitral Regurgitation International DAtabase-Quantitative (MIDA-Q) registry includes patients with isolated DMR from centres across North America, Europe, and the Middle East. Patient enrolment extended from January 2003 to January 2020. All patients undergoing mitral valve surgery within 1 year of registry enrolment were selected. A total of 2276 patients (65 [55-73] years, 32% male) across 5 centres met study eligibility criteria. Over a median follow-up of 5.6 (3.6 to 8.7) years, 278 patients (12.2%) died. In a comprehensive multivariable Cox regression model adjusted for age, EuroSCORE II, symptoms, LVEF, LV ESD and DMR severity, the number of secondary outcome determinants was independently associated with post-operative all-cause mortality, with adjusted HRs of 1.56 (95% CI 1.11 to 2.20, P=0.011), 1.78 (95% CI 1.23 to 2.58, P=0.002) and 2.58 (95% CI 1.73 to 3.83, P<0.0001) for patients with one, two and three or four secondary outcome determinants, respectively. A model incorporating the number of secondary outcome determinants demonstrated a higher C-index and was significantly more concordant with post-operative mortality than models incorporating traditional Class I indications alone (the presence of symptoms [P=0.0003], or LVEF ≤60% [P=0.006], or LV ESD ≥40mm [P=0.014]), while there was no significant difference in concordance observed compared to a model that incorporated the number of Class I indications for surgery combined (P=0.71).

Conclusion

In this large cohort of patients treated surgically for DMR the presence and number of secondary outcome determinants was independently associated with post-surgical survival and demonstrated better outcome discrimination than traditional Class I indi-

cations for surgery. Randomised controlled trials are needed to determine if patients with severe DMR who demonstrate a cardiac phenotype with an increasing number of secondary outcome determinants would benefit from earlier surgery.

INTRODUCTION

Degenerative mitral regurgitation (DMR) characterised by mitral valve prolapse (MVP), the most common type of organic mitral valve disease[1,2], is associated with increased morbidity and mortality compared to the general population[3], and is highly amenable to surgical intervention[4,5]. However, despite guideline recommendations, severe undertreatment of the condition is observed with tremendous excess-mortality[6], suggesting the need for additional data to guide DMR surgical correction[4,7].

Although the importance of Class I indications (based on symptoms and left ventricular [LV] function) for surgery are well-acknowledged (culminating as strong recommendations in contemporary guidelines)[5], recent studies have also demonstrated the prognostic importance of secondary outcome determinants, such as pulmonary artery systolic pressure (PASP), atrial fibrillation, tricuspid regurgitation (TR) and left atrial volume index (LAVI)[3,4,8-10]. These secondary outcome determinants, although widely acknowledged and supported by observational data, do not at present represent strong recommendations or Class I indications for surgery in current guidelines[3-5,8-10]. In addition, evaluation of the cumulative importance of the number of secondary outcome determinants, reflecting increased atrial, pulmonary and right ventricular consequences of DMR and a high-risk phenotype, has not been studied in a contemporary population undergoing mitral valve surgery for DMR due to a variety of aetiologies. Whether such phenotype even in the absence of overt LV systolic dysfunction (LV ejection fraction [LVEF] ≤60% and LV end-systolic diameter [LV ESD] ≥40mm)[5] or symptoms, reflects DMR severity or a DMR-linked physiologic response with substantial increase in left atrial pressure, pulmonary venous and possibly arterial pressure[11] is uncertain. This could result in considerable adverse remodelling of the left atrium, pulmonary vasculature, and tricuspid valve, leading to poor outcome. We hypothesised that patients with increased atrial, pulmonary and right ventricular consequences of isolated DMR are a particularly high-risk cohort, even after surgical DMR correction, which could be of critical importance in the consideration of the indication for DMR surgical intervention. We further hypothesised that accounting for the number of secondary outcome markers could provide similar prognostic utility to established class I indications for surgery.

Therefore, the aim of this study was three-fold: (1) To evaluate and validate the prognostic value of LAVI, atrial fibrillation, PASP and moderate to severe TR in a large, international cohort of DMR patients undergoing surgery, (2) To evaluate the prognostic implications of an increasing number of these secondary outcome determinants in DMR, and (3) to evaluate the relative prognostic importance of the number of secondary outcome determinants in comparison with established class I indications for surgery.

METHODS

Study Design

The Mitral Regurgitation International DAtabase-Quantitative (MIDA-Q) registry was created by systematically merging a series of prospectively assembled electronic institutional databases of patients with quantified isolated DMR from countries in North America (Mayo Clinic, Rochester, MN, USA), Europe (Leiden University Medical Center, Leiden, the Netherlands; University of Amiens, Amiens, France; University of Nantes, Nantes, France) and the Middle East (Tel Aviv Medical Center, Tel Aviv, Israel). Patient enrolment extended from January 2003 to January 2020, according to each centre's database. Eligibility criteria included the following: 1) inclusion of consecutive patients with a diagnosis of DMR (due to mitral valve prolapse or flail leaflet) by transthoracic echocardiography; 2) availability of comprehensive clinical evaluation recorded prospectively at the time of index echocardiography; 3) exclusion of functional MR of any aetiology, significant concomitant aortic valve disease, mitral stenosis, congenital heart disease, rheumatic heart disease, active endocarditis, and prior valve surgery. All patients undergoing mitral valve surgery within 1 year of registry enrolment were selected. The study was approved by the Institutional Review Board of each centre, conducted in accordance with institutional guidelines, national legal requirements, and the *Declaration of Helsinki*.

Echocardiography

Echocardiographic studies were performed with commercially available ultrasound systems and analysed by experienced investigators from each centre. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method. LV ESD and LV end-diastolic diameter (LV EDD) were measured using the 2D linear method, as per guideline recommendations[12]. LAVI was calculated from apical 2- and 4-chamber views using the biplane method, indexed for body surface area. PASP was estimated by applying the modified Bernoulli equation to the TR jet peak velocity and adding estimated right atrial pressure. Estimated right atrial pressure was calculated from the inferior vena cava diameter and its collapsibility. TR grade was evaluated using a multiparametric approach according to guideline recommendations, integrating qualitative, semiquantitative and quantitative parameters[13]. MR severity was quantitatively assessed according to current recommendations using a multiparametric approach, including quantification of the effective regurgitant orifice area (EROA) and MR regurgitant volume[4,13].

Follow-up and Study Endpoint

Follow-up began from the date of mitral valve surgery. The primary endpoint of the study was post-surgical all-cause mortality. Follow-up data were complete for all patients and were included up to the last date of follow-up.

Statistical Analysis

Categorical variables are expressed as numbers and percentages, while continuous variables are presented as median and interquartile range (IQR). To evaluate the prognostic importance of LAVI, atrial fibrillation, PASP, TR and an increasing number of secondary outcome determinants (LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR) indicative of atrial, pulmonary and right ventricular consequences of isolated DMR, the population was divided into four groups: Group I – No secondary outcome determinants; Group II – One secondary outcome determinant, Group III – Two secondary outcome determinants, Group IV – Three or four secondary outcome determinants. The decision to add the number of secondary outcome determinants together to identify high-risk phenotypes was pre-specified. Pearson's correlation was utilized to evaluate for multicollinearity between secondary outcome determinants (Table S1). Cumulative survival according to group was calculated using the Kaplan–Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was used to evaluate the association of each secondary outcome determinant and for an increasing number of parameters and all-cause mortality. Multivariable Cox proportional hazards regression analyses were performed using two levels of adjustment: first, adjusted for baseline clinical characteristics: age, sex, EuroSCORE II, symptoms (core model); second, adjusting additionally for prognostically important echocardiographic factors: LVEF, LV ESD and MR grade (comprehensive model). Hazard ratio (HR) and 95% confidence intervals (CIs) were reported for each model. The proportional hazards assumption was verified through the evaluation of scaled Schoenfeld residuals. To compare the prognostic value of the number of secondary outcome determinants with Class I surgical indications (the presence of symptoms, LVEF ≤60% and LV ESD ≥40mm)[5] and an increasing number of Class I indications, the discriminative value of each model was assessed with the C-index. The rank correlation U-statistic for paired censored data was used to compare the concordance of each model with the model including the number of secondary outcome determinants[14]. All tests were two-sided and P-values <0.05 were considered statistically significant. Statistical analysis was performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 2276 patients meeting study eligibility criteria from 5 international centres were included. The baseline characteristics of the population according to number of secondary outcome determinants are presented in Table 1. A total of 874 patients (38.4%) had no secondary outcome determinants, 795 (34.9%) had one secondary outcome determinant, 391 (17.2%) had two secondary outcome determinants and 216 (9.5%) had three or four secondary outcome determinants. Patients with an increasing number of secondary outcome determinants were older, more symptomatic, more likely to be male and had a higher EuroSCORE II. In addition, patients with one or more secondary outcome determinants had larger EROAs and MR regurgitant volumes than those with no secondary outcome determinants, indicating an association with increasing MR severity. The proportion of patients using various medications is provided in Table S2.

Prognostic value of LAVI, atrial fibrillation, PASP and TR for post-surgical survival in DMR

Over a median follow-up of 5.6 (3.6 to 8.7) years, 278 patients (12.2%) died. A total of 2083 (92%) patients underwent mitral valve repair and 183 (8%) underwent mitral valve replacement. Post-operative mortality at 30 days was 0.83%. Concomitant tricuspid valve repair was performed in 445 (19.5%) of patients. All secondary outcome determinants (LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR) were significantly associated with all-cause mortality on univariable Cox regression analyses (P<0.0001 for all). In addition, in multivariable Cox regression proportional hazard core models adjusted for age, sex, EuroSCORE II and symptoms, LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR were all significantly associated with post-operative mortality (Table 2). In multivariable Cox regression models further adjusted for LVEF, LV ESD and MR grade, an independent association between post-operative all-cause mortality and LAVI ≥60ml/m^2 (HR 1.38, 95% CI 1.07 to 1.78, P=0.014), atrial fibrillation (HR 1.46, 95% CI 1.14 to 1.89, P=0.003), PASP ≥50mmHg (HR 1.50, 95% CI 1.15 to 1.97, P=0.003) and the presence of moderate to severe TR (HR 1.46, 95% CI 1.09 to 1.96, P=0.010) was retained. In a sensitivity analysis, following further adjustment for specific comorbidities (hypertension, diabetes mellitus and COPD), results were consistent with the main analysis for each model (Table S3).

Table 1: Patient and Echocardiographic Characteristics Divided According to Number of Secondary Outcome Determinants

Variable	Overall N = 2,276	No Secondary Outcome Determinants* N = 874	One Secondary Outcome Determinant* N = 795	Two Secondary Outcome Determinants* N = 391	Three or Four Secondary Outcome Determinants* N = 216	P-value
Age, years	65 (55 to 73)	60 (51 to 69)	64 (55 to 72)	69 (60 to 75)	76 (69 to 81)	<0.001
Male Sex	726 (32%)	251 (29%)	241 (30%)	139 (36%)	95 (44%)	<0.001
Current Smoker	534 (40%)	233 (40%)	181 (41%)	83 (37%)	37 (41%)	0.74
COPD	96 (4.3%)	30 (3.4%)	31 (4.0%)	20 (5.2%)	15 (7.2%)	0.079
Diabetes mellitus	120 (5.3%)	42 (4.8%)	35 (4.5%)	17 (4.4%)	26 (12%)	<0.001
Hypertension	626 (35%)	261 (34%)	199 (34%)	105 (36%)	61 (45%)	0.082
Systolic Blood Pressure, mmHg	120 (110 to 130)	122 (110 to 130)	120 (110 to 13)	120 (110 to 130)	121 (110 to 137)	0.36
Symptoms	1,379 (61%)	474 (54%)	459 (58%)	285 (73%)	161 (75%)	<0.001
EuroSCORE II	0.82 (0.64 to 1.21)	0.69 (0.59 to 0.91)	0.82 (0.62 to 1.14)	1.09 (0.80 to 1.49)	1.47 (1.12 to 2.03)	<0.001
LV ejection fraction, %	65 (61 to 70)	66 (62 to 70)	66 (62 to 70)	65 (60 to 70)	64 (58 to 69)	<0.001
LV end-systolic diameter, mm	35 (31 to 39)	34 (30 to 38)	36 (32 to 40)	36 (32 to 41)	36 (32 to 41)	<0.001
EROA, mm^2	45 (35 to 58)	42 (32 to 53)	46 (37 to 59)	48 (38 to 64)	47 (34 to 61)	<0.001
MR regurgitant volume, ml	69 (54 to 86)	65 (50 to 82)	73 (58 to 92)	70 (55 to 88)	70 (55 to 85)	<0.001
LA volume indexed, ml/m^2	58 (44 to 76)	45 (37 to 51)	66 (53 to 80)	75 (62 to 94)	81 (68 to 99)	<0.001
PA systolic pressure, mmHg	36 (30 to 48)	30 (27 to 36)	36 (30 to 45)	50 (37 to 60)	59 (52 to 67)	<0.001
Moderate or severe TR	321 (14%)	0 (0%)	61 (7.7%)	90 (23%)	170 (79%)	<0.001
Data presented as median (25% to 75%); n (%)						
*Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR						

COPD = chronic obstructive pulmonary disease, EROA = effective regurgitation orifice area, LA = left atrial, LV = left ventricular, MR = mitral regurgitation, PA = pulmonary artery, TR = tricuspid regurgitation

Table 2: Univariable and multivariable hazard ratio (HR) for mortality for LAVI, PASP, atrial fibrillation and TR severity

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	LAVI ≥60 ml/m^2	1.64 (1.30 to 2.08)	<0.0001
	PASP ≥50 mmHg	2.67 (2.10 to 3.41)	<0.0001
	Atrial fibrillation	2.53 (1.99 to 3.22)	<0.0001
	Moderate or severe TR	2.57 (1.96 to 3.37)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	LAVI ≥60 ml/m^2	1.31 (1.03 to 1.67)	0.027
	PASP ≥50 mmHg	1.45 (1.12 to 1.87)	0.005
	Atrial fibrillation	1.52 (1.19 to 1.94)	0.0008
	Moderate or severe TR	1.45 (1.09 to 1.92)	0.011
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	LAVI ≥60 ml/m^2	1.38 (1.07 to 1.78)	0.014
	PASP ≥50 mmHg	1.50 (1.15 to 1.97)	0.003
	Atrial fibrillation	1.46 (1.14 to 1.89)	0.003
	Moderate or severe TR	1.46 (1.09 to 1.96)	0.010

ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

Prognostic implications of the number of secondary outcome determinants

Overall post-operative survival at 5-years was markedly different according to the number of secondary outcome determinants: 96.3% for patients with no secondary outcome determinants, versus 93.6%, 88.8% and 72.1% for patients with one, two and three or four secondary outcome determinants, respectively (P<0.0001, Figure 1). In the multivariable Cox regression proportional hazard core model adjusted for age, sex, EuroSCORE II and symptoms, the number of secondary outcome determinants remained associated with all-cause mortality (Table 3). In addition, in a comprehensive model with further adjustment for LVEF, LV ESD and MR grade, the number of secondary outcome determinants was independently associated with all-cause mortality, with adjusted HRs of 1.56 (95% CI 1.11 to 2.20, P=0.011), 1.78 (95% CI 1.23 to 2.58, P=0.002) and 2.58 (95% CI 1.73 to 3.83, P<0.0001) for patients with one, two and three or four secondary outcome determinants, respectively, compared to those with no secondary outcome determinants (Table 3, Figure 2). When added to the comprehensive multivariable Cox regression model, the year of surgery was significantly associated with reduced all-cause mortality (HR 0.96 per year, 95% CI 0.93 to 1.00, P=0.031), while the number of secondary outcome determinants remained significantly associated with the primary endpoint, with adjusted HRs of 1.58 (95% CI 1.12 to 2.23, P=0.009), 1.80 (95% CI 1.24 to 2.61, P=0.002) and 2.60 (95% CI 1.75 to 3.87, P<0.0001) for patients with one, two and three or four secondary outcome determinants, respectively. There was no significant interaction between the year of surgery and the number of secondary outcome determinants ($P_{interaction}$=0.98). In a sensitivity analysis, following additional adjustment for spe-

cific comorbidities (hypertension, diabetes mellitus and COPD), results were consistent with the main analysis (Table S4). The net reclassification improvement according to ≥1, 2 and 3 secondary outcome determinants is demonstrated in Table S5.

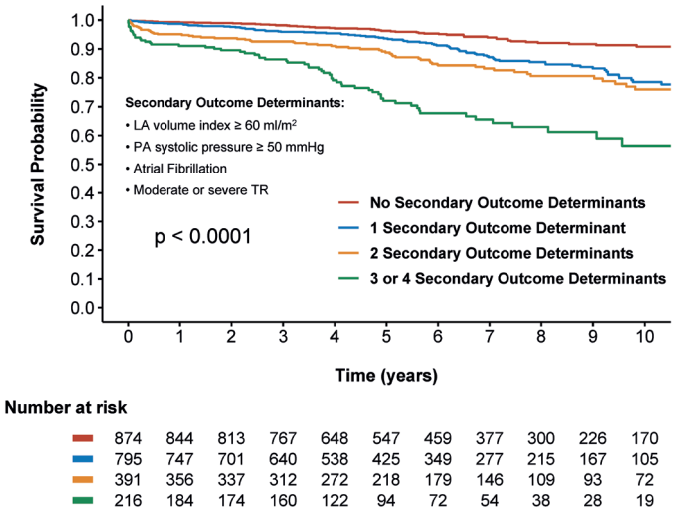

Figure 1: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR.
LA = left atrial, DMR = degenerative mitral regurgitation, PA = pulmonary artery, TR = tricuspid regurgitation

Prognostic implications of the number of secondary outcome determinants according to patient subgroup

Further sensitivity analyses were performed to evaluate the prognostic implications of the number of secondary outcome determinants according to patient subgroup (Figure 3, Figures S1-S7). Analyses demonstrated the consistent prognostic value of the number of secondary outcome determinants in patient subgroups divided according to age (Figure S1), LVEF (Figure S2), LV ESD (Figure S3), the presence of symptoms (Figure S4) and the presence of any Class I surgical indication (Figure S7) (P for interaction >0.05 for all, Figure 3). However, while the presence of one or two secondary outcome determinants was associated with all-cause mortality in patients of lower surgical risk (EuroSCORE II <1%), it was not significantly associated with mortality for the patient subgroup of higher (EuroSCORE II ≥1%) surgical risk (HR 1.10, 95% CI 0.77 to 1.58, P=0.60; $P_{interaction}$=0.017, Figure 3). No significant interaction between EuroSCORE II group and the presence of three or four secondary outcome determinants was observed ($P_{interaction}$=0.50), suggesting that this phenotype has a similar association with mortality regardless of surgical risk (Figure S5). There was no significant interaction between mitral valve replacement versus repair group and the number of secondary outcome determinants ($P_{interaction}$=0.13).

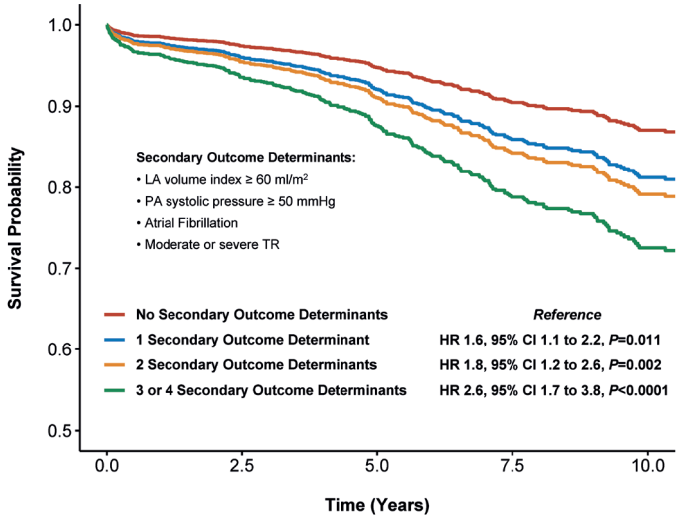

Figure 2: Adjusted survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR following adjustment for age, EuroSCORE II, symptoms, LV ejection fraction, LV end-systolic diameter and DMR severity.
LA = left atrial, LV = left ventricular, DMR = degenerative mitral regurgitation, PA = pulmonary artery, TR = tricuspid regurgitation

Superior Prognostic Value of the Number of Secondary Outcome Determinants

To compare the prognostic value of the number of secondary outcome determinants with Class I guideline recommendations for surgery, model discrimination was evaluated. A basal model (comprised of age and EuroSCORE II) incorporating the number of secondary outcome determinants demonstrated a higher C-index value (C-index 0.782, 95% CI 0.752 to 0.811) than models incorporating the presence of symptoms (C-index 0.772, 95% CI 0.743 to 0.802), LVEF ≤60% (C-index 0.773, 95% CI 0.743 to 0.803), LV ESD ≥40mm (C-index 0.771, 95% CI 0.741 to 0.801), or the number of Class I indications combined (C-index 0.776, 95% CI 0.746 to 0.806). The model incorporating the number of secondary outcome determinants was significantly more concordant with all-cause post-operative mortality than models including traditional Class I indications alone (the presence of symptoms (P=0.0003), or LVEF ≤60% (P=0.006), or LVESD ≥40mm (P=0.014)), with no significant difference in concordance compared to the model accounting for an increasing number of Class I indications (P=0.71).

Table 3: Univariable and multivariable hazard ratio (HR) for mortality for the number of secondary outcome determinants

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.90 (1.36 to 2.65)	0.0001
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.74 (1.93 to 3.89)	<0.0001
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	6.40 (4.50 to 9.11)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.45 (1.04 to 2.03)	0.027
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.69 (1.18 to 2.42)	0.004
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.43 (1.67 to 3.54)	<0.0001
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.56 (1.11 to 2.20)	0.011
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.78 (1.23 to 2.58)	0.002
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.58 (1.73 to 3.83)	<0.0001

AF = atrial fibrillation, ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

DISCUSSION

In this large, international, multicenter study including 2276 patients with isolated DMR undergoing surgery, we observed that: (i) LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg and the presence of moderate to severe TR were independently associated with poor outcome even in a selected patient cohort undergoing surgery for severe DMR, (ii) an increasing number of secondary outcome determinants was independently associated with all-cause post-operative mortality, following adjustment for Class I surgical indications including symptoms, EuroSCORE II, age and quantified DMR severity, and (iii) accounting for the number of secondary outcome determinants demonstrated significantly better discrimination for post-surgical survival than traditional Class I indications for surgery.

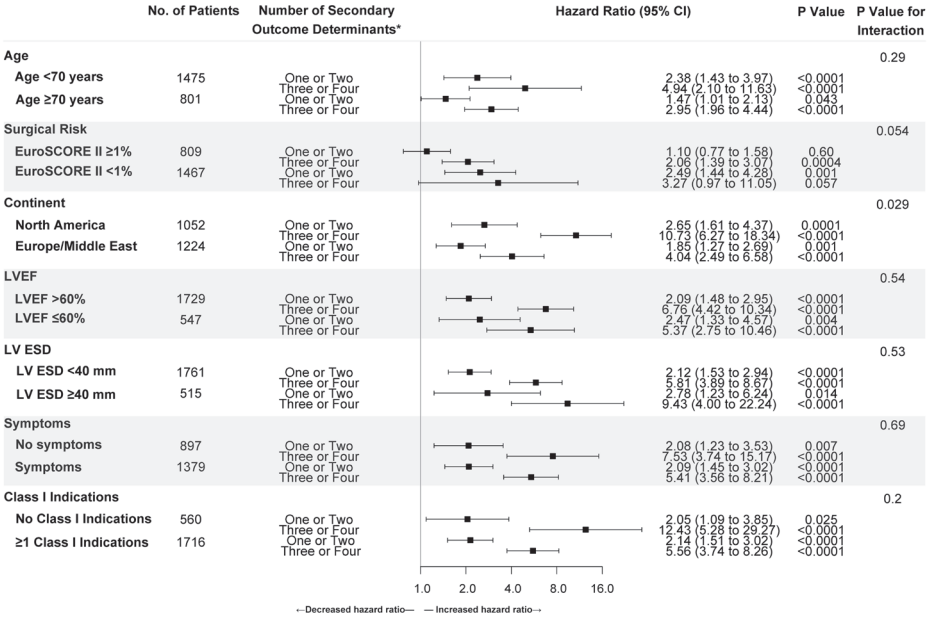

Figure 3: Association of the Number of Secondary Outcome Determinants with Mortality in Selected Sub-groups of Patients with DMR.

The number of secondary outcome determinants were related to outcome across subgroups according to age, surgical risk, geographical location, LVEF, LV ESD, symptoms, and Class I surgical indications.

*Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR. Hazard ratios are in reference to patients with no secondary outcome determinants.

CI=confidence interval, DMR = degenerative mitral regurgitation, ESD = end-systolic diameter, LAVI = left atrial volume index, LV=left ventricular, LVEF=left ventricular ejection fraction, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation.

Prognostic validation of left atrial, pulmonary arterial and tricuspid valve remodelling in DMR

The present study demonstrates the independent association of LAVI, atrial fibrillation, PASP and the presence of moderate to severe TR with post-surgical clinical outcome in a large, unique, contemporary, multicenter registry of patients with DMR due to mitral valve prolapse and/or flail leaflet, providing additional supporting data for guideline recommendations regarding surgical timing[4]. Indeed, previous evidence for the association of LA enlargement with post-operative mortality was limited to either smaller studies or to a larger, real-world cohort from a single center[9,15,16]. Conversely, the present study, derived from an expansive international cohort, confirms that LAVI ≥60ml/m^2 retains independent prognostic value, supporting the wider generalisability of the findings from prior studies. Likewise, the prognostic importance of atrial fibrillation in DMR has remained somewhat contentious, with several studies showing no significant association with outcome[17,18], although other larger cohorts have shown an important relationship with mortality[10,19]. In the present study, atrial fibrillation was

independently related to post-operative mortality, strengthening the evidence-base for inclusion in guideline recommendations. In addition, our study confirms the findings of previous studies[20,21] demonstrating that increased PASP is associated with reduced post-surgical survival in patients with DMR. The present study also suggests that moderate or severe tricuspid regurgitation is related to post-operative mortality in patients with severe DMR, in accordance with recently published data[8]. Current guidelines suggest concomitant tricuspid valve repair of mild or moderate TR in the presence of tricuspid annular dilation of ≥40mm[5]. However, in a recent multicenter trial, 401 patients with moderate TR or annular dilatation undergoing mitral-valve surgery were randomised to tricuspid valve repair and mitral valve surgery, or mitral valve surgery alone[22]. This study demonstrated a significant reduction in progression to severe TR, although at the cost of a significant increase in the requirement for permanent pacemaker implantation. Longer term follow-up of the participants in this trial and additional research is required to determine how the presence of moderate or severe TR in severe DMR should influence clinical management, including intervention with tricuspid valve surgery/tricuspid transcatheter repair and for the timing of mitral valve surgery.

Prognostic Implications of the Number of Secondary Outcome Determinants

The present study shows that an increasing number of secondary outcome determinants is independently associated with increased long-term post-surgical mortality. It is probable that an increasing number of secondary outcome determinants identifies patients with more profound atrial, pulmonary and right ventricular consequences of isolated DMR, either due to more hemodynamically severe DMR or a reduced capacity to adapt to the associated volume overload. In severe DMR, the regurgitant jet causes substantial left atrial volume overload and may directly result in progressive left atrial dilatation, reduced compliance, fibrillation and eventually, elevation of left atrial pressures. Backward transmission of elevated left atrial pressure can result in increased pulmonary venous and arterial pressures. Initially, this is a passive process characterised by high left atrial and pulmonary capillary wedge pressures and low pulmonary vascular resistance[23]. However, chronic and/or recurrent increases in left atrial pressure may induce irreversible remodelling of the alveolar capillary membrane and pathological changes in the pulmonary veins and arteries, leading to an elevation of transpulmonary gradient, pulmonary vascular resistance and combined pre-capillary and post-capillary pulmonary hypertension[11]. Progressive right ventricular dilation and hypertrophy secondary to pulmonary hypertension is frequently associated with progressive tricuspid annular dilatation and papillary muscle tethering, and an increase in secondary tricuspid regurgitation severity[11]. Importantly, in patients with DMR, these pathophysiological changes can be observed even in the absence of overt left ventricular systolic or

diastolic dysfunction[23]. Therefore, in accordance with the findings of the present study, it is logical that even when adjusting for LV function, a phenotype of increased left atrial, pulmonary, and right ventricular damage would be associated with disease progression and reduced long-term survival. Furthermore, this association was also observed in patient subgroups with preserved and reduced LV function, suggesting that this phenotype should be considered as a potentially important marker of disease progression, regardless of the presence of LV dysfunction. Moreover, only the presence of three or four secondary outcome determinants was associated with outcome in patients with higher surgical risk (EuroSCORE ≥1%), suggesting that identification of this high-risk phenotype may be particularly important for the risk stratification of this patient group.

Clinical Implications

The present study provides additional evidence supporting current guideline recommendations[4] for surgical intervention for patients with severe DMR and either LAVI ≥60ml/m^2, atrial fibrillation or PASP ≥50mmHg. In addition, this study has demonstrated that the identification of a progressively higher risk cardiac phenotype with increased left atrial, pulmonary, and right ventricular consequences of DMR may better stratify risk again, providing better discrimination than well-established Class I surgical indications (the presence of symptoms, LVEF ≤60% and LV ESD ≥40mm) that are strongly recommended to be used, even in isolation, as triggers for surgery due to their association with poor outcome[4,5]. Furthermore, when compared to the number of Class I indications combined, accounting for the number of secondary outcome determinants provided similar and numerically higher indices of discrimination. Indeed, the presence of three or more secondary outcome determinants likely suggests that important haemodynamic consequences of progressive DMR have occurred, and earlier intervention, even in the absence of symptoms or LV dysfunction, may be crucial. However, surgery is probably warranted prior to the development of a cardiac phenotype with three or more secondary outcome determinants, as the prognosis of this subgroup is exceptionally poor, with an estimated mortality of 28% at 5 years, despite surgical intervention. In addition, this study demonstrates that the number of secondary outcome determinants has prognostic value in patients with and without Class I indications for surgery. In clinical practice it is not uncommon to have borderline Class I indications for intervention (i.e., very mild symptoms, LVEF of 59 to 61%, LV ESD 39 to 41 mm) or valvular properties which suggests a lower probability of successful valve repair. In these circumstances, identification of patients with an increasing number of secondary outcome determinants could strengthen any decision to intervene. This study also demonstrates that a paradigm shift in guideline recommendations could be useful: In addition to the well-established thresholds of individual imaging parameters for intervention (LAVI ≥60ml/m^2, atrial fibrillation, PASP ≥50mmHg, LVEF ≤60% and LV ESD ≥40mm), accounting for

the overall cardiac phenotype represented by the presence of multiple prognostically important parameters, may improve patient selection for earlier surgery. Indeed, those with multiple prognostically important parameters probably warrant a stronger recommendation for intervention than any single parameter in isolation.

Limitations

The study is subject to all of the inherent limitations of an observational, non-randomised design, although representing the largest international cohort of patients with isolated DMR undergoing surgery with long-term post-operative follow-up. Definitive recommendations regarding surgical timing would ideally be made following randomised clinical trials enrolling selected patient subgroups (i.e., patients with LAVI ≥60ml/m^2 or with 3 or more secondary outcome determinants). Nonetheless, contemporary guideline recommendations regarding the timing of surgical intervention in DMR are currently only based on strong observational data, and it remains unlikely that such trials will ever be conducted[4,5]. While study cohort identification was retrospective, all measurements were performed prospectively by numerous operators and recorded electronically, reflecting prospective DMR evaluation and quantitation in routine practice with transthoracic echocardiography. This may allow for increased generalizability of the results into clinical practice compared with core laboratory evaluation, which while offering improved uniformity of evaluation, has more limited generalizability. In addition, data pertaining to the cause of death and incident heart failure were not available, precluding these analyses. However, any excess in incident heart failure or cardiovascular death would likely translate into an increase in all-cause mortality. Data regarding post-operative stroke, residual MR, frequency of concomitant AF ablation and mitral valve reintervention were not available, precluding additional analyses. In addition, this study was likely inadequately powered to detect between group differences for mitral valve repair versus replacement. Further studies investigating the prognostic value of Class I indications and secondary outcome determinants are required for patients undergoing mitral valve replacement and in patients with multiple and/or mixed valvular disease. In addition, more research is required to determine if healthcare systems can provide for the increasing number of patients with severe DMR who may benefit from earlier surgery.

CONCLUSION

An increasing number of secondary outcome determinants was independently associated with post-surgical survival in patients with DMR and demonstrated significantly better discrimination than traditional Class I indications for surgery. Randomised con-

trolled trials are needed to determine if patients with severe DMR who demonstrate a cardiac phenotype with an increasing number of secondary outcome determinants would benefit from earlier surgery.

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SUPPLEMENTARY MATERIAL

Table S1: Correlation between Secondary Outcome Determinants

Parameters	Pearson *R* (95% confidence interval)
Atrial fibrillation and moderate or severe TR	0.19 (0.15 to 0.23)
Atrial fibrillation and LAVI ≥60 ml/m^2	0.16 (0.12 to 0.20)
Atrial fibrillation and PASP ≥50 mmHg	0.12 (0.08 to 0.16)
Moderate or severe TR and LAVI ≥60 ml/m^2	0.12 (0.08 to 0.16)
Moderate or severe TR and PASP ≥50 mmHg	0.30 (0.26 to 0.34)
LAVI ≥60 ml/m^2 and PASP ≥50 mmHg	0.16 (0.12 to 0.20)

LAVI = left atrial volume index; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation

Table S2: Proportion of Patients on Specific Medications

Medication	Percentage of Population
Vasodilating antihypertensives	38.4%
Diuretics	29.0%
Digoxin	8.1%

Table S3: Univariable and multivariable hazard ratio (HR) for mortality for LAVI, PASP, atrial fibrillation and TR severity

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	LAVI ≥60 ml/m^2	1.64 (1.30 to 2.08)	<0.0001
	PASP ≥50 mmHg	2.67 (2.10 to 3.41)	<0.0001
	Atrial fibrillation	2.53 (1.99 to 3.22)	<0.0001
	Moderate or severe TR	2.57 (1.96 to 3.37)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	LAVI ≥60 ml/m^2	1.31 (1.03 to 1.67)	0.027
	PASP ≥50 mmHg	1.45 (1.12 to 1.87)	0.005
	Atrial fibrillation	1.52 (1.19 to 1.94)	0.0008
	Moderate or severe TR	1.45 (1.09 to 1.92)	0.011
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	LAVI ≥60 ml/m^2	1.38 (1.07 to 1.78)	0.014
	PASP ≥50 mmHg	1.50 (1.15 to 1.97)	0.003
	Atrial fibrillation	1.46 (1.14 to 1.89)	0.003
	Moderate or severe TR	1.46 (1.09 to 1.96)	0.010
Further adjustment for COPD, hypertension and diabetes mellitus (extended comorbidity adjusted model)	LAVI ≥60 ml/m^2	1.52 (1.16 to 2.00)	0.002
	PASP ≥50 mmHg	1.46 (1.08 to 1.98)	0.013
	Atrial fibrillation	1.53 (1.16 to 2.01)	0.002
	Moderate or severe TR	1.66 (1.20 to 2.31)	0.002

COPD = chronic obstructive pulmonary disease, ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

Table S4: Univariable and multivariable hazard ratio (HR) for mortality for the number of secondary outcome determinants

	Secondary Outcome Determinant Subgroups	Hazard Ratio (95% CI)	P-value
Univariable	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.90 (1.36 to 2.65)	0.0001
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.74 (1.93 to 3.89)	<0.0001
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	6.40 (4.50 to 9.11)	<0.0001
Adjusted for age, sex, EuroSCORE II, symptoms (core model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.45 (1.04 to 2.03)	0.027
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.69 (1.18 to 2.42)	0.004
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.43 (1.67 to 3.54)	<0.0001
Further adjustment for LVEF, LV ESD and MR grade (comprehensive model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.56 (1.11 to 2.20)	0.011
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.78 (1.23 to 2.58)	0.002
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	2.58 (1.73 to 3.83)	<0.0001
Further adjustment for COPD, hypertension and diabetes mellitus (extended comorbidity adjusted model)	None of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	*Reference*	
	1 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.65 (1.15 to 2.37)	0.006
	2 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	1.78 (1.20 to 2.65)	0.005
	3 or 4 of LAVI ≥60 ml/m^2, PASP ≥50 mmHg, AF, moderate or severe TR	3.02 (1.96 to 4.66)	<0.0001

AF = atrial fibrillation, COPD = chronic obstructive pulmonary disease, ESD = end-systolic diameter, LAVI = left atrial volume index, LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

Table S5: Net Reclassification Improvement over comprehensive multivariable model according to secondary outcome determinants

	NRI for 2.5% threshold (95% CI)	NRI for 5.0% threshold (95% CI)	NRI for 7.5% threshold (95% CI)
≥1 secondary outcome determinant	0.16 (-0.05 to 0.36)	0.00 (-0.03 to 0.08)	-0.01 (-0.04 to 0.02)
≥2 secondary outcome determinants	0.33 (0.10 to 0.39)	0.16 (-0.03 to 0.37)	0.00 (-0.03 to 0.25)
≥3 secondary outcome determinants	0.07 (0.00 to 0.18)	0.16 (0.07 to 0.23)	0.17 (0.00 to 0.23)

NRI = Net Reclassification Improvement

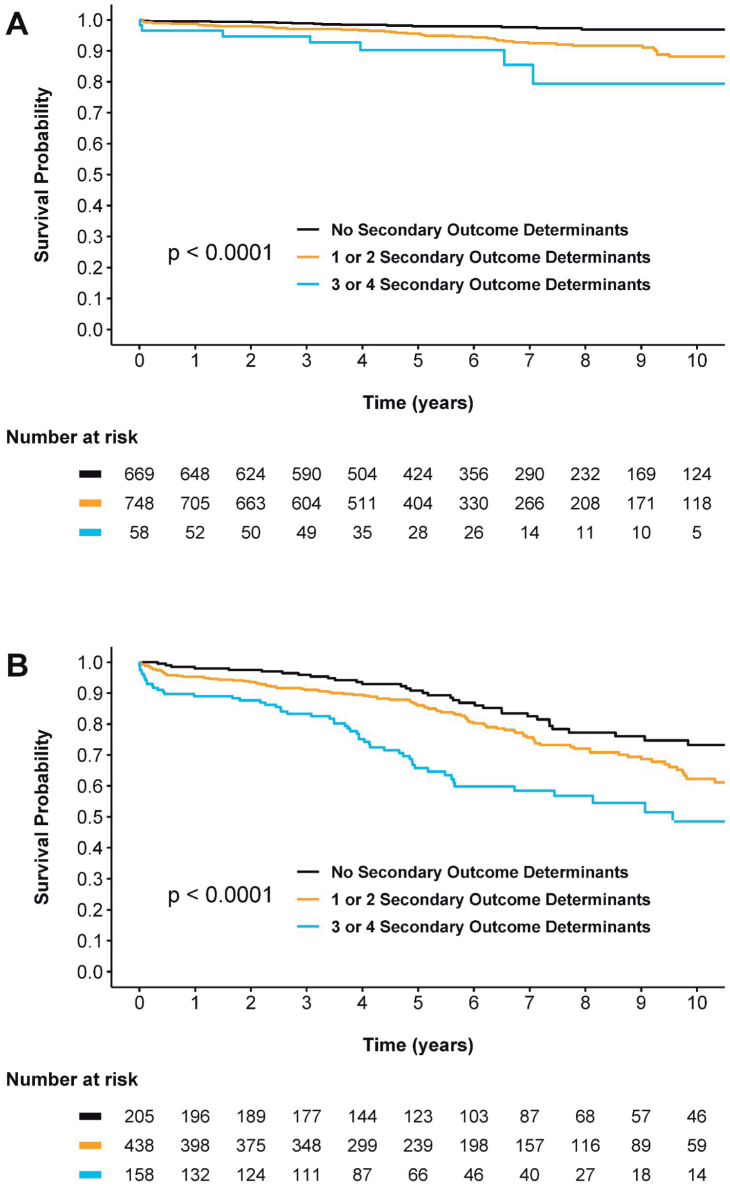

Figure S1: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to age. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups <70 years (A) and ≥70 years (B). Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

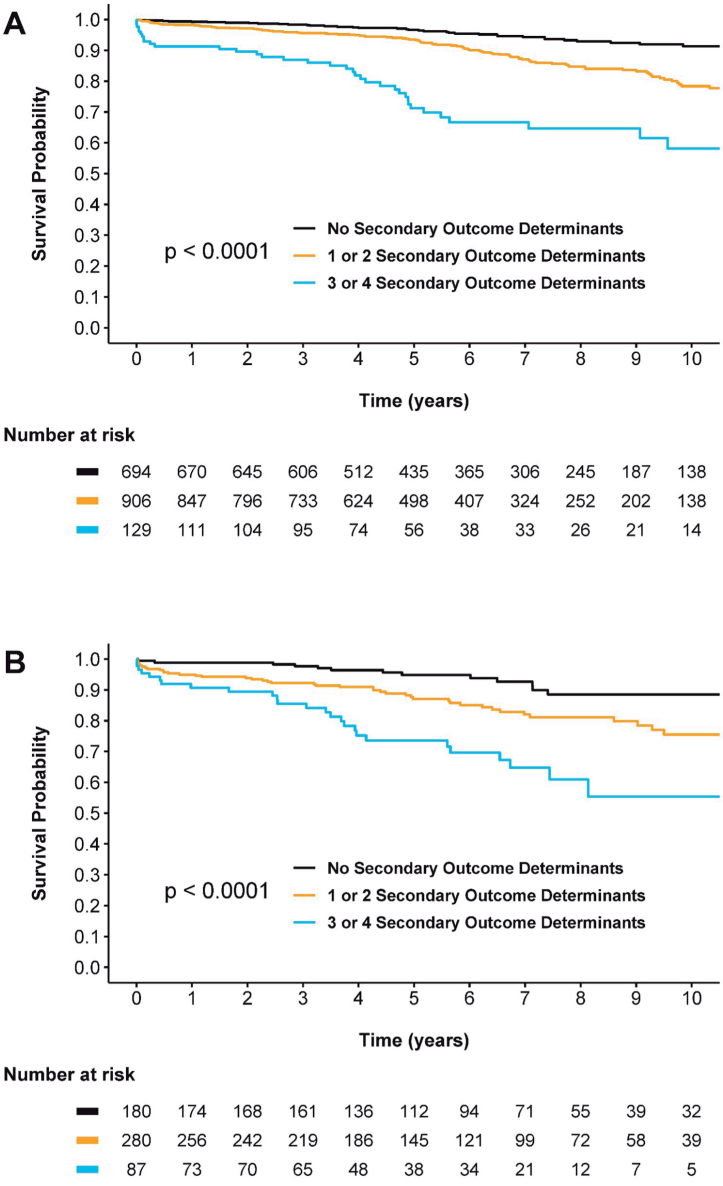

Figure S2: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to LVEF. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with a LVEF >60% (A) and ≤60% (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, LVEF = left ventricular ejection fraction, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

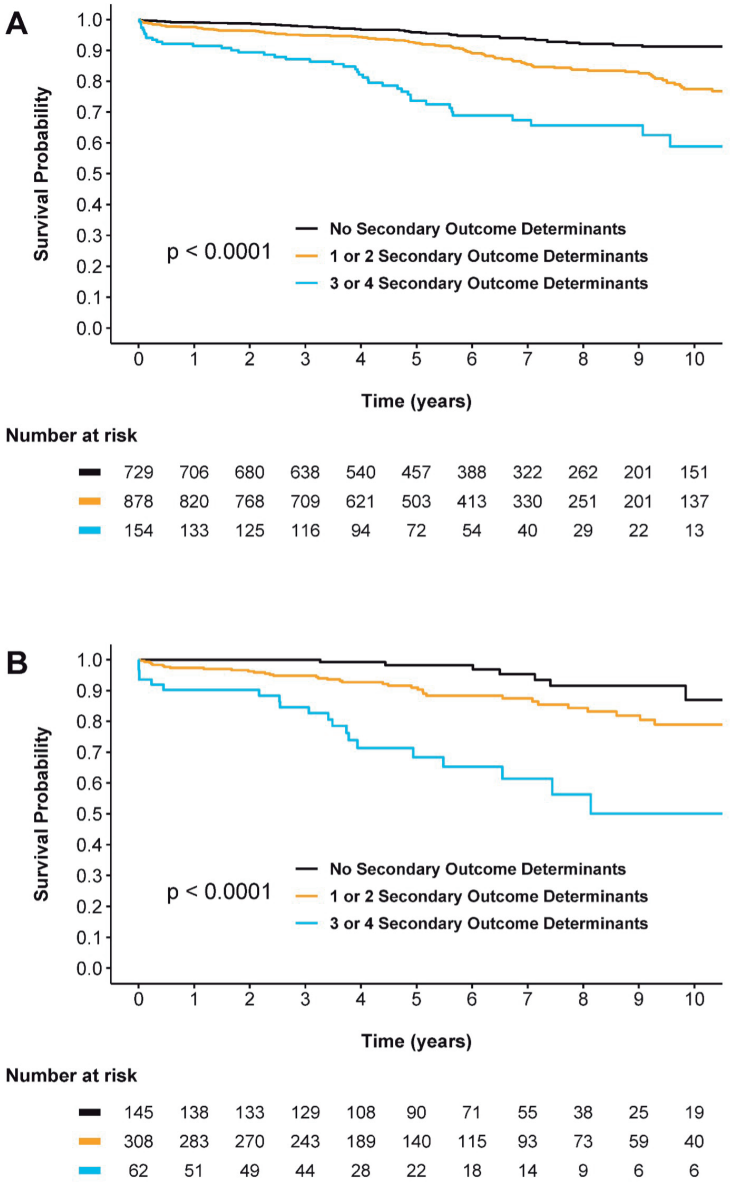

Figure S3: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to LV ESD. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with a LVESD <40 mm (A) and ≥40 mm (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, LV ESD = left ventricular end-systolic diameter, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

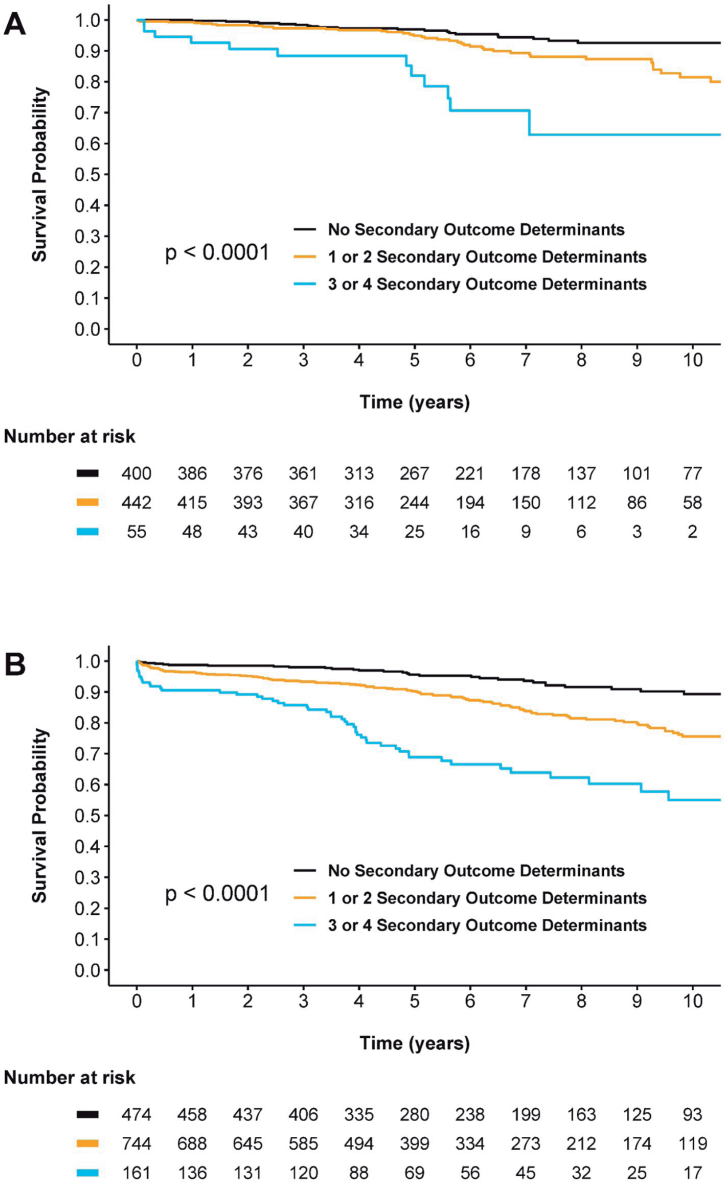

Figure S4: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to symptoms. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups without symptoms (A) and with symptoms (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

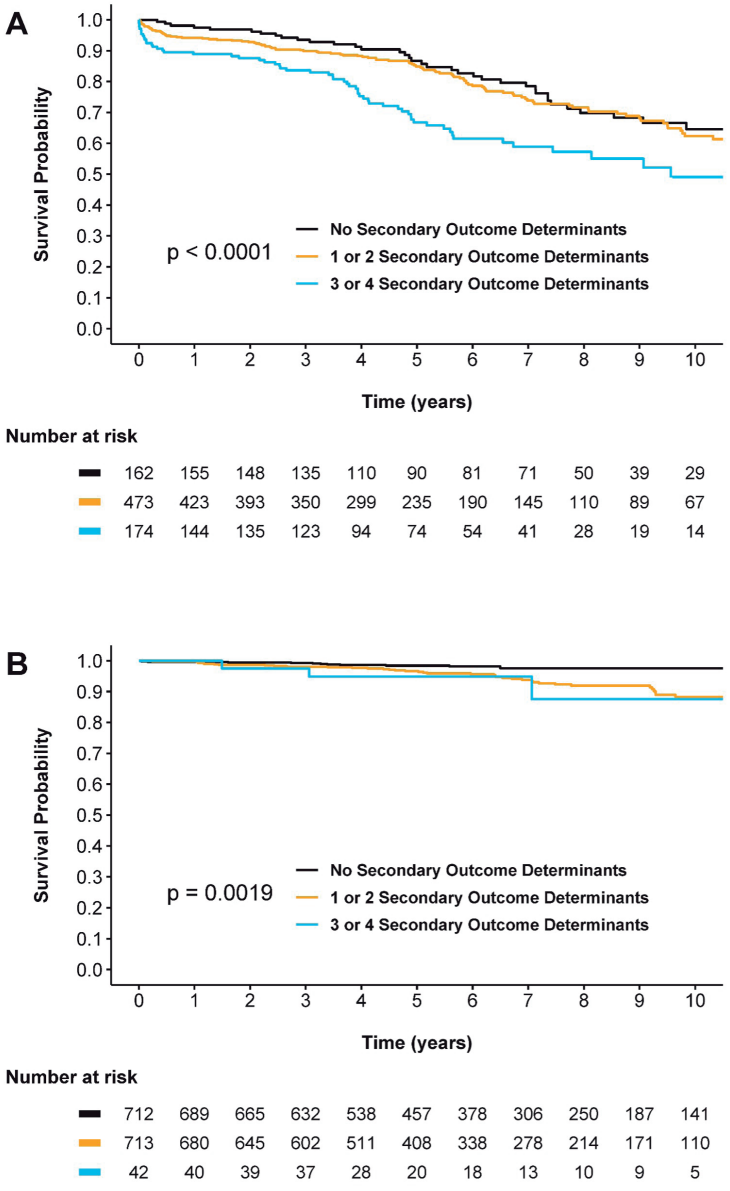

Figure S5: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to EuroSCORE II. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with a EuroSCORE II ≥1% (A) and <1% (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

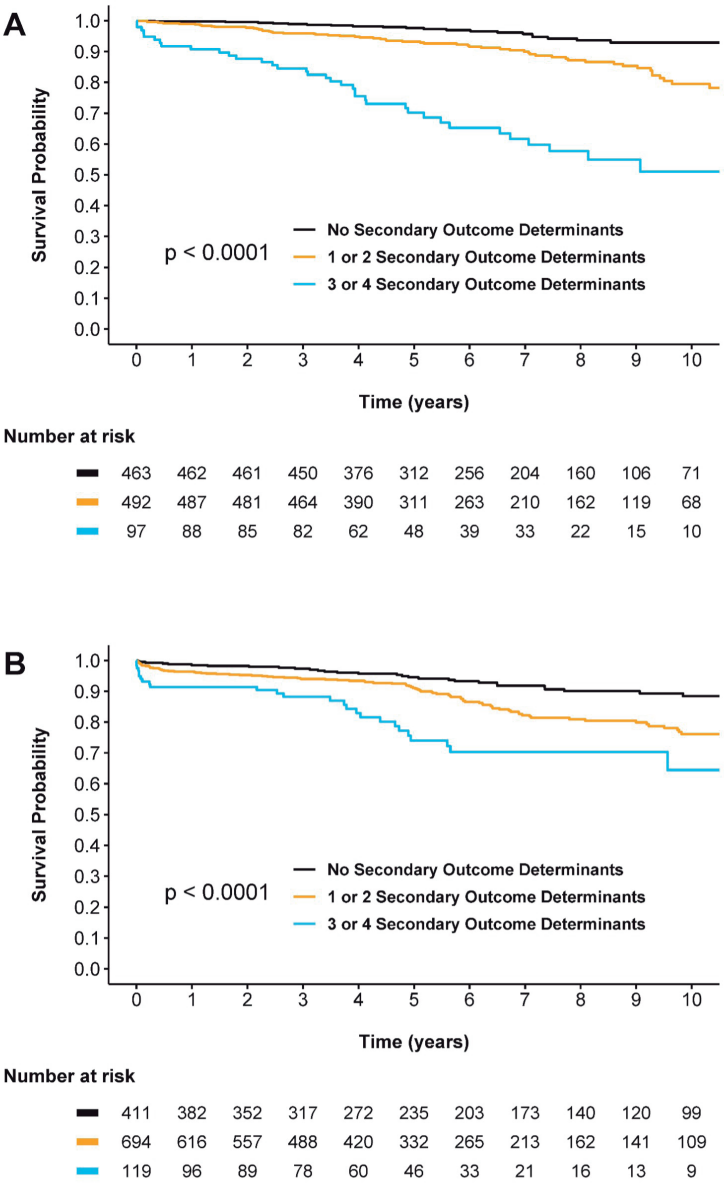

Figure S6: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to geographical location. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups from North America (A) and from Europe/Middle East (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

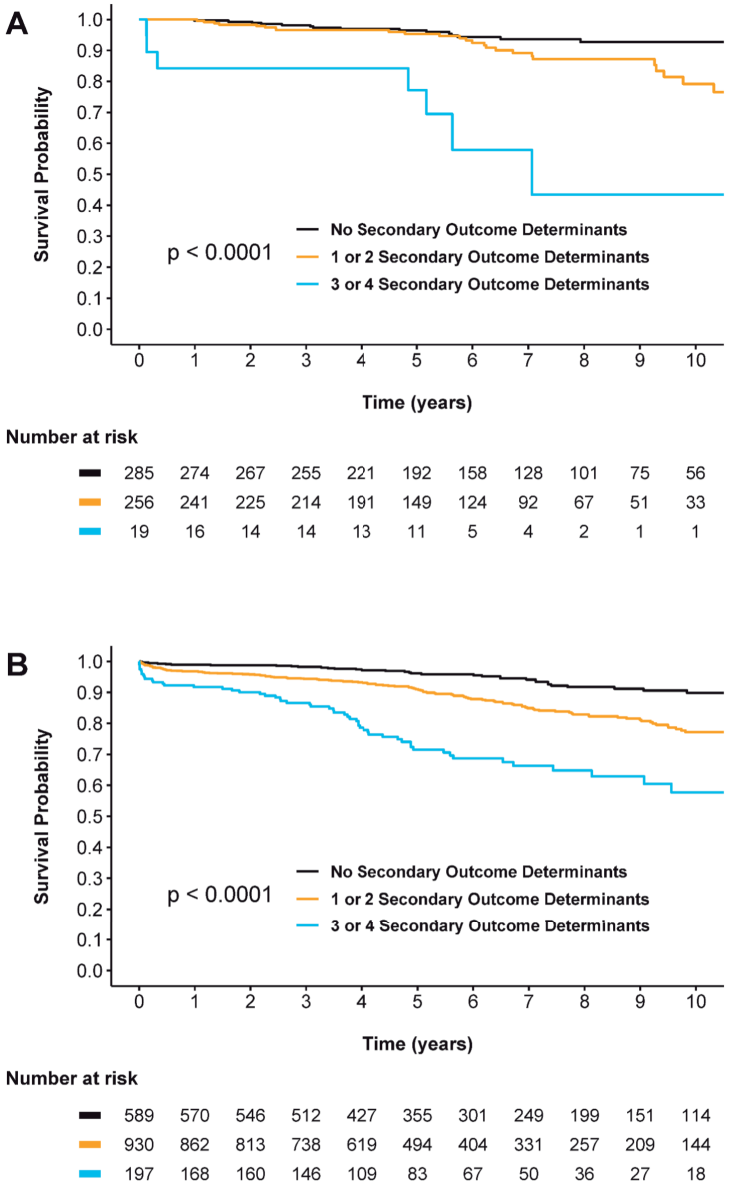

Figure S7: Kaplan Meier survival curves demonstrating the association between the number of secondary outcome determinants and all-cause mortality in DMR according to the presence of a Class I indication for surgery. Increasing number of secondary outcome determinants was associated with worse post-operative survival in patients with DMR in subgroups with no Class I indications (A) and with ≥1 Class I indications (B).

Secondary Outcome Determinants include atrial fibrillation, LAVI ≥60ml/m^2, PASP ≥50mmHg and/or the presence of moderate to severe TR.

DMR = degenerative mitral regurgitation, LA = left atrial volume index, PASP = pulmonary artery systolic pressure, TR = tricuspid regurgitation

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SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY OF PART I: Non-invasive right ventricular myocardial work analysis

Contemporary echocardiographic methods of evaluating right ventricular (RV) function, including RV longitudinal strain and tricuspid annular plane systolic excursion (TAPSE), do not adequately account for RV afterload and mechanical efficiency in their quantification. In **chapter 2**, a novel echocardiographic method of evaluating RV function with RV pressure strain loops was developed, utilizing software originally designed for the assessment of left ventricular (LV) function. In 22 patients with heart failure and reduced ejection fraction undergoing right heart catheterization, the evaluation of RV myocardial work derived from RV pressure-strain loops was demonstrated to be feasible, with excellent reproducibility. Furthermore, two parameters of RV myocardial work, RV global work index and RV global constructive work, but not conventional parameters of RV systolic function (RV longitudinal strain, TAPSE, RV fractional area change), were shown to be moderately correlated with stroke volume index measured invasively during right heart catheterization.

Chapter 3 demonstrated that parameters of RV myocardial work were also associated with several invasive hemodynamic parameters, including RV stroke work index and pulmonary vascular resistance, in a cohort of patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In addition, RV global work index and RV global constructive were demonstrated to be significantly and non-linearly associated with all-cause mortality, whereas standard echocardiographic parameters related to RV function (pulmonary artery systolic pressure, RV strain, TAPSE, and RV fractional area change) were not.

SUMMARY OF PART II: New insights into risk stratification of patients with valvular heart disease

In part II, **chapter 4** demonstrated that LV remodeling is dependent on the underlying bicuspid aortic valve pathology, with important differences in LV remodeling observed between patients with significant (≥moderate) isolated aortic stenosis, isolated aortic regurgitation, and mixed aortic valve disease. In addition, the prognostic significance of LV geometric patterns and LV hypertrophy varied according to the type of aortic valve disease. The presence of concentric remodeling, concentric hypertrophy and eccentric hypertrophy were independently related to a composite endpoint of aortic valve repair/replacement and all-cause mortality in patients with isolated AS, while concentric hypertrophy and eccentric hypertrophy were independently associated with the combined endpoint for patients with isolated aortic regurgitation. Unexpectedly, there was

no adjusted association observed between indices of LV remodeling and outcome in patients with mixed aortic valve disease.

Chapter 5 showed that left atrial dilation is present in approximately one-third of patients with significant aortic regurgitation due to bicuspid aortic valve and was independently associated with a combined endpoint of aortic valve repair/replacement and all-cause mortality. The presence of left atrial dilation in significant aortic regurgitation may identify patients with worse subclinical LV diastolic function, who are more likely to develop symptoms, thus requiring surgical intervention. **Chapter 6** demonstrated that the prevalence of significant mitral regurgitation in patients with bicuspid aortic valve was 5%. In addition, patients with a type 1 raphe with left and non-coronary cusp fusion were shown to be significantly more likely to have ≥moderate mitral regurgitation due to prolapse of the anterior mitral valve leaflet when compared to other bicuspid aortic valve phenotypes. Interestingly, following adjustment for important confounding variables, significant mitral regurgitation was not associated with adverse prognosis, except for the patient subgroup with moderate to severe aortic regurgitation. Nonetheless, when stratifying by the etiology of mitral regurgitation, the presence of significant mitral regurgitation not due to aortic valve disease was independently associated with increased all-cause mortality. This suggests that consideration of the etiology of significant MR is essential in the setting of treatable aortic valve disease. **Chapter 7** demonstrated increased mortality with a LV ejection fraction below 60% in patients with significant bicuspid aortic valve disease, providing data supporting recent guideline recommendations for aortic valve replacement if the LV ejection fraction is <60% in patients with severe aortic stenosis and aortic regurgitation. Importantly, data supporting those recommendations was previously based almost entirely on studies of patients with a tricuspid aortic valve. Given the younger age and vastly different comorbidity profile of patients with bicuspid aortic valve, the results of this study are important, suggesting that similar recommendations may also be applied to this patient group. Ideally, randomized controlled trials will be performed to determine if asymptomatic patients with severe BAV disease and LV ejection fraction <60% benefit from early aortic valve replacement.

Chapter 8 demonstrated that of the pathophysiological mechanisms (including tricuspid regurgitation [TR] regurgitant volume, RV size, pulmonary artery systolic pressure, right atrial pressure) identified by echocardiography that are associated with significant secondary TR, only severe RV dysfunction was independently associated with the presence of significant renal impairment. It is possible that previous associations observed between significant renal impairment and the TR grade were indicative of the increased incidence of RV dysfunction observed with increasing TR severity. In addition, the presence of severe RV dysfunction was shown to be associated with reduced overall survival in patients with stage 1-3 chronic kidney disease, but not in patients

with stage 4–5 chronic kidney disease. **Chapter 9** showed that the number of secondary outcome determinants (left atrial volume index ≥60ml/m^2, atrial fibrillation, pulmonary artery systolic pressure ≥50mmHg and ≥moderate TR) are strongly independently associated with post-surgical survival in patients with degenerative mitral regurgitation, likely identifying patients with high-risk cardiac phenotypes. Furthermore, the presence and number of secondary outcome determinants demonstrated better outcome discrimination than traditional Class I indications for surgery, including the presence of symptoms, LV ejection fraction ≤60%, or LV end-systolic diameter ≥40mm. This study suggests that a paradigm shift in guideline recommendations could be considered: In addition to the use of clinically established thresholds of individual imaging parameters for intervention, accounting for the overall cardiac phenotype represented by the presence of multiple prognostically important parameters may improve discrimination and therefore, patient selection for early surgery. Furthermore, the presence of multiple prognostically important parameters probably warrants a stronger recommendation for intervention than any single parameter in isolation.

CONCLUSIONS AND FUTURE PERSPECTIVES

RV myocardial work analysis with RV pressure-strain loops holds much promise for improving the non-invasive understanding of RV pathophysiology for an individual patient. Although this thesis has demonstrated the utility of RV myocardial work for the risk stratification of patients with pre-capillary pulmonary hypertension, larger prospective studies are required to confirm these results and facilitate extensive multivariable analyses. Future research is also needed to examine the prognostic value of RV myocardial work in patients with significant TR, significant mitral regurgitation, left ventricular assist devices, heart failure with preserved ejection fraction and for heart transplant recipients. The potential for improving risk stratification in these important patient groups by providing a more complete quantification of RV function that accounts for RV afterload and mechanical efficiency, represents many exciting research opportunities.

The evaluation of myocardial remodeling and function is essential in valvular heart disease. Indeed, imaging parameters are a direct reflection of the hemodynamic burden imposed by a particular valvular lesion. However, opportunities for improving risk stratification and refining the selection of patients for intervention requires both the development of novel imaging techniques and the use of methods for the identification of patients with high-risk cardiac phenotypes. In addition, further research is desperately needed for patients with a bicuspid aortic valve, in whom accurate selection for intervention is paramount due to their young age and the associated ramifications of early aortic valve replacement. For this cohort in particular, randomized data is needed to inform current clinical practice, which until now, has been driven by a combination of observational data and expert opinion.

SAMENVATTING, CONCLUSIES EN TOEKOMSTIGE PERSPECTIEVEN

SAMENVATTING VAN DEEL I: niet-invasieve analyse van de rechter ventrikel myocardial work

Hedendaagse methoden om de rechter ventrikel (RV) functie te meten op echocardiografie, waaronder de RV longitudinal strain en tricuspidalis annular plane systolic excursion (TAPSE), houden onvoldoende rekening met de RV afterload en mechanische efficiëntie in hun analyse. In **hoofdstuk 2** werd een nieuwe echocardiografische methode ontwikkeld voor de evaluatie van de RV functie met RV druk curves, gebruikmakend van software wat oorspronkelijk was ontworpen voor de analyse van de linker ventrikel (LV) functie. Bij 22 patiënten met hartfalen en verminderde ejectiefractie die een rechtshartkatheterisatie ondergingen, werd aangetoond dat de evaluatie van RV myocardial work afgeleid van RV druk-strain curves haalbaar was, met uitstekende reproduceerbaarheid. Verder werd aangetoond dat twee parameters van RV myocardial work, de RV global work index en de RV global constructive work, maar niet conventionele parameters van RV systolische functie (RV longitudinal strain, TAPSE, RV fractionele oppervlakte verandering), matig gecorreleerd waren met de slagvolume index, invasief gemeten tijdens rechter hartkatheterisatie.

Hoofdstuk 3 toonde aan dat parameters van RV myocardial work ook geassocieerd waren met verschillende invasieve hemodynamische parameters, waaronder RV stroke work index en de pulmonale vasculaire weerstand, in een cohort van patiënten met pulmonale arteriële hypertensie en chronische trombo-embolische pulmonale hypertensie. Bovendien werd aangetoond dat de RV global work index en de RV global constructive significant en niet-lineair geassocieerd waren met mortaliteit, terwijl standaard echocardiografische parameters gerelateerd aan RV functie (als de systolische druk van de longslagader, RV strain, TAPSE, en RV fractional area change) dat niet waren.

SAMENVATTING VAN DEEL II: Nieuwe inzichten in risicostratificatie van patiënten met hartklepziekten

In deel II, **hoofdstuk 4**, werd aangetoond dat LV remodelering afhankelijk is van de onderliggende pathologie van de bicuspide aortaklep, waarbij belangrijke verschillen in LV remodelering werden waargenomen tussen patiënten met significante (≥matige) geïsoleerde aortaklepstenose, geïsoleerde aortaklepregurgitatie en gemengde aortaklepziekte. Bovendien varieerde de prognostische betekenis van LV geometrische patronen en LV hypertrofie afhankelijk van het type aortaklepziekte. In patiënten met geïsoleerde aortaklepstenose waren concentrische remodelering, concentrische hypertrofie en excentrische hypertrofie onafhankelijk gerelateerd aan een samengesteld eindpunt van aortaklepreparatie of -vervanging en mortaliteit, terwijl concentrische hypertrofie en excentrische hypertrofie onafhankelijk gerelateerd waren aan het gecombineerde

eindpunt in patiënten met geïsoleerde aortaklepregurgitatie. Verrassend genoeg werd er geen verband waargenomen tussen indices van LV remodelering en uitkomsten in patiënten met gemengde aortaklepziekte.

In **hoofdstuk 5** werd aangetoond dat bij ongeveer een derde van de patiënten met significante aortaklepregurgitatie ten gevolge van een bicuspide aortaklep, er sprake is van linker atriumdilatatie dat onafhankelijk geassocieerd was met een gecombineerd eindpunt van aortaklepreparatie of -vervanging en mortaliteit. De aanwezigheid van linker atriumdilatatie in patiënten met significante aortaklepregurgitatie kan patiënten identificeren met een slechtere subklinische diastolische LV functie en meer kans hebben om klachten te ontwikkelen waardoor chirurgisch ingrijpen noodzakelijk is. **Hoofdstuk 6** toonde aan dat de prevalentie van significante mitralisklepregurgitatie bij patiënten met een bicuspide aortaklep 5% was. Bovendien bleek dat patiënten met een raphe type 1, met fusie van het linker- en niet-coronaire klepblad, significant meer kans hebben op ≥matige mitralisklepregurgitatie als gevolg van prolaps van het voorste mitralisklepblad in vergelijking met andere bicuspide aortaklep fenotypes. Significante mitralisklepregurgitatie was niet geassocieerd met een ongunstige prognose na correctie voor belangrijke verstorende variabelen, behalve voor de subgroep van patiënten met matige tot ernstige aortaklepregurgitatie. Wanneer er wordt gekeken naar de etiologie van mitralisklepregurgitatie, was de aanwezigheid van significante mitralisklepregurgitatie die niet het gevolg was van aortaklepziekte onafhankelijk geassocieerd met verhoogde mortaliteit. Dit suggereert dat de etiologie van significante mitralisklepregurgitatie essentieel is in behandelbare aortaklepziekten. **Hoofdstuk 7** toonde een verhoogde mortaliteit van patiënten met significante bicuspide aortaklepziekte met een LV ejectiefractie <60% en ondersteunt hiermee recente richtlijnen over aortaklepvervanging in patiënten met ernstige aortaklepstenose en aortaklepregurgitatie met een LV ejectiefractie <60%. Voorheen was data die deze richtlijnen ondersteunden bijna volledig gebaseerd op studies over patiënten met een tricuspide aortaklep. Gezien de jongere leeftijd en het sterk afwijkende comorbiditeitsprofiel van patiënten met een bicuspide aortaklep zijn de resultaten van dit onderzoek belangrijk omdat dit suggereert dat soortgelijke aanbevelingen ook op deze patiëntengroep kunnen worden toegepast. Idealiter zullen gerandomiseerde gecontroleerde studies moeten worden uitgevoerd om te bepalen of asymptomatische patiënten met ernstige bicuspide aortaklepziekte en een LV ejectiefractie <60% baat hebben bij vroegtijdige vervanging van de aortaklep.

Hoofdstuk 8 toonde aan dat van de pathofysiologische mechanismen (waaronder tricuspidalis regurgitatie [TR] regurgitatie volume, RV grootte, systolische druk van de a. pulmonalis en rechter atriumdruk) op echocardiografie die zijn geassocieerd met significante secundaire TR, alleen ernstige RV disfunctie onafhankelijk geassocieerd was met de aanwezigheid van significante nierinsufficiëntie. Het is mogelijk dat eerdere verbanden tussen significante nierinsufficiëntie en de graad van TR een indicatie waren

van de toegenomen incidentie van RV disfunctie die werd waargenomen bij toenemende ernst van TR. Bovendien bleek de aanwezigheid van ernstige RV disfunctie geassocieerd te zijn met verminderde algehele overleving in patiënten met stadium 1-3 chronische nierziekte, maar niet bij patiënten met stadium 4-5 chronische nierziekte. **Hoofdstuk 9** liet zien dat het aantal secundaire uitkomstbepalende factoren (linker atrium volume index ≥60ml/m^2, atriumfibrilleren, pulmonale arteriële systolische druk ≥50mmHg en ≥matige TR) sterk geassocieerd zijn met de postoperatieve overleving in patiënten met degeneratieve mitralisklepregurgitatie, waarbij waarschijnlijk patiënten met hoog-risico cardiale fenotypes worden geïdentificeerd. Bovendien bleek de aanwezigheid en het aantal secundaire uitkomstdeterminanten een betere uitkomstdiscriminatie op te leveren dan traditionele klasse I-indicaties voor chirurgie, waaronder de aanwezigheid van symptomen, LV-ejectiefractie ≤60% of LV eind-systolische diameter ≥40 mm. Deze studie suggereert dat een paradigmaverschuiving in de aanbevelingen voor richtlijnen kan worden overwogen: In aanvulling op het gebruik van klinisch vastgestelde drempelwaarden van de afzonderlijke beeldvormingsparameters voor interventie, kan rekening gehouden worden met het totale cardiale fenotype bestaande uit meerdere prognostisch belangrijke parameters en daarmee de selectie van patiënten voor vroegtijdige chirurgie verbeteren. Bovendien rechtvaardigt de aanwezigheid van meerdere prognostisch belangrijke parameters waarschijnlijk een sterkere aanbeveling voor interventie dan elke parameter afzonderlijk.

CONCLUSIES EN TOEKOMSTIGE PERSPECTIEVEN

Analyse van de RV myocardial work met RV druk-strain curves hebben veel potentieel voor het verbeteren van de kennis over de pathofysiologie van het RV voor de individuele patiënt. Hoewel deze thesis heeft laten zien dat de RV myocardial work bruikbaar is voor risicostratificatie van patiënten met pre-capillaire pulmonale hypertensie, zijn grotere prospectieve studies nodig om deze resultaten te valideren en het faciliteren van uitgebreide multivariabele analyses. Toekomstig onderzoek is ook nodig om de prognostische waarde van RV myocardial work te onderzoeken in patiënten met significante TR, significante mitralisklepregurgitatie, steunharten, hartfalen met bewaarde ejectiefractie en in patiënten met een harttransplantatie. Het potentieel om risicostratificatie te verbeteren in deze belangrijke patiëntengroepen door het voorzien van een meer complete kwantificatie van de RV functie dat rekening houdt met de RV afterload en de mechanische efficiëntie, biedt veel opwindende onderzoeksmogelijkheden.

De oppuntstelling van de hartfunctie en remodelering zijn essentieel in hartklepziekten. Beeldvormingsparameters zijn immers een directe afspiegeling van de hemodynamische belasting door een bepaalde hartklepaandoening. Echter, om de risicostratificatie te verbeteren en de patiëntenselectie voor interventie te verfijnen zijn zowel nieuwe beeldvormingstechnieken noodzakelijk als methoden om hoog-risicopatiënten

te identificeren. Daarnaast is verder onderzoek nodig naar patiënten met een bicuspide aortaklep, waarbij een zorgvuldige selectie voor interventie van groot belang is vanwege hun jonge leeftijd en de daarmee samenhangende gevolgen van vroegtijdige aortaklepvervanging. Met name voor dit cohort zijn gerandomiseerde data nodig om de hedendaagse kliniek te onderbouwen, dat tot op heden was gebaseerd op een combinatie van observationele data en deskundigenoordeel.

LIST OF PUBLICATIONS

Fortuni F, Dietz MF, **Butcher SC**, Prihadi EA, van der Bijl P, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic Implications of Increased Right Ventricular Wall Tension in Secondary Tricuspid Regurgitation. Am J Cardiol. 2020 Dec 1;136:131-139. doi: 10.1016/j.amjcard.2020.09.022. Epub 2020 Sep 15. PMID: 32941816.

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CURRICULUM VITAE

Steele Butcher was born on September 8, 1989, in Perth, Western Australia. He graduated from high school in Perth in 2006, before beginning a Bachelor of Science at Murdoch University. He completed his Bachelor of Science in 2009, and subsequently completed a Bachelor of Chiropractic in 2011, also at Murdoch University. Following working for several years as a Chiropractor in private practice, he returned to study Medicine at the University of Notre Dame Australia in 2014. He won the Australian Medical Association prize for highest achieving student in Year 1, 2, 3 and 4 of his medical degree, achieving a high distinction and 4.0/4.0 GPA in each year, and the Australian Medical Association DUX prize, in addition to many other individual awards. He graduated with an MD degree in 2017. In his final year of medical school training, he began studying a Master of Philosophy at the University of Notre Dame Australia, with his thesis focusing on the role of Computed Tomography Coronary Angiography for the risk assessment of acute coronary syndrome patients. He graduated from the Master of Philosophy degree in 2021, achieving a 4.0/4.0 GPA in degree units. He completed his internship at Royal Perth Hospital in 2018 and the first year of his Basic Physician Training at Royal Perth Hospital in 2019, before beginning his PhD late in 2019 at Leiden University Medical Centre under the guidance of Prof. Dr. J.J. Bax, Dr. V. Delgado and Dr. N. Ajmone Marsan. During his time at Leiden University Medical Center, Steele focused his research on novel methods of evaluating right ventricular function, valvular heart disease, and cardiac involvement in systemic sclerosis.

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