Universiteit
Leiden
The Netherlands

Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy

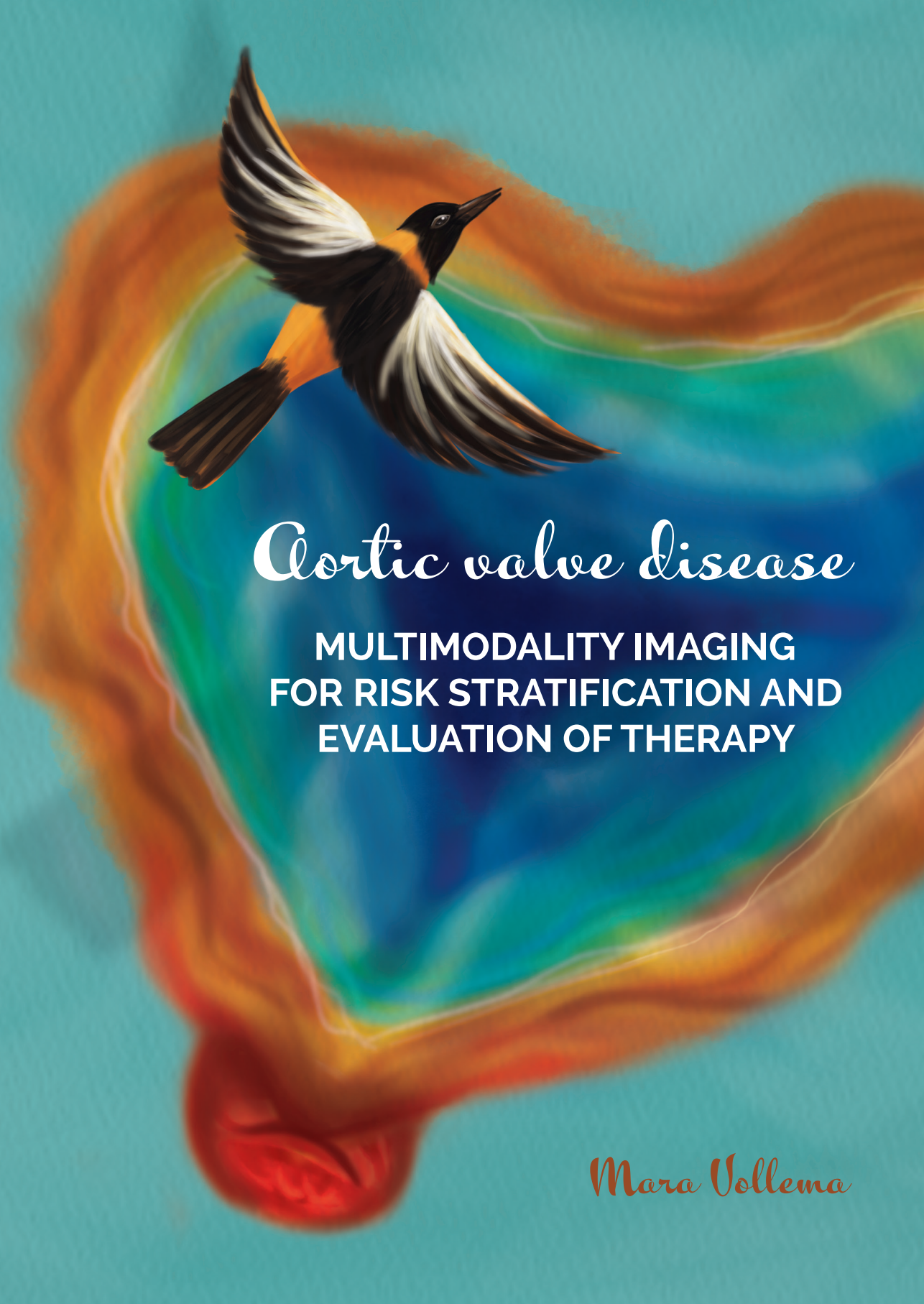
Vollema, E.M.

Citation

Vollema, E. M. (2022, September 6). *Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy*. Retrieved from https://hdl.handle.net/1887/3455179

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3455179

Note: To cite this publication please use the final published version (if applicable).


Aortic valve disease
MULTIMODALITY IMAGING FOR RISK STRATIFICATION AND EVALUATION OF THERAPY
Mara Vollema

AORTIC VALVE DISEASE

MULTIMODALITY IMAGING FOR RISK STRATIFICATION AND EVALUATION OF THERAPY

Elise Mara VOLLEMA

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

Cover: Evelien Jagtman, © evelienjagtman.com

Lay-out: E.M. Vollema, F.E. Kalff, H.C. Kalff

Printed by: Gildeprint - Enschede

ISBN: 978-94-6419-547-7

Copyright © 2022 E.M. Vollema. All rights reserved. No part of this thesis may be reproduced, stored or transmitted in any way or by any means without the prior permission of the author, of when applicable, of the publishers of the scientific papers.

Financial support by Canon Medical Systems Nederland and ChipSoft b.v. for the publication of this thesis is gratefully acknowledged.

AORTIC VALVE DISEASE

MULTIMODALITY IMAGING FOR RISK STRATIFICATION AND EVALUATION OF THERAPY

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op dinsdag 6 september 2022
klokke 10.00 uur

door

Elise Mara VOLLEMA

geboren te 's-Gravenhage
in 1989

Promotor:
Prof. dr. J.J. Bax

Co-promotor:
Dr. V. Delgado

Leden promotiecommissie:
Prof. dr. M.J. Schalij
Dr. N. Ajmone Marsan
Dr. P.R.M. van Dijkman
Prof. dr. M.E.J. Reinders (Erasmus Medisch Centrum)
Prof. dr. P. van der Meer (Universitair Medisch Centrum Groningen)

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Aan Floris. Aan mijn ouders.

CONTENTS

1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

1

INTRODUCTION

AORTIC valve disease, i.e., aortic stenosis (AS) and aortic regurgitation (AR), is the most common cause of native valvular heart disease and a major cause of cardiovascular morbidity and mortality [1, 2]. Recently, the EURObservational Research Programme Valvular Heart Disease II survey [3] showed that AS was present in 41% of patients referred with severe native valvular heart disease. Aortic regurgitation was present in 5% of patients. Importantly, aortic valve disease was shown to be of a predominantly degenerative pathogenesis (>90% in AS and >40% in AR, respectively) [3]. Therefore, with the increasing age of the general population worldwide, aortic valve disease will become a more prevalent health issue.

Both AS and AR are regarded as diseases of the aortic valve and the left ventricle (LV), but differ in pathophysiology. In AS, only a pressure overload is imposed on the LV, while AR induces both a pressure and volume overload. These abnormal hemodynamic states induce different LV remodelling responses in order to normalize wall stress: eccentric remodelling and LV dilatation occur in AR due to growth of cardiomyocytes and addition of new sarcomeres in series, and concentric hypertrophy is seen in AS due to increased diameter of muscle fibers and parallel addition of myofibrils (Figure 1) [4]. However, in both valvular diseases, overload conditions may cause irreversible formation of myocar-

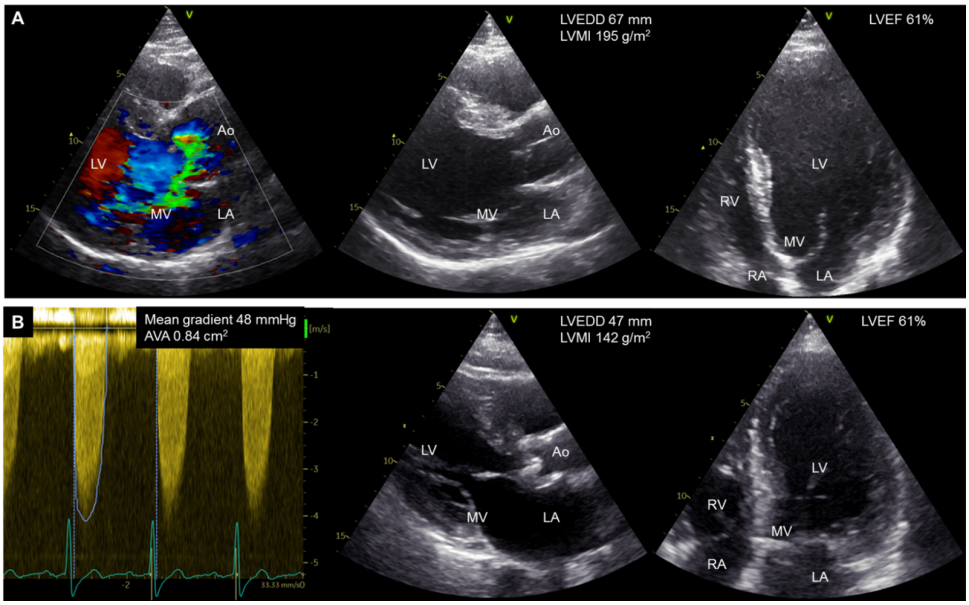


Figure 1: Examples of the differences in left ventricular (LV) remodelling in AR vs. AS. In this patient with severe AR (*panel A*), an eccentric aortic regurgitant jet towards the mitral valve is observed. Due to the volume overload by AR, eccentric remodelling with LV dilatation occurs. In this patient with severe AS (*panel B*), the pressure and volume overload imposed by the stenotic aortic valve results in concentric hypertrophy. Ao, aorta; AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MV, mitral valve; RA, right atrium; RV, right ventricle.

dial fibrosis which may result in LV dysfunction [4, 5].

Aortic valve intervention is the only effective treatment for severe AS and severe AR and is indicated in patients presenting with symptoms due to the valvular disease or when LV dysfunction is present [6]. In addition, in AR, the presence of severe dilation (i.e., aneurysm) of the aortic root and/or ascending aorta may be the underlying pathophysiological mechanism of AR and may form the primary indication for aortic valve intervention. For AS, surgical aortic valve replacement (AVR) is recommended for patient with low surgical risk and absence of surgical risk factors (e.g., frailty). In patients unsuitable for surgical AVR, transcatheter aortic valve implantation (TAVI) may be considered after assessment by the Heart Team [6]. In AR, aortic valve repair may be a feasible alternative for AVR in selected patients [6]. Significant mortality has been reported in severe AS and severe AR patients who remain untreated. For AS, a recent study reported a 5-year mortality of 67% in these patients [7]. Similarly, a recent study of severe chronic AR patients with preserved LV ejection fraction observed a 10-year mortality of 29% for patients who remained untreated vs. 13% for patients undergoing aortic valve surgery (P<0.001) [8].

Correct assessment of AS and AR severity and careful risk evaluation are crucial for the proper selection of patients and timing of AVR. Multimodality imaging, particularly echocardiography and multi-detector row computed tomography, is of paramount importance herein.

Multimodality imaging in risk stratification and timing of intervention

For the assessment of AS and AR severity and aortic valve morphology (i.e., tricuspid vs. bicuspid), two-dimensional and Doppler transthoracic echocardiography is the imaging technique of first choice. It also provides information on LV dimensions and function and associated conditions such as pulmonary hypertension.

Severity of AS is determined by several hemodynamic parameters using the continuity equation: peak aortic jet velocity, (indexed) aortic valve area (AVA) and transvalvular pressure gradient (Table 1) [9]. Low-gradient severe AS, defined by an AVA <1.0 m^2 and a mean gradient <40 mmHg, is seen in approximately one third of patients with severe AS and more frequently in those with low flow due to LV dysfunction. Low-dose dobutamine stress echocardiography can be utilized to discern true severe AS from pseudosevere AS in these patients. Alternatively, the presence of a high aortic valve calcification burden as detected by aortic valve calcium scoring using computed tomography may be of ad-

Table 1: Diagnostic criteria for severity of aortic stenosis.

	Aortic sclerosis	Mild AS	Moderate AS	Severe AS
Peak velocity (m/s)	≤2.5	2.6-2.9	3.0-4.0	≥4.0
Mean gradient (mmHg)	-	<20	20-40	≥40
AVA (cm^2)	-	>1.5	1.0-1.5	<1.0
Indexed AVA (cm^2/m^2)	-	>0.85	0.60-0.85	<0.6

AS, aortic stenosis; AVA, aortic valve area.

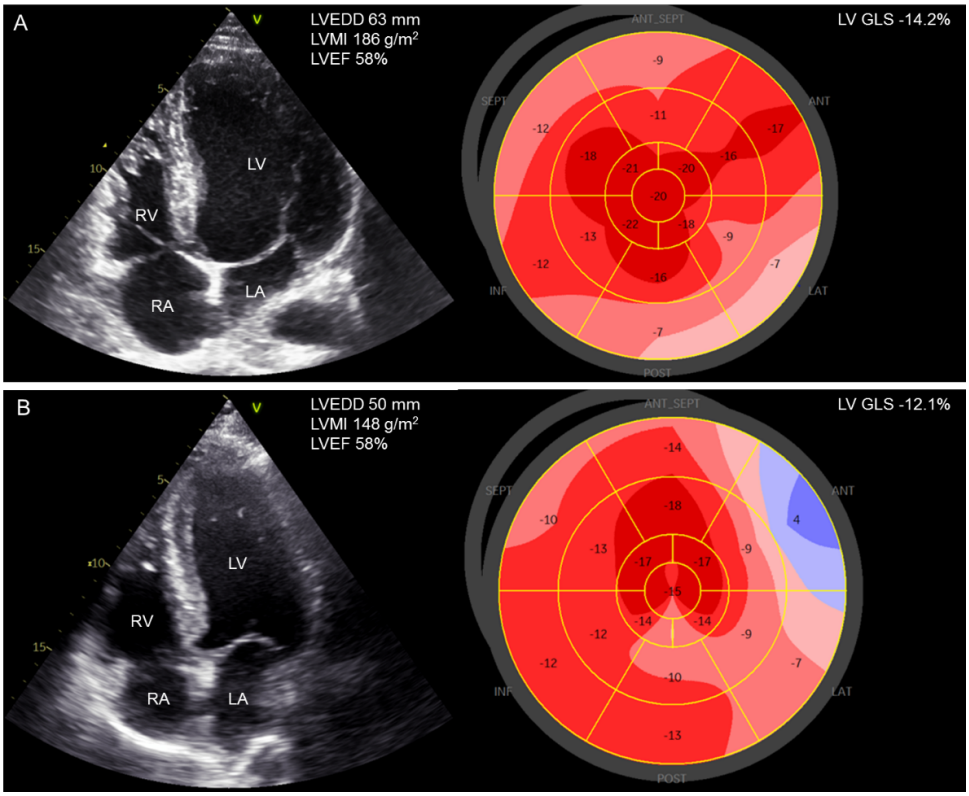


Figure 2: Examples of a patient with severe AR (*panel A*) and of a patient with severe AS (*panel B*) with preserved LVEF but impaired LV GLS, suggesting the presence of subclinical myocardial dysfunction. AR, aortic regurgitation; AS, aortic stenosis; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MV, mitral valve; RA, right atrium; RV, right ventricle.

ditional value in the identification of true severe AS (as compared to moderate AS) in low-gradient AS patients [10–12]. For AR, severity is assessed using a multi-parametric approach including qualitative and (semi-)quantitative parameters (Table 2) [13].

Assessment of LV function is paramount in the selection of patients for AVR and timing of intervention, as LV dysfunction (defined as LV ejection fraction [EF] <50%) is a class I indication for aortic valve intervention in both AS and AR [6]. However, subclinical myocardial dysfunction may be present in patients with preserved LVEF and can be detected by the assessment of LV global longitudinal strain (GLS) using speckle tracking echocardiography (Figure 2) [14]. Impaired LV GLS in patients with preserved LVEF has been associated with worse prognosis in both AS [15] and AR [16]. The role of LV GLS in asymptomatic severe AS and its implications for timing of intervention has not yet been elucidated.

Recent studies have shown a high prevalence of mitral and tricuspid regurgitation (13 to 20% and 11 to 27%, respectively) [17–19], pulmonary hypertension (10 to 36%)

Table 2: Diagnostic criteria for severity of aortic regurgitation.

Parameters	Severity of paravalvular regurgitation		
	Mild	**Moderate**	**Severe**
Qualitative			
Aortic valve morphology	Normal/abnormal	Normal/abnormal	Abnormal/flail/ large coaptation defect
Colour flow AR jet width	Small in central jets	Intermediate	Large in central jet, variable in eccentric jets
CW signal of AR jet	Incomplete/faint	Dense	Dense
Diastolic flow reversal in descending aorta	Brief, protodiastolic flow reversal	Intermediate	Holodiastolic flow reversal (end-diastolic velocity >20 cm/s)
Diastolic flow reversal in abdominal aorta	Absent	Absent	Present
Semi-quantitative			
VC width (mm)	<3	Intermediate	≥6
Pressure half-time (ms)	>500	Intermediate	<200
Quantitative			
EROA (mm^2)	<10	10-19; 20-29*	≥30
Regurgitant volume (ml)	<30	30-44; 45-59*	≥60

AR, aortic regurgitation; CW, continuous wave; EROA, effective regurgitant orifice area; VC, vena contracta.
*Subclassification of moderate AR in "mild-to-moderate" (EROA of 10-19 mm^2 or regurgitant volume of 30-44 ml) and "moderate-to-severe" (EROA of 20-29 mm^2 or regurgitant volume of 45-59 ml).

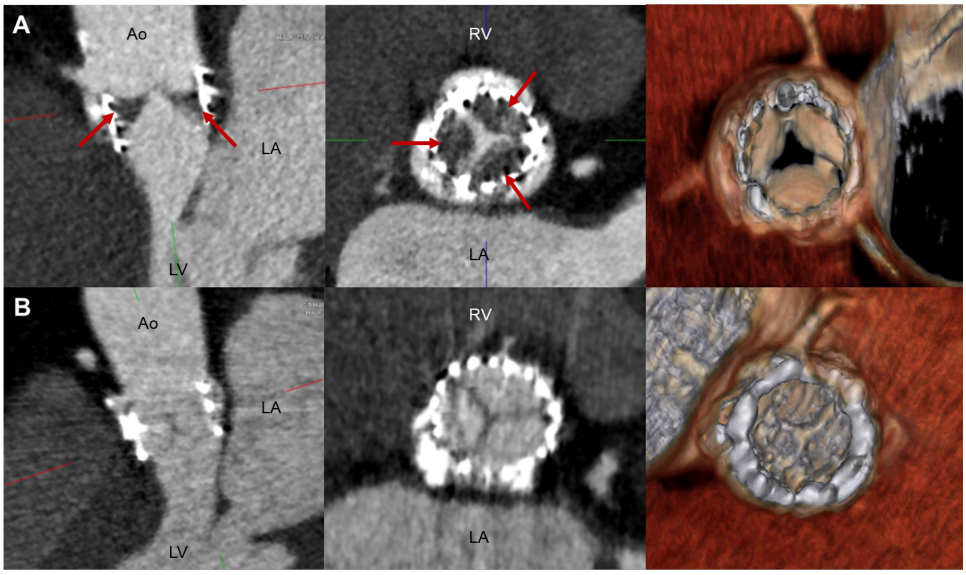


Figure 3: Four-dimensional multidetector row computed tomography reconstructions after TAVI of a patient with hypo-attenuated leaflet thickening (HALT) with reduced leaflet mobility (*panel A*) and of a patient without HALT (*panel B*). The red arrows depict the hypo-attenuated lesions suggestive of the presence of subclinical leaflet thrombosis. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; TAVI, transcatheter aortic valve implantation.

[20, 21] and RV dysfunction (24 to 29%) [22, 23] in severe AS patients. The presence of these markers of cardiac injury, as categorized in a novel proposed staging classification, have been reported to have a significant prognostic impact in this patient population [24]. Therefore, echocardiography can provide important information for further risk stratification by identification of these markers of cardiac damage. Improvement of this staging classification by incorporation of advanced imaging parameters, e.g., LV GLS, may provide further refinement of risk stratification in severe AS patients.

MULTIMODALITY IMAGING IN THE EVALUATION OF THERAPY

For the evaluation of therapy, multi-modality imaging plays a pivotal role. Echocardiography is the mainstay imaging modality for the evaluation of prosthesis function and durability after surgical AVR or TAVI and for the detection of potential late complications. It may also be used to evaluate LV function (i.e., using LVEF or LV GLS) and regression of LV hypertrophy after intervention.

Recently, multi-detector row computed tomography has been used to detect hypo-attenuated leaflet thickening (HALT) with or without reduced leaflet motion after TAVI, which may suggest subclinical leaflet thrombosis in the absence of symptoms and increased transprosthetic gradients (Figure 3) [25–27]. The prevalence of HALT and its clinical implications remain unclear.

OUTLINE OF THE THESIS

THE objective of this thesis was to evaluate the role of multimodality imaging, in particular two-dimensional (speckle tracking) echocardiography and multi-detector row computed tomography, in risk stratification and evaluation of therapy in patients with aortic valve disease, specifically AS.

In **Part I**, the role of conventional echocardiography and LV GLS measured by speckle tracking echocardiography is evaluated for patient selection and risk stratification in AS. In Chapter 2, the prevalence and prognostic impact of the presence of extra-aortic valvular cardiac injury assessed by conventional echocardiography and categorized according to a newly proposed staging classification is investigated in symptomatic severe AS patients. Chapter 3 evaluates the incremental prognostic value of LV GLS over proposed stages of cardiac damage in symptomatic severe AS patients. Chapter 4 describes the prevalence of impaired LV GLS, the time course of LV GLS and its prognostic implications in asymptomatic severe AS with preserved LV ejection fraction. In Chapter 5, the prevalence and prognostic impact of renal dysfunction in patients with aortic sclerosis and patients with mild to severe AS is assessed. Chapter 6 discusses the role of multi-detector row computed tomography in the evaluation of aortic valve calcification for the identification of patients with true severe AS among those with low-gradient AS.

Part II focusses on the role of echocardiography and multi-detector row computed tomography in the evaluation of therapy, particularly follow-up after surgical and transcatheter AVR. Chapter 7 provides an overview of the clinical applications and current role of echocardiography in the patient selection, prosthesis sizing, periprocedural guidance and post-procedural follow-up in TAVR. In Chapter 8, the prevalence of hypo-attenuated leaflet thickening after TAVR is evaluated using multi-detector row computed tomography and its association with abnormal valve hemodynamics on echocardiography and occurrence of ischemic stroke and/or transient ischemic attack is studied. Chapter 9 characterizes and compares the time course of LV mass index and LV mechanics as assessed by LV GLS in patients with AS vs. patients with AR after aortic valve surgery.

1

REFERENCES

[1] D'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J. 2016;37(47):3515-22.

[2] Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.

[3] Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, et al. Contemporary Presentation and Management of Valvular Heart Disease: The EURObservational Research Programme Valvular Heart Disease II Survey. Circulation. 2019;140(14):1156-69.

[4] Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. Circulation. 1989;79(4):744-55.

[5] Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, et al. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. J Am Coll Cardiol Img. 2017;10(11):1320-33.

[6] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[7] Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, et al. Poor Long-Term Survival in Patients With Moderate Aortic Stenosis. J Am Coll Cardiol. 2019;74(15):1851-63.

[8] Mentias A, Feng K, Alashi A, Rodriguez LL, Gillinov AM, Johnston DR, et al. Long-Term Outcomes in Patients With Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction. J Am Coll Cardiol. 2016;68(20):2144-53.

[9] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[10] Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013;62(24):2329-38.

[11] Aggarwal SR, Clavel MA, Messika-Zeitoun D, Cueff C, Malouf J, Araoz PA, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging. 2013;6(1):40-7.

[12] Pawade T, Clavel MA, Tribouilloy C, Dreyfus J, Mathieu T, Tastet L, et al. Computed Tomography Aortic Valve Calcium Scoring in Patients with Aortic Stenosis. Circ Cardiovasc Imaging. 2018;11(3):1-11.

[13] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013;14(7):611-44.

[14] Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, et al. Geometry as a Confounder When Assessing Ventricular Systolic Function: Comparison Between Ejection Fraction and Strain. J Am Coll Cardiol. 2017;70(8):942-54.

[15] Ng ACT, Prihadi EA, Antoni ML, Bertini M, Ewe SH, Marsan NA, et al. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. Eur Heart J Cardiovasc Imaging. 2018;19(8):859-67.

[16] Ewe SH, Haeck MLA, Ng ACT, Witkowski TG, Auger D, Leong DP, et al. Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis. Eur Heart J Cardiovasc Imaging. 2015;16:992-9.

[17] Unger P, Dedobbeleer C, Van Camp G, Plein D, Cosyns B, Lancellotti P. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. Heart. 2010;96(1):9-14.

[18] Zilberszac R, Gleiss A, Binder T, Laufer G, Grimm M, Gabriel H, et al. Prognostic relevance of mitral and tricuspid regurgitation in patients with severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2018;43:1-8.

[19] Lindman BR, Maniar HS, Jaber WA, Lerakis S, Mack MJ, Suri RM, et al. Effect of Tricuspid Regurgitation and the Right Heart on Survival after Transcatheter Aortic Valve Replacement: Insights From the Placement of Aortic Transcatheter Valves II Inoperable Cohort. Circ Cardiovasc Interv. 2015;8(4):1-10.

[20] Alushi B, Beckhoff F, Leistner D, Franz M, Reinthaler M, Stähli BE, et al. Pulmonary Hypertension in Patients With Severe Aortic Stenosis: Prognostic Impact After Transcatheter Aortic Valve Replacement: Pulmonary Hypertension in Patients Undergoing TAVR. J Am Coll Cardiol Img. 2019;12(4):591-601.

[21] Zlotnick DM, Ouellette ML, Malenka DJ, Desimone JP, Leavitt BJ, Helm RE, et al. Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. Am J Cardiol. 2013;112(10):1635-40.

[22] Asami M, Stortecky S, Praz F, Lanz J, Räber L, Franzone A, et al. Prognostic Value of Right Ventricular Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Img. 2019;12(4):577-87.

[23] Galli E, Guirette Y, Feneon D, Daudin M, Fournet M, Leguerrier A, et al. Prevalence and prognostic value of right ventricular dysfunction in severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2015;16(5):531-8.

[24] Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J. 2017;38(45):3351-8.

[25] Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2016;37(28):2263-71.

[26] Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017;389(10087):2383-92.

[27] Bax JJ, Delgado V. Further insight into transcatheter and surgical aortic bioprosthetic valve thrombosis. Eur Heart J. 2017;38(28):2208-10.

Part I

RISK STRATIFICATION AND TIMING OF INTERVENTION

2

STAGING CARDIAC DAMAGE IN PATIENTS WITH SYMPTOMATIC AORTIC VALVE STENOSIS

E. Mara Vollema*, Mohammed R. Amanullah*, Arnold C.T. Ng,
Pieter van der Bijl, Francesca Prevedello, Yoong Kong Sin,
Edgard A. Prihadi, Nina Ajmone Marsan, Zee Pin Ding,
Philippe Généreux, Philippe Pibarot, Martin B. Leon, Jagat Narula,
See Hooi Ewe, Victoria Delgado, Jeroen J. Bax

*Drs. Vollema and drs. Amanullah contributed equally to this manuscript.

Published in J Am Coll Cardiol. 2019; 74: 538-549.

ABSTRACT

BACKGROUND

In severe aortic stenosis (AS), patients often show extra-aortic valvular injury. Recently, a new staging system for severe AS has been proposed based on the extent of cardiac damage.

OBJECTIVES

The present study evaluated the prevalence and prognostic impact of these different stages of cardiac damage in a large, real-world, multicenter cohort of symptomatic severe AS patients.

METHODS

From the ongoing registries from 2 academic institutions, a total of 1189 symptomatic severe AS patients were selected and retrospectively analysed. According to the extent of cardiac damage on echocardiography, patients were classified as Stage 0 (no cardiac damage), Stage 1 (left ventricular damage), Stage 2 (mitral valve or left atrial damage), Stage 3 (tricuspid valve or pulmonary artery vasculature damage) or Stage 4 (right ventricular damage). Patients were followed for all-cause mortality and combined endpoint (all-cause mortality, stroke and cardiac-related hospitalization).

RESULTS

On the basis of the proposed classification, 8% of patients were classified as Stage 0, 24% as Stage 1, 49% as Stage 2, 7% as Stage 3 and 12% as Stage 4. On multivariable analysis, cardiac damage was independently associated with all-cause mortality and combined outcome, although this was mainly determined by Stages 3 and 4.

CONCLUSIONS

In this large multicenter cohort of symptomatic severe AS patients, stage of cardiac injury as classified by a novel staging system was independently associated with all-cause mortality and combined endpoint, although this seemed to be predominantly driven by tricuspid valve or pulmonary artery vasculature damage (Stage 3) and right ventricular dysfunction (Stage 4).

Introduction

In aortic stenosis (AS), referral for aortic valve replacement (AVR) is currently driven by the severity of AS and by the presence of AS related symptoms or signs of left ventricular (LV) systolic dysfunction (defined as a LV ejection fraction <50%) [1, 2]. Severity of AS is primarily quantified on echocardiography using hemodynamic parameters of the aortic valve specifically, that is, mean transvalvular pressure gradient, peak aortic jet velocity and aortic valve area [3]. However, the clinical outcomes of severe AS patients are not influenced by the stenotic aortic valve only. Changes in the LV structure and function as well as hemodynamic consequences beyond the left ventricle such as significant mitral [4, 5] and tricuspid regurgitation [5, 6] and right ventricular (RV) dysfunction [7, 8] have been associated with poor outcomes in severe AS patients undergoing AVR. Recently, a new staging system for severe AS has been proposed based on the extent of anatomic and functional cardiac damage [9]. Généreux et al. [9] demonstrated the strong predictive value of a proposed model to stage severe AS patients who were included for the PARTNER II (Placement of AoRTic TraNscathetER Valves) trial. The generalization of this staging model to an unselected symptomatic severe AS population has not been tested. Therefore, the present study aimed at evaluating the prevalence of the different stages of extra-aortic valvular cardiac damage and its impact on prognosis in a large, real-world, multicenter cohort of symptomatic severe AS patients.

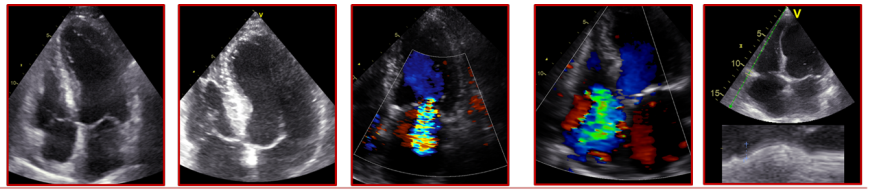
Methods

Patient population and data collection

From the ongoing registries of patients with aortic valve disease from 2 academic institutions (Leiden University Medical Center, Leiden, The Netherlands and National Heart Centre, Singapore, Singapore) between 1999 and 2017, a total of 1189 symptomatic severe AS patients were selected upon available echocardiographic data at baseline (defined as the first available echocardiogram with symptomatic severe AS). Severe AS was defined according to current guidelines as a mean aortic valve gradient ≥40 mmHg and/or aortic valve area <1.0 cm^2 (or an indexed aortic valve area <0.6 cm^2/m^2) and/or a peak aortic jet velocity ≥4 m/s [1–3]. At each participating center, echocardiographic measurements were performed by experienced observers. Patients with previous AVR were excluded. Baseline demographic and clinical data, including cardiovascular risk factors and medication use, and clinical follow-up data were collected using the hospital records and departmental patient information systems and analyzed retrospectively. This retrospective analysis of clinically acquired data was approved by the respective institutional review boards of each participating center and the need for patient written informed consent was waived due to the retrospective nature of the study.

Transthoracic echocardiography

Using commercially available ultrasound systems, 2-dimensional, colour, pulsed and continuous wave Doppler images were obtained from the apical and parasternal views according to current recommendations with the patient at rest in left lateral decubitus position [10]. From the apical 3- or 5-chamber views, continuous wave Doppler recordings were obtained to estimate peak aortic jet velocity [3]. Mean and peak transvalvular



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	Left ventricular damage	Left atrial or mitral damage	Pulmonary vasculature or tricuspid damage	Right ventricular damage
Echocardiographic criteria		LV mass index ♂ >115 g/m² ♀ > 95 g/m² LV ejection fraction <50% E/e' ratio >14	Left atrial volume index >34 ml/m² Presence of atrial fibrillation Moderate/severe mitral regurgitation	Systolic pulmonary arterial pressure ≥60 mmHg Moderate/severe tricuspid regurgitation	TAPSE <16 mm

Figure 1: Stages of cardiac damage in severe AS. Proposed staging classification based on the extent of echocardiographic signs of extra-aortic valvular cardiac damage. AS, aortic stenosis; LA, left atrial; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion.

pressure gradients were calculated using the Bernoulli equation [3]. Aortic valve area (AVA) was calculated according to the continuity equation using velocity time integrals of the LV outflow tract and aortic valve and indexed for body surface area (indexed AVA) [3]. In the parasternal long-axis view, LV dimensions were assessed and LV mass was calculated by Devereux's formula and indexed for body surface area (LV mass index) [10]. LV end-diastolic and end-systolic volumes were evaluated in the apical 2- and 4-chamber views and the LV ejection fraction was calculated according to the Simpson's biplane method [10]. Using the biplane method of disks, left atrial volumes were measured at end-systole in the apical 2- and 4-chamber views and indexed for body surface area (left atrial [LA] volume index) [10]. Pulsed-wave Doppler recordings of the transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities to assess LV diastolic function [11]. Using tissue Doppler imaging of the mitral annulus on the apical 4-chamber view, the e' was measured at both the lateral and septal side and averaged to calculate the E/e' ratio for estimation of LV filling pressures [11]. Severity of mitral and tricuspid regurgitation was graded according to a multi-parametric approach, as recommended [12]. The RV pressure was calculated from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation, adding the right atrial pressure determined by the inspiratory collapse and diameter of the inferior vena cava to estimate the systolic arterial pulmonary pressure [10, 13]. For the evaluation of RV systolic function, anatomical M-mode was applied on the focused apical 4-chamber view of the right ventricle to measure tricuspid annular plane systolic excursion (TAPSE) [10].

DEFINITIONS STAGING CLASSIFICATION

The presence and extent of extra-aortic valvular cardiac damage was evaluated on baseline transthoracic echocardiography (i.e., the first available echocardiogram with symptomatic severe AS) and accordingly, patients were classified into 5 independent stages as proposed by Généreux et al. [9] (Figure 1): Stage 0 – no signs of cardiac damage; Stage 1 – LV damage (LV ejection fraction <50%, LV mass index >95 g/m^2 for women or >115 g/m^2 for men or E/e' >14) [10, 11], Stage 2 – mitral valve or LA damage (LA volume index >34 ml/m^2 or mitral regurgitation (MR) ≥ grade 3 or presence of atrial fibrillation at

the moment of echocardiography) [10, 12], Stage 3 – tricuspid valve or pulmonary artery vasculature damage (systolic pulmonary artery pressure ≥60 mmHg or tricuspid regurgitation (TR) ≥ grade 3) [12] or Stage 4 – RV damage (TAPSE <16 mm) [13]. Patients were classified according to the criteria of the worst (i.e., highest) stage present.

Clinical endpoints and follow-up

All patients were followed-up for the occurrence of surgical or transcatheter AVR, all-cause mortality, stroke and hospitalization for cardiac cause. The primary outcome was all-cause mortality, as ascertained by review of hospital records linked to the governmental death registry database. The secondary outcome was a composite of all-cause mortality, stroke (major or minor) and cardiac-related hospitalization, occurring between baseline echocardiography and last follow-up.

Statistical analysis

Continuous data are presented as mean±SD or median (interquartile range [IQR]), as appropriate. Categorical data are presented as frequencies and percentages. Patients were divided according to stage of cardiac damage. For comparison of continuous variables between groups, the analysis of variance test with Bonferroni's post hoc analysis or the Kruskal-Wallis test was used for normally and non-normally distributed variables, respectively. Categorical variables were compared using the χ^2 test. The Kaplan-Meier method was used to calculate survival and event rates for the different stages of cardiac damage, comparison of cumulative event rates between these groups was performed by log-rank test. For the secondary outcome, patients were censored at the occurrence of the first event. To evaluate the association of the staging classification and other clinical and echocardiographic parameters with the primary and secondary endpoints, univariable Cox proportional hazards analyses were performed. From this analysis, statistically significant ($P \leq 0.05$) or clinically relevant variables were selected and introduced as covariates in multivariable Cox proportional hazards models. The occurrence of surgical or transcatheter AVR was entered as a time-dependent covariate. For both uni- and multivariable analyses, hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. SPSS software version 23.0 (IBM, Armonk, New York) was used for statistical analyses. A 2-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

Baseline clinical characteristics for the overall study population (mean age 73±11 years, 53% male) are listed in Table 1. The majority of patients had cardiovascular risk factors: hypertension and hypercholesterolemia were present in 72% and 66% of the population, respectively, and almost one-half of the patients (47%) had coronary artery disease. As per design of the study, all patients were symptomatic and one-third (33%) had New York Heart Association (NYHA) functional class III or IV symptoms. Patients were divided by the presence and extent of extra-aortic valvular cardiac damage seen on echocardiography (Figure 1): 8% (97) of patients were classified as Stage 0 (no cardiac damage), 24% (282) as Stage 1 (LV damage), 49% (588) as Stage 2 (mitral valve or LA damage), 7% (82) as

Table 1: Clinical characteristics of total patient population and according to stage of cardiac damage.

Variables	Total population (N = 1189)	Stage 0 (N = 97)	Stage 1 (N = 282)	Stage 2 (N = 588)	Stage 3 (N = 82)	Stage 4 (N = 140)	*P* value*
Age (years)	73.4±10.8	72.7±9.9	71.6±11.4	73.8±10.7	75.0±10.3	75.3±10.2†	**0.004**
Male gender, *N* (%)	624 (53)	65 (67)	139 (49)	301 (51)	34 (42)	85 (61)	**0.002**
Body mass index (kg/m^2)	25.5±4.6	26.1±4.7	25.5±4.2	25.6±4.9	24.6±4.6‡	24.8±4.4	0.098
Body surface area (m^2)	1.74±0.24	1.79±0.24	1.76±0.23	1.74±0.25	1.68±0.24	1.75±0.25	**0.048**
Hypertension, *N* (%)	857 (72)	67 (69)	210 (75)	430 (73)	56 (68)	94 (67)	0.429
Hypercholesterolemia, *N* (%)	790 (66)	67 (69)	185 (66)	397 (68)	49 (60)	92 (66)	0.668
Diabetes mellitus, *N* (%)	317 (27)	30 (31)	80 (28)	144 (25)	18 (22)	45 (32)	0.069
Coronary artery disease, *N* (%)	563 (47)	42 (43)	131 (47)	267 (45)	30 (37)	93 (66)	**<0.001**
Previous MI, *N* (%)	189 (16)	12 (12)	36 (13)	85 (15)	14 (17)	42 (30)	**<0.001**
History of smoking, *N* (%)	330 (28)	36 (37)	82 (29)	158 (27)	20 (24)	34 (24)	0.198
COPD, *N* (%)	129 (11)	11 (11)	31 (11)	49 (8)	17 (21)	21 (15)	**0.005**
History of atrial fibrillation, *N* (%)	354 (30)	8 (8)	35 (12)	184 (31)	45 (55)	82 (59)	**<0.001**
NYHA class ≥III, *N* (%)	393 (33)	27 (31)	67 (26)	189 (35)	44 (55)	66 (49)	**<0.001**
Symptoms, *N* (%)							
Angina	358 (30)	33 (34)	98 (35)	175 (30)	18 (22)	34 (24)	0.072
Dyspnea	956 (81)	72 (74)	207 (74)	473 (81)	77 (94)	127 (91)	**<0.001**
Syncope	103 (9)	9 (9)	37 (13)	53 (9)	0 (0)	4 (3)	**<0.001**
Estimated GFR (ml/min/1.73 m^2)	61.8±24.9	69.1±22.0	64.7±24.5	62.8±24.7	49.3±24.3†‡§	53.9±25.5†‡§	**<0.001**
Systolic BP (mmHg)	135.6±24.0	139.6±21.9	137.1±24.3	136.9±23.8	129.6±26.5	128.1±22.1†‡§	**<0.001**
Diastolic BP (mmHg)	71.0±13.0	73.4±13.3	73.0±12.5	70.0±12.8†	70.1±13.7	70.2±13.5	**0.007**
Medication, *N* (%):							
Beta blocker	644 (54)	41 (42)	152 (54)	325 (55)	42 (51)	84 (60)	0.090
ACE inhibitor/ARB	548 (46)	45 (46)	128 (45)	275 (47)	37 (45)	63 (45)	0.992
Aspirin/thienopyridines	556 (47)	46 (47)	144 (51)	262 (45)	37 (45)	67 (48)	0.491
Oral anticoagulant	263 (22)	12 (12)	26 (9)	127 (22)	33 (40)	65 (46)	**<0.001**
Statin	757 (64)	67 (69)	186 (66)	367 (62)	46 (56)	91 (65)	0.354
Calcium channel blocker	359 (30)	27 (29)	89 (32)	190 (32)	20 (24)	33 (24)	0.200
Diuretic agents	515 (43)	25 (26)	100 (36)	252 (43)	59 (72)	79 (56)	**<0.001**

Continuous variables are presented as mean±SD or median [interquartile range]. Categorical variables are expressed as number (percentage). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. † $P<0.05$ vs. Stage 1 with Bonferroni's post hoc analysis. ‡ $P<0.05$ vs. Stage 0 with Bonferroni's post hoc analysis. § $P<0.05$ vs. Stage 2 with Bonferroni's post hoc analysis.

Table 2: Echocardiographic characteristics of total patient population and according to stage of cardiac damage.

Variables	Total population (N = 1189)	Stage 0 (N = 97)	Stage 1 (N = 282)	Stage 2 (N = 588)	Stage 3 (N = 82)	Stage 4 (N = 140)	*P* value*
Heart rate at TTE (bpm)	74.7±14.8	76.4±13.2	72.2±12.5	73.6±14.4	81.0±18.7†‡	79.6±16.9†‡	**<0.001**
Valve morphology, *N* (%):							**<0.001**
Tricuspid	1049 (88)	76 (78)	228 (81)	535 (91)	77 (94)	133 (95)	
Bicuspid	140 (12)	21 (22)	54 (19)	53 (9)	5 (6)	7 (5)	
Atrial fibrillation at TTE, *N* (%)	165 (14)	0 (0)	0 (0)	81 (14)	28 (34)	56 (40)	**<0.001**
LV end-diastolic diameter (mm)	48.2±8.0	41.4±5.3	47.4±6.9§	48.8±8.1§	50.2±8.0†§	50.9±8.2†‡§	**<0.001**
LV end-systolic diameter (mm)	33.4±9.6	26.8±6.0	32.1±8.2§	33.2±9.4§	36.4±10.2†‡§	39.4±10.8†‡§	**<0.001**
Septal wall thickness (mm)	12.5±2.4	11.4±1.5	12.3±1.9§	12.9±2.6†§	12.2±2.3	12.3±2.5‡§	**<0.001**
Posterior wall thickness (mm)	11.9±2.2	10.9±1.4	11.7±1.8§	12.2±2.3§	11.8±2.0§	11.5±2.3‡	**<0.001**
LV mass index (g/m^2)	132.6±39.7	87.7±14.5	124.5±30.0§	140.7±42.4†§	142.3±36.6†§	138.2±34.9†§	**<0.001**
LV end-diastolic volume (ml)	107.3±46.8	79.4±25.2	97.4±41.8§	111.9±49.3†§	113.1±45.5§	123.6±46.1†§	**<0.001**
LV end-systolic volume (ml)	54.7±40.0	31.1±14.1	46.5±34.1§	55.6±40.9†§	64.9±40.3†§	77.5±45.3†‡§	**<0.001**
LV ejection fraction (%)	54.2±14.3	62.9±7.0	57.8±12.0§	55.1±13.4†§	46.9±14.9†‡§	41.6±16.1†‡§‖	**<0.001**
LV ejection fraction <50%	339 (29)	0 (0)	52 (18)	156 (27)	39 (48)	92 (66)	**<0.001**
Peak E-wave velocity (cm/s)	96.2±43.0	68.5±16.7	78.0±27.8	100.2±42.1†§	132.5±51.3†‡§	115.0±51.5†‡§‖	**<0.001**
E' (cm/s)	5.3±2.0	6.5±2.3	4.7±1.5§	5.4±2.0†§	5.7±1.9†	5.3±2.1§	**<0.001**
E/e' ratio	19.3±10.2	10.8±2.2	18.0±8.0§	19.8±10.3§	24.2±11.4†‡§	23.3±12.7†‡§	**<0.001**
Left atrial volume index (ml/m^2)	44.5±23.1	24.8±5.9	26.1±6.1	50.8±19.1†§	60.4±34.3†‡§	57.9±28.2†‡§	**<0.001**
Significant MR, *N* (%)	68 (6)	0 (0)	0 (0)	35 (6)	14 (17)	19 (14)	**<0.001**
Systolic PAP (mmHg)	36.5±14.0	26.9±8.7	30.4±8.5	34.9±10.0†§	61.4±14.6†‡§	42.8±16.6†‡§‖	**<0.001**
Significant TR, *N* (%)	65 (6)	0 (0)	0 (0)	0 (0)	39 (48)	26 (19)	**<0.001**
TAPSE (mm)	20.8±4.4	22.2±3.3	21.9±3.5	21.8±3.6	20.1±3.6†‡§	13.3±1.9†‡§‖	**<0.001**
Mean AV gradient (mmHg)	43.1±15.5	41.9±12.5	43.9±14.4	46.0±16.0	38.2±14.1†‡	33.5±14.3†‡§	**<0.001**
Peak aortic jet velocity (m/s)	4.1±0.7	4.1±0.6	4.1±0.6	4.2±0.7	3.9±0.7†‡	3.6±0.7†‡§‖	**<0.001**
AVA (cm^2)	0.78±0.18	0.84±0.19	0.78±0.17§	0.78±0.18	0.75±0.20§	0.73±0.17‡§	**<0.001**
Indexed AVA (cm^2/m^2)	0.45±0.11	0.47±0.11	0.45±0.10	0.46±0.12	0.45±0.12	0.43±0.12§	**0.021**
Low-flow low-gradient AS, *N* (%)	224 (19)	15 (16)	39 (14)	81 (14)	24 (29)	65 (46)	**<0.001**

Continuous variables are presented as mean±SD. Categorical variables are expressed as number (percentage). AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; Bpm, beats per minute; LV, left ventricular; MR, mitral regurgitation; PAP, pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. † $P<0.05$ vs. Stage 1 with Bonferroni's post hoc analysis. ‡ $P<0.05$ vs. Stage 2 with Bonferroni's post hoc analysis. § $P<0.05$ vs. Stage 0 with Bonferroni's post hoc analysis. ‖ $P<0.05$ vs. Stage 3 with Bonferroni's post hoc analysis.

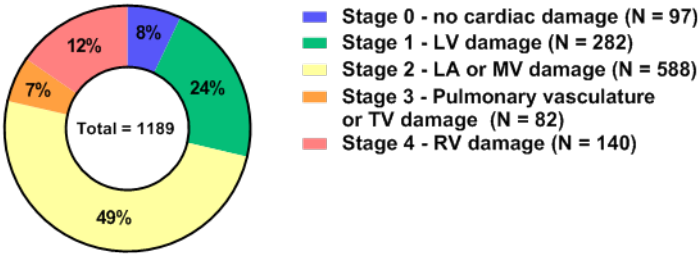


Figure 2: Distribution of stages of cardiac damage in total population. LA, left atrial; LV, left ventricular; MV, mitral valve; RV, right ventricular; TV, tricuspid valve.

Stage 3 (tricuspid valve or pulmonary artery vasculature damage) and 12% (140) as Stage 4 (RV damage) (Figure 2). Compared to patients in less advanced stages, the patients in the higher stages were older, had more severe symptoms (NYHA functional class ≥III), worse kidney function and more frequently had a history of coronary artery disease, previous myocardial infarction and atrial fibrillation. In addition, these patients more often used oral anticoagulation and diuretic agents.

Baseline echocardiographic parameters for the overall study population and per separate stage of cardiac damage are presented in Table 2. The mean LV ejection fraction was 54±14%, LV mass index 133±40 g/m^2, mean aortic valve gradient 43±16 mmHg, peak aortic jet velocity 4.1±0.7 m/s and AVA 0.78±0.18 cm^2. Interestingly, patients in Stage 3 and 4 showed a lower mean aortic valve gradient and peak aortic jet velocity, corresponding with a higher percentage of low-flow low-gradient severe AS (29% in Stage 3 and 46% in Stage 4 compared with ≤16% in less advanced stages; P<0.001). Patients in more advanced stages had lower LV ejection fraction and more often had an LV ejection fraction <50%, had higher E/e' ratios and LA volume indices and more often had significant mitral and tricuspid regurgitation compared with patients in lower stages. The incidences of the individual staging components of cardiac damage in the total study population are presented in Table 3.

LONG-TERM OUTCOMES

During follow-up, 917 patients (77%) underwent AVR within a median time of 67 (IQR: 5 to 197) days, of whom 47% received a transcatheter AVR and 53% a surgical AVR. During a median follow-up of 42 (IQR: 20 to 77) months, 472 patients (40%) died and over a median time of 35 (IQR: 14 to 67) months, 617 patients (52%) reached the combined endpoint (all-cause mortality, stroke and cardiac-related hospitalization). The clinical outcomes during follow-up per stage of cardiac damage are presented in Table 4.

SURVIVAL ANALYSIS

Kaplan-Meier curve analysis showed that patients with more advanced stages of cardiac damage had significantly higher 5-year cumulative event rates (Figure 3 *panel A*) (log-rank χ^2 93.4; P<0.001). Particularly for Stage ≥2, significantly higher 5-year cumulative event rates were noted compared to Stage 0 (P<0.02 for all) and Stage 1 (P<0.01

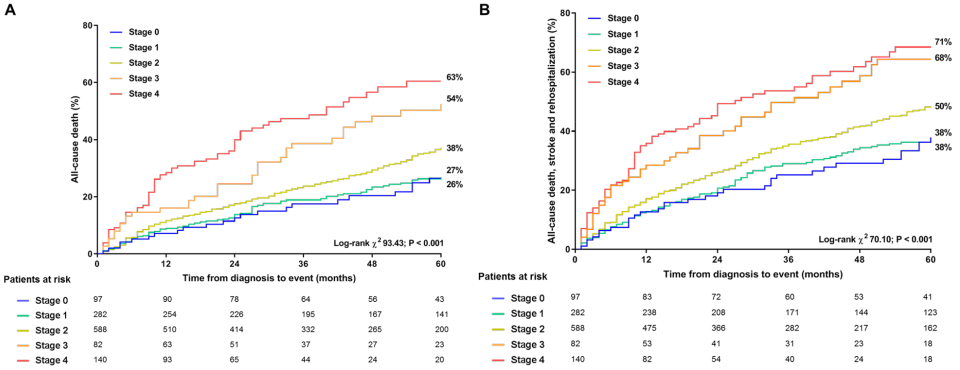


Figure 3: Survival analyses according to stage of cardiac damage for total population. Kaplan-Meier estimates for the cumulative event rates of all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage.

Table 3: Incidence of the individual staging components of cardiac damage in total population.

Stage 0 – no damage	**97/1189**
Stage 1 – left ventricular damage	**282/1189**
Increased LV mass index (>95 for women or >115 g/m^2 for men), *N* (%)	882 (74)
LV ejection fraction <50%, *N* (%)	339 (29)
E/e' ratio >14, *N* (%)	625 (53)
Stage 2 – left atrial or mitral valve damage	**588/1189**
Indexed left atrial volume >34 ml/m^2, *N* (%)	757 (64)
Moderate or severe mitral regurgitation (≥ grade 3), *N* (%)	68 (6)
Presence of atrial fibrillation at time echocardiography, *N* (%)	165 (14)
Stage 3 – pulmonary vasculature or tricuspid valve damage	**82/1189**
Systolic pulmonary artery pressure ≥60 mmHg, *N* (%)	74 (6)
Moderate or severe tricuspid regurgitation (≥grade 3), *N* (%)	65 (6)
Stage 4 – right ventricular damage	**140/1189**
Tricuspid annular plane systolic excursion <16 mm, *N* (%)	140 (12)

LV, left ventricular.

Table 4: Clinical outcomes during follow-up per stage of cardiac damage.

	Stage 0 (N = 97)	**Stage 1 (N = 282)**	**Stage 2 (N = 588)**	**Stage 3 (N = 82)**	**Stage 4 (N = 140)**	***P* value***
Surgical or transcatheter AVR, % (*N*)	80% (78)	84% (238)	77% (452)	66% (54)	68% (95)	**<0.001**
All-cause death, % (*N*)	27% (26)	32% (90)	39% (229)	55% (45)	59% (82)	**<0.001**
1 year	7% (7)	10% (28)	13% (78)	23% (19)	34% (47)	
Any stroke, % (*N*)	12% (11)	9% (25)	10% (58)	12% (10)	17% (24)	0.104
Major stroke	6	11	37	5	11	
Minor stroke	5	14	21	5	13	
Cardiac-related hospitalization, % (*N*)	12% (12)	16% (46)	22% (131)	24% (20)	18% (25)	0.055
Combined endpoint (all-cause death, any stroke and cardiac-related rehospitalisation), % (*N*)	40% (39)	46% (128)	52% (303)	66% (54)	66% (93)	**<0.001**

AVR, aortic valve replacement. **P* values are calculated by χ^2 test.

Table 5: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in the total study population.

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.033 (1.024-1.043)	**<0.001**	1.020 (1.009-1.031)	**<0.001**
Male gender (yes/no)	0.926 (0.773-1.110)	0.406	1.027 (0.837-1.261)	0.802
Coronary artery disease (yes/no)	1.386 (1.157-1.662)	**<0.001**	0.933 (0.741-1.173)	0.551
Previous MI (yes/no)	2.092 (1.684-2.597)	**<0.001**	1.698 (1.285-2.244)	**<0.001**
COPD (yes/no)	1.134 (0.841-1.529)	0.409		
History of atrial fibrillation (yes/no)	1.531 (1.264-1.854)	**<0.001**	1.016 (0.812-1.270)	0.892
NYHA class ≥III (yes/no)	1.541 (1.267-1.874)	**<0.001**	1.205 (0.976-1.487)	0.083
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.976 (0.972-0.979)	**<0.001**	0.981 (0.977-0.985)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.995 (0.991-0.999)	**0.012**	0.996 (0.992-1.000)	0.059
Diuretic agents (yes/no)	1.332 (1.111-1.596)	**0.002**	1.041 (0.844-1.284)	0.709
Peak aortic jet velocity (per 1 m/s increase)	0.678 (0.595-0.772)	**<0.001**	0.952 (0.817-1.110)	0.531
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.005 (0.997-1.014)	0.197	2.001 (0.793-5.046)	0.142
Surgical or transcatheter AVR (yes/no)	0.395 (0.323-0.483)	**<0.001**	0.498 (0.397-0.625)	**<0.001**
Stage of cardiac damage (per 1 stage increase)	1.481 (1.358-1.616)	**<0.001**	1.283 (0.158-1.422)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.111 (0.718-1.720)	0.635	1.126 (0.682-1.858)	0.644
Stage 0 vs. Stage 2	1.611 (1.074-2.417)	**0.021**	1.486 (0.930-2.374)	0.098
Stage 0 vs. Stage 3	2.736 (1.688-4.435)	**<0.001**	1.975 (1.125-3.469)	**0.018**
Stage 0 vs. Stage 4	3.847 (2.470-5.991)	**<0.001**	2.472 (1.471-4.155)	**0.001**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 5: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in the total study population (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.026 (1.018-1.034)	**<0.001**	1.013 (1.004-1.022)	**0.007**
Male gender (yes/no)	0.991 (0.845-1.161)	0.911	1.013 (0.850-1.207)	0.887
Coronary artery disease (yes/no)	1.419 (1.210-1.663)	**<0.001**	1.000 (0.822-1.217)	1.000
Previous MI (yes/no)	1.862 (1.531-2.266)	**<0.001**	1.474 (1.156-1.880)	**0.002**
COPD (yes/no)	1.116 (0.859-1.448)	0.411		
History of atrial fibrillation (yes/no)	1.447 (1.221-1.714)	**<0.001**	1.095 (0.899-1.333)	0.368
NYHA class ≥III (yes/no)	1.379 (1.162-1.638)	**<0.001**	1.110 (0.923-1.335)	0.268
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.982 (0.979-0.985)	**<0.001**	0.986 (0.983-0.990)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.993-0.999)	**0.018**	0.997 (0.944-1.001)	0.165
Diuretic agents (yes/no)	1.420 (1.211-1.664)	**<0.001**	1.124 (0.938-1.346)	0.206
Peak aortic jet velocity (per 1 m/s increase)	0.729 (0.650-0.817)	**<0.001**	0.937 (0.821-1.069)	0.333
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.000 (0.993-1.007)	0.938	1.664 (0.743-3.726)	0.216
Surgical or transcatheter AVR (yes/no)	0.677 (0.564-0.813)	**<0.001**	0.798 (0.651-0.979)	**0.031**
Stage of cardiac damage (per 1 stage increase)	1.355 (1.256-1.462)	**<0.001**	1.191 (1.091-1.299)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.117 (0.780-1.598)	0.547	1.157 (0.777-1.724)	0.474
Stage 0 vs. Stage 2	1.508 (1.080-2.106)	**0.016**	1.456 (1.002-2.118)	**0.049**
Stage 0 vs. Stage 3	2.356 (1.560-3.559)	**<0.001**	1.764 (1.104-2.819)	**0.018**
Stage 0 vs. Stage 4	2.901 (1.993-4.223)	**<0.001**	1.947 (1.268-2.988)	**0.002**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

for all). Similarly, for the combined outcome, the more advanced stages showed significantly higher cumulative 5-year event rates (Figure 3 *panel B*)(log-rank χ^2 70.1; *P*<0.001), specifically for Stage ≥2 compared to Stage 0 (*P*<0.02 for all) and Stage 1 (*P*<0.01 for all). For the subgroup of patients treated with surgical or transcatheter AVR, patients with more advanced cardiac damage showed higher cumulative events rates for both total and post-operative only all-cause mortality and combined outcome (Supplementary Figure 5 and 6, respectively).

Prognostic value of proposed staging classification

The correlates of all-cause mortality and the combined endpoint on univariable and multivariable Cox regression analyses are shown in Table 5. On multivariable analysis, age, previous myocardial infarction, renal function, surgical or transcatheter AVR, and stage of cardiac damage were independently associated with all-cause mortality. For each increase in stage, a 28% higher risk for all-cause mortality was observed (95% CI: 1.158-1.422, *P*<0.001). When evaluating each separate stage of cardiac damage, only Stage 3 (HR: 1.975, 95% CI: 1.125-3.469; *P*=0.018) and Stage 4 (HR: 2.472, 95% CI: 1.471-4.155; *P*=0.001) were independently associated with all-cause mortality. For the combined endpoint, age, previous myocardial infarction, renal function, surgical or transcatheter AVR and stage of cardiac damage were independent predictors on multivariable analysis. A 19% increase in risk for the combined outcome was observed for each increasing stage (95% CI: 1.091-1.299); P<0.001). However, only Stage 2 (HR: 1.456, 95% CI: 1.002-2.118; *P*=0.049), Stage 3 (HR: 1.764, 95% CI: 1.104-2.819; *P*=0.018) and Stage 4 (HR: 1.947, 95% CI: 1.268-2.988; *P*=0.002) were independently associated with all-cause mortality, stroke and cardiac-related hospitalization. In patients treated with surgical or transcatheter AVR, stage of cardiac damage was significantly associated with both total and postoperative only all-cause mortality and combined outcome, respectively, although only Stage 4 was independently associated with these outcomes when considering separate stages of cardiac damage (Supplementary Tables 6 and 7).

Discussion

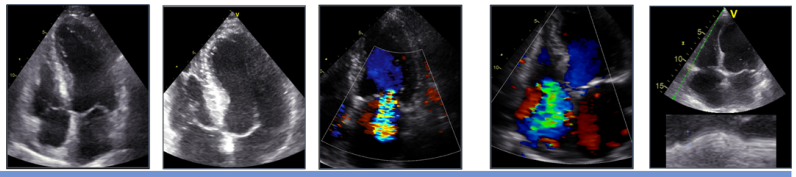
The present study demonstrated that, in a large real-world and multicenter cohort of symptomatic severe AS patients, extra-aortic valvular cardiac injury such as LA dilation, MR, and RV dysfunction is highly prevalent (Figure 4). Classified according to a newly proposed staging system, extra-aortic valvular cardiac damage is independently associated with all-cause mortality and a combined outcome of all-cause mortality, stroke and cardiac-related hospitalization, although this effect seems to be primarily driven by the Stages 3 (tricuspid valve or pulmonary artery vasculature damage) and 4 (RV damage).

Prevalence of cardiac damage in severe AS

In severe AS, chronic pressure overload imposed on the LV by progressive calcification and narrowing of the aortic valve induces a compensatory concentric hypertrophic response of the LV myocardium. After this initial adaptive response to normalize LV wall pressure and maintain cardiac output, ongoing development of LV hypertrophy will neg-

CENTRAL ILLUSTRATION Staging of Cardiac Damage in Severe AS: Clinical Outcomes in a Large Multicenter Cohort

Staging Classification According to Extent of Cardiac Damage



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	**Left ventricular damage**	**Left atrial or mitral valve damage**	**Pulmonary vasculature or tricuspid valve damage**	**Right ventricular damage**
Echocardiographic criteria		LV mass index ♂ >115 g/m² ♀ > 95 g/m² LV ejection fraction < 50% E/e' ratio > 14	Left atrial volume index > 34 ml/m² Presence of atrial fibrillation Moderate/severe mitral regurgitation	Systolic pulmonary arterial pressure ≥ 60 mmHg Moderate/severe tricuspid regurgitation	TAPSE < 16 mm
Prevalence in cohort	**8% (N = 97)**	**24% (N = 282)**	**49% (N = 588)**	**7% (N = 82)**	**12% (N = 140)**

Outcomes According to Stages of Cardiac Damage

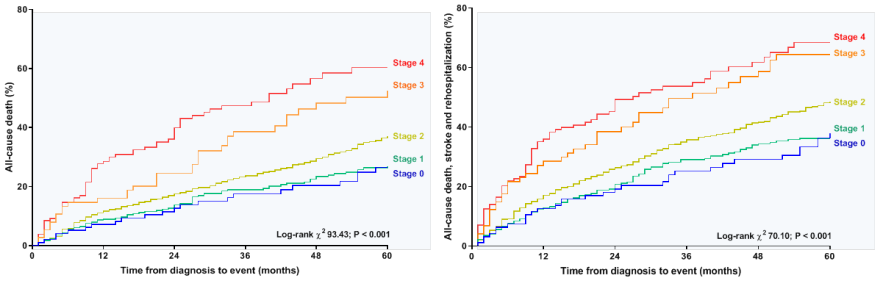


Figure 4: Clinical outcomes of stages of cardiac damage in a real-world multicenter severe symptomatic aortic stenosis cohort. **(Top)** After classification of patients with symptomatic severe AS according to the recently proposed staging system based on the presence and extent of extra-aortic valvular cardiac injury on echocardiography, a high prevalence of cardiac damage (e.g., left atrial enlargement and right ventricular dysfunction) was seen in the study population. **(Bottom)** For both all-cause mortality **(left)** and the combined outcome of all-cause mortality, stroke, and cardiac rehospitalization **(right)**, the more advanced stages (i.e., Stage ≥2) showed significantly higher cumulative 5-year event rates.

atively influence both LV systolic and diastolic function, and will eventually result in the formation of myocardial fibrosis [14]. At this time, most patients will be symptomatic [14]. Currently, AVR is indicated in patients with severe AS who are symptomatic or have reduced LV systolic function (i.e., LV ejection fraction <50%) [1, 2]. However, the hemodynamic effects of chronic pressure overload in severe AS are not limited to the LV only. Elevated LV filling pressures may lead to LA dilation, and this LA remodelling together with changes in LV geometry have been associated with an increased risk for the development of atrial fibrillation and MR [4, 15]. Rising LA pressure gradients will then contribute to an increase in pulmonary artery pressure, which may eventually lead to right atrial and ventricular remodelling, inducing TR and, ultimately, RV dysfunction [16].

Multiple studies have demonstrated a high prevalence of extra-aortic valvular cardiac damage in severe AS patients. Atrial fibrillation has been reported in 8% to 13% of patients undergoing surgical AVR and in up to 51% of transcatheter AVR patients [15]. Both significant MR and TR are frequently observed, with reported rates ranging from 13% to 20% for MR [4, 17] and 11% to 27% for TR [6, 18–20]. Severe pulmonary hypertension has been reported in 10% of surgical AVR and in up to 36% of transcatheter AVR patients [21, 22]. For RV dysfunction, prevalence rates of 24% to 29% have been observed [7, 8, 23].

These percentages are largely consistent with the reported prevalence of cardiac damage by Généreux et al. [9] and by the present study. Interestingly, higher rates of low-flow low-gradient severe AS were seen in Stage 3 (tricuspid valve or pulmonary artery vasculature damage) and Stage 4 (RV damage) (29% and 46% vs. 14% to 16% in the less advanced stages, respectively), consistent with previous studies [7, 20, 24].

Prognostic relevance of cardiac damage in AS

Multiple studies have reported a negative prognostic impact of the individual cardiac damage components in severe AS patients, irrespective of the underlying etiology (either severe AS itself or concomitant comorbidities). Although the presence of LV damage (i.e., LV systolic or diastolic dysfunction or LV hypertrophy [Stage 1]) [25, 26] and of LA and mitral valve damage (i.e., significant MR, atrial fibrillation or LA enlargement [Stage 2]) [5, 15, 17, 27] have independently been associated with an increased risk for mortality, this effect was not observed in the present study when taking into account the whole extent of cardiac injury. This discrepancy may be attributed to the high prevalence of Stage 1 and Stage 2 in the current population and the stronger association between more advanced stages and clinical outcomes. Importantly, pulmonary artery vasculature or tricuspid valve damage (i.e., severe pulmonary hypertension or significant TR [Stage 3]) and RV dysfunction (Stage 4) were shown to be the strongest predictors for all-cause mortality in the present study, as shown previously in studies focusing on the effects of pulmonary hypertension [21], significant TR [6, 20], and RV dysfunction in severe AS patients [7, 8, 19].

Studies considering the collective prognostic effect of the different expressions of extra-aortic valvular cardiac injury are limited. In a cohort of 432 severe AS patients undergoing surgical AVR, Tan et al. [28] assessed the incremental predictive value of multiple pre-operatively assessed echocardiographic variables, including LV ejection fraction, E/e', LV mass index, LA volume index, MR and TR grade, systolic pulmonary artery pres-

sure, and several right atrial and ventricular functional parameters. After correcting for operative risk, only LV mass index, right atrial area index, mean gradient <40 mmHg, MR grade and LV end-diastolic volume index were independently predictive for 2-year all-cause mortality [28]. In the more recently proposed staging classification based on the anatomic and functional extent of cardiac damage, stages of cardiac injury were independently associated with an increased risk of 1-year mortality and adverse events in intermediate-risk severe AS patients undergoing either transcatheter or surgical AVR [9]. To our knowledge, the present study is the first to confirm the prognostic impact of this staging model in a large unselected real-world and multicenter cohort of symptomatic severe AS patients over longer term follow-up (median follow-up time 42 [IQR: 20 to 77] months) and to extend the earlier findings by demonstrating that the prognostic impact of this classification is mainly determined by the presence of significant TR or pulmonary artery hypertension (Stage 3) and RV dysfunction (Stage 4). Our results suggest that incorporation of the proposed staging system in future risk models, in particular the components of these advanced stages, could potentially aid in the risk stratification of severe AS patients, because these aspects are generally not included in current risk prediction models. Future prospective studies are needed to confirm the prognostic value of this staging classification and to determine its additional incremental value in the risk assessment of specific AS subpopulations.

LIMITATIONS

The present study has limitations inherent to its retrospective nature. The participating centers were referral centers for cardiac surgery and the decision for AVR was made at the discretion of the respective heart teams (as recommended by current guidelines [1, 2]); therefore selection and referral bias may be present. However, in this real-world, multicenter cohort, patients were included regardless of treatment or operative risk category. In the proposed staging classification, reduced LV ejection fraction (<50%) was included as criterium for Stage 1 (Figure 1) [9]. However, low LV ejection fraction is associated with a worse prognosis than atrial fibrillation (i.e., Stage 2) [29], potentially resulting in an underestimation of prognosis of patients in Stage 1. In the present study, subanalyses excluding Stage 1 patients with a LV ejection fraction <50% (Supplementary Figure 7 and Supplementary Table 8) showed similar results as the analyses using the proposed staging classification (Figure 3 and Table 5). The modest impact on prognosis of LV ejection fraction <50% in Stage 1 may be explained by the low prevalence of reduced LV ejection fraction in this stage versus increasing stages of cardiac damage (Table 2). Distinction between subtypes of significant TR (i.e., due to pulmonary hypertension or due to atrial fibrillation only) was beyond the scope of this paper; future studies will need to elucidate the role of different underlying pathophysiological mechanisms of TR on prognosis in severe AS patients. In the present study, only TAPSE was used to estimate RV systolic dysfunction. Consideration of other RV systolic function parameters could have resulted in a more accurate assessment of RV function, because TAPSE only takes into account the tricuspid lateral annulus displacement. However, TAPSE is easy to obtain, less dependent on image quality, and has been validated in large patient cohorts [13, 19]. Furthermore, TAPSE as a measure of RV dysfunction has been demonstrated to have prognostic implications in severe AS patients [7, 8, 19]. Future studies incorporating 3-

dimensional imaging techniques or RV free wall longitudinal strain for the assessment of RV systolic function in the proposed staging system might provide a more accurate evaluation of RV damage [30, 31].

Conclusions

In this large multicenter cohort of symptomatic severe AS patients, extra-aortic valvular cardiac injury was present in the majority of patients. Stage of cardiac damage as classified by a novel proposed staging system [9] was independently associated with all-cause mortality, although pulmonary artery hypertension and TR (Stage 3) and RV dysfunction (Stage 4) seemed to be the main determinants of this association. Incorporation of this proposed staging system into current risk stratification models, in particular the components of these advanced stages, may aid in the risk assessment of severe AS patients and their different subpopulations.

REFERENCES

[1] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

[2] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[3] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[4] Unger P, Dedobbeleer C, Van Camp G, Plein D, Cosyns B, Lancellotti P. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. Heart. 2010;96(1):9-14.

[5] Zilberszac R, Gleiss A, Binder T, Laufer G, Grimm M, Gabriel H, et al. Prognostic relevance of mitral and tricuspid regurgitation in patients with severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2018;43:1-8.

[6] Lindman BR, Maniar HS, Jaber WA, Lerakis S, Mack MJ, Suri RM, et al. Effect of Tricuspid Regurgitation and the Right Heart on Survival after Transcatheter Aortic Valve Replacement: Insights From the Placement of Aortic Transcatheter Valves II Inoperable Cohort. Circ Cardiovasc Interv. 2015;8(4):1-10.

[7] Galli E, Guirette Y, Feneon D, Daudin M, Fournet M, Leguerrier A, et al. Prevalence and prognostic value of right ventricular dysfunction in severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2015;16(5):531-8.

[8] Asami M, Stortecky S, Praz F, Lanz J, Räber L, Franzone A, et al. Prognostic Value of Right Ventricular Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Img. 2019;12(4):577-87.

[9] Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J. 2017;38(45):3351-8.

[10] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[11] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-60.

[12] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013;14(7):611-44.

[13] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and . J Am Soc Echocardiogr. 2010;23(7):685-713.

[14] Carabello BA, Paulus WJ. Aortic stenosis. Lancet. 2009;373(9667):956-66.

[15] Tarantini G, Mojoli M, Urena M, Vahanian A. Atrial fibrillation in patients undergoing transcatheter aortic valve implantation: epidemiology, timing, predictors, and outcome. Eur Heart J. 2017;38(17):1285-93.

[16] Kammerlander AA, Marzluf BA, Graf A, Bachmann A, Kocher A, Bonderman D, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcome late after left heart valve procedure. J Am Coll Cardiol. 2014;64(24):2633-42.

[17] Barbanti M, Webb JG, Hahn RT, Feldman T, Boone RH, Smith CR, et al. Impact of Preoperative Moderate/Severe Mitral Regurgitation on 2-Year Outcome After Transcatheter and Surgical Aortic Valve Replacement: Insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. Circulation. 2013 dec;128(25):2776-84.

[18] Barbanti M, Binder RK, Dvir D, Tan J, Freeman M, Thompson CR, et al. Prevalence and impact of preoperative moderate/severe tricuspid regurgitation on patients undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2015;85(4):677-83.

[19] Schwartz LA, Rozenbaum Z, Ghantous E, Kramarz J, Biner S, Ghermezi M, et al. Impact of Right Ventricular Dysfunction and Tricuspid Regurgitation on Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement. J Am Soc Echocardiogr. 2017;30(1):36-46.

[20] Amano M, Izumi C, Taniguchi T, Morimoto T, Miyake M, Nishimura S, et al. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2019;20(3):353-60.

[21] Zlotnick DM, Ouellette ML, Malenka DJ, Desimone JP, Leavitt BJ, Helm RE, et al. Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. Am J Cardiol. 2013;112(10):1635-40.

[22] Alushi B, Beckhoff F, Leistner D, Franz M, Reinthaler M, Stähli BE, et al. Pulmonary Hypertension in Patients With Severe Aortic Stenosis: Prognostic Impact After Transcatheter Aortic Valve Replacement: Pulmonary Hypertension in Patients Undergoing TAVR. J Am Coll Cardiol Img. 2019;12(4):591-601.

[23] Koifman E, Didier R, Patel N, Jerusalem Z, Kiramijyan S, Ben-Dor I, et al. Impact of right ventricular function on outcome of severe aortic stenosis patients undergoing transcatheter aortic valve replacement. Am Heart J. 2017;184:141-7.

[24] Cavalcante JL, Rijal S, Althouse AD, Delgado-Montero A, Katz WE, Schindler JT, et al. Right Ventricular Function and Prognosis in Patients with Low-Flow, Low-Gradient Severe Aortic Stenosis. J Am Soc Echocardiogr. 2016;29(4):325-33.

[25] Asami M, Lanz J, Stortecky S, Räber L, Franzone A, Heg D, et al. The Impact of Left Ventricular Diastolic Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv. 2018;11(6):593-601.

[26] Minamino-Muta E, Kato T, Morimoto T, Taniguchi T, Inoko M, Haruna T, et al. Impact of the left ventricular mass index on the outcomes of severe aortic stenosis. Heart. 2017;103(24):1992-9.

[27] Beach JM, Mihaljevic T, Rajeswaran J, Marwick T, Edwards ST, Nowicki ER, et al. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. J Thorac Cardiovasc Surg. 2014;147(1):362-9.e8.

[28] Tan TC, Flynn AW, Chen-Tournoux A, Rudski LG, Mehrotra P, Nunes MC, et al. Risk prediction in aortic valve replacement: incremental value of the preoperative echocardiogram. J Am Heart Assoc. 2015;4(10):1-9.

[29] Ito S, Miranda WR, Nkomo VT, Connolly HM, Pislaru SV, Greason KL, et al. Reduced Left Ventricular Ejection Fraction in Patients With Aortic Stenosis. J Am Coll Cardiol. 2018;71(12):1313-21.

[30] Dahou A, Clavel MA, Capoulade R, Bartko PE, Magne J, Mundigler G, et al. Right ventricular longitudinal strain for risk stratification in low-flow, low-gradient aortic stenosis with low ejection fraction. Heart. 2016;102(7):548-54.

[31] Carluccio E, Biagioli P, Alunni G, Murrone A, Zuchi C, Coiro S, et al. Prognostic value of right ventricular dysfunction in heart failure with reduced ejection fraction: superiority of longitudinal strain over tricuspid annular plane systolic excursion. Circ Cardiovasc Imaging. 2018;11(1):e006894.

SUPPLEMENTARY MATERIAL

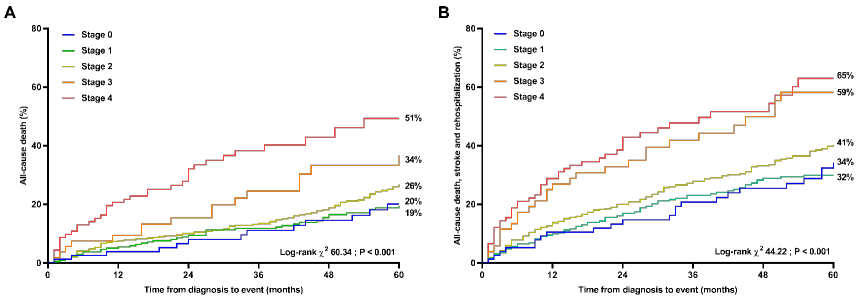


Figure 5: Survival analyses according to stage of cardiac damage for patients undergoing surgical or transcatheter aortic valve replacement. Kaplan-Meier estimates for the cumulative event rates of all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage.

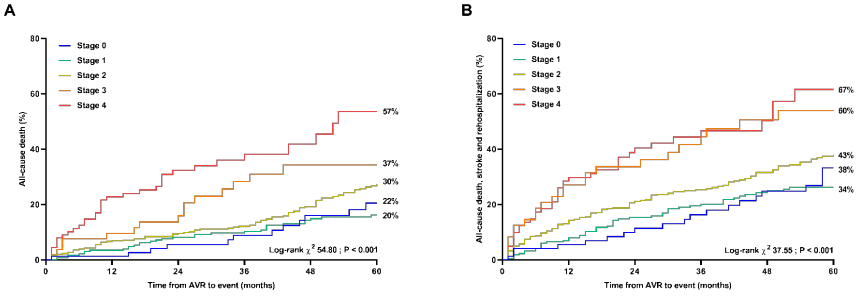


Figure 6: Survival analyses according to stage of cardiac damage for postoperative adverse events in patients undergoing surgical or transcatheter aortic valve replacement. Kaplan-Meier estimates for the cumulative event rates of postoperative all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage. AVR, aortic valve replacement.

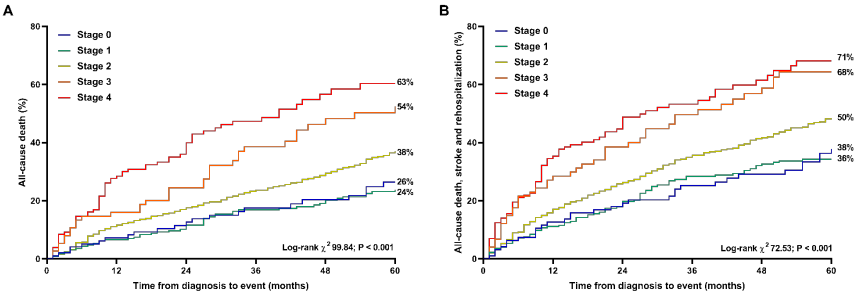


Figure 7: Survival analyses according to stage of cardiac damage for patients undergoing surgical or transcatheter AVR after exclusion of patients in Stage 1 with LV ejection fraction <50%. Kaplan-Meier estimates for the cumulative event rates of all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage. AVR, aortic valve replacement; LV, left ventricular.

Table 6: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.038 (1.025-1.051)	**<0.001**	1.029 (1.014-1.043)	**<0.001**
Male gender (yes/no)	1.028 (0.806-1.310)	0.825	1.075 (0.821-1.407)	0.599
Coronary artery disease (yes/no)	1.708 (1.336-2.182)	**<0.001**	1.038 (0.772-1.396)	0.804
Previous MI (yes/no)	2.335 (1.749-3.117)	**<0.001**	1.604 (1.129-2.278)	**0.008**
COPD (yes/no)	1.222 (0.830-1.798)	0.310		
History of atrial fibrillation (yes/no)	1.301 (0.991-1.708)	0.058	0.870 (0.638-1.185)	0.377
NYHA class ≥III (yes/no)	1.806 (1.395-2.337)	**<0.001**	1.339 (1.017-1.763)	**0.038**
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.976 (0.971-0.981)	**<0.001**	0.982 (0.976-0.987)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.994 (0.989-0.999)	**0.019**	0.993 (0.988-0.999)	**0.017**
Diuretic agents (yes/no)	1.458 (1.145-1.857)	**0.002**	0.927 (0.704-1.221)	0.589
Peak aortic jet velocity (per 1 m/s increase)	0.642 (0.534-0.771)	**<0.001**	0.868 (0.705-1.068)	0.181
Indexed AVA (per 0.01 cm^2/m^2 increase)	0.974 (0.319-2.972)	0.963	2.901 (0.836-10.07)	0.093
Stage of cardiac damage (per 1 stage increase)	1.486 (1.319-1.675)	**<0.001**	1.320 (1.158-1.505)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.035 (0.603-1.777)	0.901	1.057 (0.598-1.868)	0.849
Stage 0 vs. Stage 2	1.387 (0.836-2.304)	0.206	1.386 (0.811-2.369)	0.233
Stage 0 vs. Stage 3	1.967 (1.022-3.785)	**0.043**	1.329 (0.654-2.698)	0.432
Stage 0 vs. Stage 4	4.005 (2.286-7.019)	**<0.001**	2.878 (1.571-5.271)	**0.001**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 6: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917) (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.028 (1.018-1.038)	**<0.001**	1.015 (1.004-1.027)	**0.007**
Male gender (yes/no)	1.071 (0.881-1.302)	0.492	1.038 (0.839-1.284)	0.733
Coronary artery disease (yes/no)	1.609 (1.322-1.959)	**<0.001**	1.104 (0.874-1.396)	0.406
Previous MI (yes/no)	2.022 (1.585-2.579)	**<0.001**	1.482 (1.110-1.978)	**0.008**
COPD (yes/no)	1.149 (0.840-1.572)	0.386		
History of atrial fibrillation (yes/no)	1.256 (1.07-1.567)	**0.043**	0.960 (0.748-1.232)	0.747
NYHA class ≥III (yes/no)	1.427 (1.156-1.761)	**0.001**	1.086 (0.867-1.360)	0.472
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.984 (0.980-0.988)	**<0.001**	0.990 (0.985-0.994)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.992-1.000)	0.059	0.997 (0.992-1.001)	0.187
Diuretic agents (yes/no)	1.544 (1.270-1.877)	**<0.001**	1.161 (0.932-1.445)	0.183
Peak aortic jet velocity (per 1 m/s increase)	0.713 (0.616-0.827)	**<0.001**	0.880 (0.747-1.036)	0.124
Indexed AVA (per 0.01 cm^2/m^2 increase)	0.694 (0.286-1.689)	0.421	1.541 (0.566-4.193)	0.397
Stage of cardiac damage (per 1 stage increase)	1.338 (1.215-1.473)	**<0.001**	1.211 (1.089-1.346)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.034 (0.686-1.558)	0.874	1.077 (0.700-1.658)	0.736
Stage 0 vs. Stage 2	1.316 (0.896-1.934)	0.161	1.287 (0.856-1.934)	0.225
Stage 0 vs. Stage 3	1.926 (1.160-3.195)	**0.011**	1.449 (0.839-2.503)	0.183
Stage 0 vs. Stage 4	2.788 (1.784-4.355)	**<0.001**	2.091 (1.292-3.385)	**0.003**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 7: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of postoperative all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.034 (1.021-1.047)	**<0.001**	1.026 (1.012-1.041)	**<0.001**
Male gender (yes/no)	1.029 (0.807-1.312)	0.816	1.103 (0.843-1.444)	0.474
Coronary artery disease (yes/no)	1.672 (1.308-2.136)	**<0.001**	1.063 (0.791-1.429)	0.686
Previous MI (yes/no)	2.179 (1.633-2.908)	**<0.001**	1.487 (1.047-2.113)	**0.027**
COPD (yes/no)	1.178 (0.800-1.735)	0.406		
History of atrial fibrillation (yes/no)	1.337 (1.018-1.756)	**0.037**	0.907 (0.665-1.236)	0.536
NYHA class ≥III (yes/no)	1.688 (1.304-2.184)	**<0.001**	1.268 (0.963-1.669)	0.091
Estimated GFR (per 1 ml/min/1.73m^2 increase)	0.977 (0.972-0.981)	**<0.001**	0.982 (0.976-0.988)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.994 (0.989-0.999)	**0.017**	0.994 (0.988-0.999)	**0.027**
Diuretic agents (yes/no)	1.411 (1.108-1.797)	**0.005**	0.933 (0.709-1.227)	0.620
Peak aortic jet velocity (per 1 m/s increase)	0.652 (0.544-0.782)	**<0.001**	0.886 (0.720-1.090)	0.252
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.484 (0.481-4.573)	0.492	4.093 (1.185-14.14)	**0.026**
Stage of cardiac damage (per 1 stage increase)	1.466 (1.303-1.651)	**<0.001**	1.319 (1.158-1.503)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.058 (0.616-1.816)	0.839	1.094 (0.619-1.934)	0.756
Stage 0 vs. Stage 2	1.446 (0.871-2.401)	0.154	1.458 (0.853-2.491)	0.168
Stage 0 vs. Stage 3	1.995 (1.037-3.840)	**0.039**	1.501 (0.740-3.046)	0.260
Stage 0 vs. Stage 4	3.874 (2.209-6.793)	**<0.001**	2.871 (1.563-5.273)	**0.001**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 7: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of postoperative all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917) (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.023 (1.013-1.033)	**<0.001**	1.012 (1.001-1.023)	**0.029**
Male gender (yes/no)	1.073 (0.882-1.304)	0.483	1.061 (0.858-1.313)	0.586
Coronary artery disease (yes/no)	1.561 (1.282-1.899)	**<0.001**	1.124 (0.890-1.421)	0.327
Previous MI(yes/no)	1.868 (1.465-2.381)	**<0.001**	1.390 (1.040-1.856)	**0.026**
COPD (yes/no)	1.089 (0.796-1.490)	0.595		
History of atrial fibrillation (yes/no)	1.267 (1.015-1.580)	**0.036**	0.975 (0.759-1.251)	0.840
NYHA class ≥III (yes/no)	1.303 (1.056-1.609)	**0.014**	1.018 (0.813-1.275)	0.875
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.985 (0.981-0.989)	**<0.001**	0.990 (0.985-0.995)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.992-1.000)	0.057	0.997 (0.993-1.002)	0.232
Diuretic agents (yes/no)	1.465 (1.206-1.781)	**<0.001**	1.155 (0.929-1.437)	0.195
Peak aortic jet velocity (per 1 m/s increase)	0.732 (0.633-0.848)	**<0.001**	0.901 (0.765-1.062)	0.214
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.075 (0.438-2.638)	0.874	2.162 (0.795-5.883)	0.131
Stage of cardiac damage (per 1 stage increase)	1.310 (1.191-1.441)	**<0.001**	1.205 (1.085-1.340)	**0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.053 (0.699-1.587)	0.805	1.090 (0.708-1.677)	0.696
Stage 0 vs. Stage 2	1.353 (0.921-1.988)	0.123	1.325 (0.882-1.991)	0.176
Stage 0 vs. Stage 3	1.922 (1.158-3.189)	**0.012**	1.588 (0.921-2.738)	0.096
Stage 0 vs. Stage 4	2.595 (1.661-4.055)	**<0.001**	2.018 (1.244-3.274)	**0.004**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 8: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization after exclusion of patients in Stage 1 with a left ventricular ejection fraction <50% (N = 1137).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.034 (1.024-1.043)	**<0.001**	1.021 (1.010-1.032)	**<0.001**
Male gender (yes/no)	0.910 (0.756-1.096)	0.321	1.017 (0.825-1.253)	0.874
Coronary artery disease (yes/no)	1.357 (1.127-1.634)	**0.001**	0.948 (0.750-1.198)	0.655
Previous MI (yes/no)	1.998 (1.595-2.504)	**<0.001**	1.592 (1.190-2.128)	**0.002**
COPD (yes/no)	1.183 (0.871-1.606)	0.281		
History of atrial fibrillation (yes/no)	1.592 (1.310-1.935)	**<0.001**	1.040 (0.827-1.307)	0.737
NYHA class ≥III (yes/no)	1.611 (1.317-1.969)	**<0.001**	1.262 (1.017-1.566)	**0.035**
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.976 (0.972-0.979)	**<0.001**	0.981 (0.977-0.985)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.995 (0.991-0.999)	**0.008**	0.996 (0.991-1.000)	0.055
Diuretic agents (yes/no)	1.307 (1.085-1.575)	**0.005**	1.010 (0.814-1.255)	0.926
Peak aortic jet velocity (per 1 m/s increase)	0.683 (0.596-0.782)	**<0.001**	0.974 (0.831-1.141)	0.743
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.814 (0.790-4.168)	0.160	2.441 (0.951-6.266)	0.063
Surgical or transcatheter AVR (yes/no)	0.398 (0.324-0.489)	**<0.001**	0.507 (0.402-0.640)	**<0.001**
Stage of cardiac damage (per 1 stage increase)	1.518 (1.388-1.661)	**<0.001**	1.302 (1.168-1.450)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	0.963 (0.611-1.517)	0.871	1.047 (0.622-1.762)	0.864
Stage 0 vs. Stage 2	1.612 (1.074-2.418)	0.021	1.481 (0.927-2.369)	0.101
Stage 0 vs. Stage 3	2.741 (1.691-4.444)	**<0.001**	1.965 (1.117-3.458)	**0.019**
Stage 0 vs. Stage 4	3.864 (2.481-6.019)	**<0.001**	2.518 (1.495-4.242)	**0.001**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 8: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization after exclusion of patients in Stage 1 with a left ventricular ejection fraction <50% (N = 1137) (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.026 (1.018-1.034)	**<0.001**	1.014 (1.004-1.023)	**0.004**
Male gender (yes/no)	0.973 (0.827-1.143)	0.737	1.001 (0.837-1.197)	0.995
Coronary artery disease (yes/no)	1.391 (1.183-1.637)	**<0.001**	0.998 (0.817-1.220)	0.987
Previous MI (yes/no)	1.814 (1.481-2.223)	**<0.001**	1.423 (1.105-1.831)	**0.006**
COPD (yes/no)	1.139 (0.872-1.489)	0.339		
History of atrial fibrillation (yes/no)	1.475 (1.240-1.754)	**<0.001**	1.104 (0.903-1.349)	0.337
NYHA class ≥III (yes/no)	1.415 (1.186-1.688)	**<0.001**	1.153 (0.954-1.393)	0.140
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.982 (0.978-0.985)	**<0.001**	0.986 (0.982-0.990)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.992-0.999)	**0.012**	0.997 (0.993-1.001)	0.134
Diuretic agents (yes/no)	1.373 (1.166-1.616)	**<0.001**	1.076 (0.894-1.295)	0.439
Peak aortic jet velocity (per 1 m/s increase)	0.737 (0.655-0.830)	**<0.001**	0.957 (0.835-1.096)	0.523
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.087 (0.528-2.240)	0.820	1.927 (0.848-4.381)	0.117
Surgical or transcatheter AVR (yes/no)	0.396 (0.333-0.471)	**<0.001**	0.807 (0.655-0.995)	**0.044**
Stage of cardiac damage (per 1 stage increase)	1.372 (1.269-1.483)	**<0.001**	1.199 (1.094-1.313)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.023 (0.707-1.482)	0.903	1.122 (0.744-1.693)	0.583
Stage 0 vs. Stage 2	1.510 (1.082-2.108)	**0.015**	1.459 (1.003-2.123)	**0.048**
Stage 0 vs. Stage 3	2.362 (1.564-3.567)	**<0.001**	1.776 (1.110-2.842)	**0.017**
Stage 0 vs. Stage 4	2.880 (1.977-4.195)	**<0.001**	1.973 (1.282-3.035)	**0.002**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

3

INCREMENTAL VALUE OF LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN IN A NEWLY PROPOSED STAGING CLASSIFICATION BASED ON CARDIAC DAMAGE IN PATIENTS WITH SEVERE AORTIC STENOSIS

E. Mara Vollema, Mohammed R. Amanullah, Edgard A. Prihadi,
Arnold C.T. Ng, Pieter van der Bijl, Yoong Kong Sin,
Nina Ajmone Marsan, Zee Pin Ding, Philippe Généreux, Martin B. Leon,
See Hooi Ewe, Victoria Delgado, Jeroen J. Bax

Published in Eur Heart J Cardiovasc Imaging. 2020;21(11):1248-1258.

ABSTRACT

AIMS

Cardiac damage in severe aortic stenosis (AS) can be classified according to a recently proposed staging classification. The present study investigated the incremental prognostic value of left ventricular (LV) global longitudinal strain (GLS) over stages of cardiac damage in patients with severe AS.

METHODS AND RESULTS

From an ongoing registry, a total of 616 severe symptomatic AS patients with available LV GLS by speckle tracking echocardiography were selected and retrospectively analyzed. Patients were categorized according to cardiac damage on echocardiography: Stage 0 (no damage), Stage 1 (LV damage), Stage 2 (mitral valve or left atrial damage), Stage 3 (tricuspid valve or pulmonary artery vasculature damage) or Stage 4 (right ventricular damage). LV GLS was divided by quintiles and assigned to the different stages. The endpoint was all-cause mortality. Over a median follow-up of 44 [interquartile range: 24 to 89] months, 234 (38%) patients died. LV GLS was associated with all-cause mortality independent of stage of cardiac damage. After incorporation of LV GLS by quintiles into the staging classification, Stage 2 to 4 were independently associated with outcome. LV GLS showed incremental prognostic value over clinical characteristics and stages of cardiac damage.

CONCLUSION

In this large single-center cohort of severe AS patients, incorporation of LV GLS by quintiles in a novel proposed staging classification resulted in refinement of risk stratification by identifying patients with more advanced cardiac damage. LV GLS was shown to provide incremental prognostic value over the originally proposed staging classification.

Introduction

In severe aortic stenosis (AS), pressure overload caused by obstruction of the aortic valve leads to left ventricular (LV) hypertrophy and LV systolic dysfunction as a result of myocardial fibrosis formation [1]. However, it has been increasingly recognized that myocardial injury caused by severe AS is not limited to the LV myocardium and can negatively influence prognosis. For example, mitral [2] and tricuspid regurgitation (TR) [3] are frequently observed in severe AS patients. Furthermore, multiple studies have reported a high prevalence of right ventricular (RV) dysfunction in this patient population [4–6]. These expressions of cardiac damage can be classified according to a recently proposed staging classification, which has been shown to be strongly associated with prognosis, independent of other well-established predictors of poor outcome [7–10]. Left ventricular global longitudinal strain (GLS) evaluated by speckle tracking echocardiography has also been demonstrated to be independently associated with all-cause mortality and adverse outcomes in severe AS patients, both with preserved and impaired LV systolic function as assessed by LV ejection fraction (LVEF) [11–13]. The present study investigated the incremental prognostic value of LV GLS over a recently proposed staging classification algorithm according to cardiac damage and evaluated the prognostic implications of incorporating LV GLS in this staging classification.

Methods

Study population and data collection

From an ongoing registry of patients with AS from the Leiden University Medical Center, 616 patients with symptomatic severe AS and feasible analysis of LV GLS using 2-dimensional speckle tracking echocardiography at baseline (i.e., first available echocardiogram after diagnosis of symptomatic severe AS) between 2000 and 2017 were selected. As recommended by recent guidelines, severe AS was defined as a mean aortic valve gradient ≥40 mmHg and/or aortic valve area (AVA) <1.0 cm^2 (or an indexed AVA [AVAi] <0.6 cm^2/m^2) and/or a peak aortic jet velocity ≥4 m/s [14–16]. All echocardiographic data were clinically acquired and prospectively analyzed by experienced observers. Exclusion criteria were previous aortic valve replacement (AVR), lack of symptoms and inadequate speckle tracking analysis due to poor acoustic windows or insufficient data. Patient demographic and clinical data (e.g., cardiovascular medication use and comorbidities) and clinical follow-up data were gathered from the departmental patient information system (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) and hospital records (HiX; ChipSoft, Amsterdam, The Netherlands) and analyzed retrospectively. The institutional review board waived the need for patient written informed consent due to the retrospective nature of this analysis (CME 10.053).

Transthoracic echocardiography

Using commercially available ultrasound systems (GE-Vingmed, Horten, Norway), transthoracic echocardiograms were obtained with the patient at rest in a left lateral decubitus position. Two-dimensional color, pulsed-, and continuous-wave Doppler images were acquired as recommended and stored digitally for offline analysis (EchoPAC

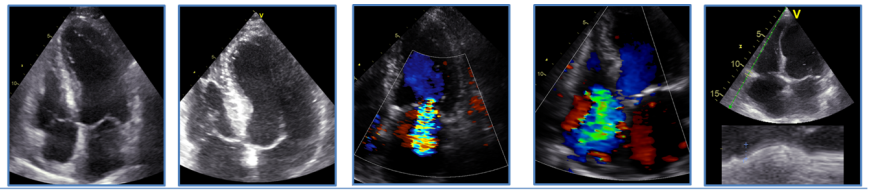
version 113.0.3; GE-Vingmed, Horten, Norway) [17]. From the parasternal long-axis view, LV dimensions were evaluated and, using the Devereux's formula, LV mass was calculated and indexed for body surface area (LVMI) [17]. In the apical 2- and 4-chamber views, LV volumes were assessed and LVEF was calculated according to Simson's biplane method [17]. Left atrial (LA) volumes were measured by the biplane method of disks and indexed for body surface area [17]. For the evaluation of LV diastolic function, peak early (E) and late (A) diastolic velocities were acquired using pulsed-wave Doppler recordings of the transmitral flow [18]. To estimate LV filling pressures, the E/e' ratio was calculated incorporating the average e' as measured at both the lateral and septal mitral annulus by tissue Doppler imaging on the apical 4-chamber view [18]. From color and continuous-wave Doppler recordings, the severity of mitral and tricuspid regurgitation was graded using a multi-parametric approach, as recommended by current guidelines [19]. For the estimation of the systolic arterial pulmonary pressure (SPAP), the right atrial pressure as determined by the diameter and inspiratory collapse of the inferior vena cava was added to the RV pressure as calculated by the Bernouilli equation using the peak velocity of the tricuspid regurgitant jet [17, 20]. On the focused apical 4-chamber view of the right ventricle, the tricuspid annular plane systolic excursion (TAPSE) was measured using anatomical M-mode to evaluate the right ventricular (RV) systolic function [20]. To assess AS severity, peak aortic jet velocity was estimated using the continuous-wave Doppler data from the apical 3- or 5-chamber views [15]. Mean and peak transvalvular pressure gradients were calculated according to the Bernoulli equation [15]. Using the LV outflow tract diameter and velocity time integrals of the aortic valve and LV outflow tract, the AVA was estimated by the continuity equation and indexed for body surface area (AVAi) [15].

Using commercially available software (EchoPAC version 113.0.3; GE-Vingmed, Horten, Norway), LV GLS was measured on the apical 4-, 3- and 2-chamber views by 2-dimensional speckle tracking analysis [17]. Conventionally, LV GLS is presented as a negative value (since it represents the myocardial shortening in the longitudinal direction), but in the present study absolute values are reported [17].

DEFINITIONS PROPOSED STAGING CLASSIFICATION AND RECLASSIFICATION BY LV GLS

Patients were classified into 5 independent stages as proposed by Généreux et al. [7] based on the presence and extent of cardiac damage as evaluated on baseline transthoracic echocardiography (Figure 1): no signs of cardiac damage was categorized as Stage 0; LV damage (LV hypertrophy [LVMI >95 g/m^2 for women or >115 g/m^2 for men], LV systolic [LVEF <50%] or diastolic dysfunction [E/e' >14])[17, 18] as Stage 1; LA or mitral valve damage (LA volume index >34 ml/m^2, significant mitral regurgitation (MR) [MR grade ≥3] or presence of atrial fibrillation at time of baseline echocardiography)[17, 19] as Stage 2; pulmonary artery vasculature or tricuspid valve damage (severe pulmonary hypertension [SPAP >60 mmHg] or significant TR [TR grade ≥3]) [19] as Stage 3 and RV damage (RV dysfunction [TAPSE <16 mm])[20] as Stage 4. Patients were classified in the most advanced stage if criteria for more than one stage were present [7].

To incorporate LV GLS in the proposed staging classification, LV GLS was divided by quintiles and assigned to the different stages of cardiac damage as depicted in Figure 1:



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	Left ventricular damage	Left atrial or mitral damage	Pulmonary vasculature or tricuspid damage	Right ventricular damage
Echocardiographic criteria		LV mass index ♂ >115 g/m² ♀ > 95 g/m² LV ejection fraction <50% E/e' ratio > 14	Left atrial volume index >34 ml/m² Presence of atrial fibrillation Moderate/severe mitral regurgitation	Systolic pulmonary arterial pressure ≥60 mmHg Moderate/severe tricuspid regurgitation	TAPSE <16 mm
LV GLS (%)	>18%	15.8 to 18%	13.2 to 15.8%	10 to 13.2%	<10%

Figure 1: Proposed staging classification according to the presence and extent of cardiac damage on echocardiography with addition of LV GLS quintiles for reclassification. GLS, global longitudinal strain; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion.

LV GLS >18% for Stage 0, 15.8 to 18% for Stage 1, 13.2 to 15.8% for Stage 2, 10 to 13.2% for Stage 3 and <10% for Stage 4. Classification of stages after taking into account LV GLS was performed using the previously described approach [7]: patients were classified into the most advanced stage for which either a criterion for cardiac damage or for LV GLS was present (Figure 1).

Follow-up and endpoint

All patients were followed-up for all-cause mortality and the occurrence of AVR (either surgical or transcatheter). The primary outcome was all-cause mortality, which was obtained by review of the departmental cardiology information system (which is linked to the governmental death registry database).

Statistical analysis

Continuous data are presented as mean±SD or median (interquartile range [IQR]), as appropriate, and were compared between patients groups as divided by stage of cardiac damage using the analysis of variance (ANOVA) test with Bonferroni's post hoc analysis or Kruskal-Wallis test when distributed normally or non-normally, respectively. Categorical data are presented as frequencies and percentages and were compared between groups using the χ^2 test. To calculate cumulative survival rates of the stages of cardiac damage, Kaplan-Meier analyses were performed. For comparison of survival rates between the different stages, the log-rank test was used. Univariable Cox proportional hazard analyses were performed to assess the association of the proposed staging classification and other relevant parameters with all-cause mortality. Statistically significant (P<0.05) or clinically relevant predictors from the univariable analysis were included in the multivariable model. Cox proportional hazard analyses were performed for both the proposed staging classification and after reclassification taking into account LV GLS. AVR (surgical or transcatheter) was entered into the analyses as a time-dependent covariate. Hazard ratio (HR) and 95% confidence interval (CI) were presented for all included variables. To assess the incremental prognostic value of LV GLS over the proposed staging

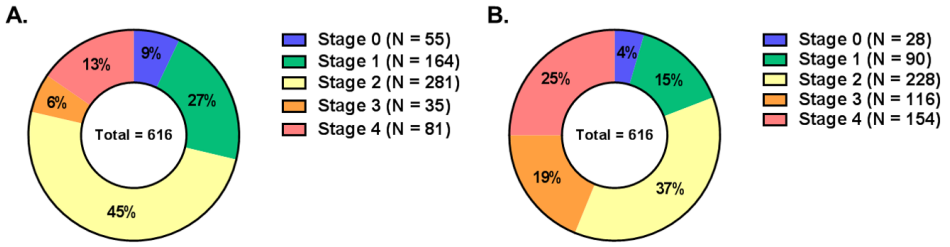


Figure 2: Distribution of stages of cardiac damage in study population according to the proposed staging classification (*panel A*) and after reclassification by incorporating LV GLS (*panel B*). GLS, global longitudinal strain; LV, left ventricular.

classification, nested regression models were constructed and changes in χ^2 value were calculated. All statistical analyses were performed on SPSS software (version 23, IBM SPSS statistics for Windows, Armonk, New York, USA) and a two-sided P value <0.05 was considered statistically significant.

RESULTS

A total of 616 symptomatic severe AS patients (mean age 75±11 years, 58% male) were classified according to the proposed staging classification (Figure 1): 55 (9%) patients had no signs of cardiac damage (Stage 0), 164 (27%) patients had LV damage (Stage 1), 281 (45%) patients had LA or mitral valve damage (Stage 2), 35 (6%) patients had pulmonary vasculature or tricuspid valve damage (Stage 3) and 81 (13%) patients had RV damage (Stage 4) (Figure 2). Patients in Stages 3 and 4 were generally older, had more comorbidities (e.g., coronary artery disease, chronic obstructive pulmonary disease and atrial fibrillation), had more severe symptoms (NYHA functional class ≥III), had worse renal function, and more often used diuretic agents when compared with patients in Stages 0-2 (Table 1). Echocardiographically, patients in more advanced stages had larger diameters of both the LV and LA, had worse LVEF, more often had significant MR and TR, and more often had low-flow low-gradient AS when compared with patients in less advanced stages (Table 2). Of note, LV GLS was gradually more impaired with each increasing stage.

PROGNOSTIC VALUE OF PROPOSED STAGING CLASSIFICATION

Over a median follow-up of 44 (IQR: 24 to 89) months, 550 (89%) patients underwent AVR (49% surgical and 51% transcatheter) and 234 (38%) patients died. Of the 234 patients who died, 57 (24%) did not receive AVR. As shown in Figure 3, the Kaplan-Meier analysis demonstrated a significantly lower survival from all-cause mortality with increasing stages of cardiac damage, especially Stages 3 and 4 (log-rank χ^2 65.2, P<0.001). Using Cox proportional hazard analyses (Table 3), stage of cardiac damage as classified by the proposed staging classification was independently associated with all-cause mortality (HR: 1.25, 95% CI: 1.09-1.45; P=0.002). This effect seemed to be determined mainly by Stage 4 (HR: 2.33, 95% CI: 1.19-4.54; P=0.013), as other stages of cardiac damage did not

Table 1: Clinical characteristics of total study population and per stage of cardiac damage classified according to proposed staging classification.

Variables	Total population (N = 616)	Stage 0 (N = 55)	Stage 1 (N = 164)	Stage 2 (N = 281)	Stage 3 (N = 35)	Stage 4 (N = 81)	*P* value*
Age (years)	75.4±10.7	72.6±10.3	72.1±12.1	76.3±10.2‡	79.6±8.3†‡	78.5±7.8†‡	**<0.001**
Male gender, *N* (%)	359 (58)	36 (66)	87 (53)	166 (59)	13 (37)	57 (70)	**0.006**
Body mass index (kg/m^2)	26.3±4.4	26.8±4.6	26.2±4.0	26.6±4.7	25.3±3.7	25.6±4.5	0.244
Body surface area (m^2)	1.87±0.21	1.88±0.21	1.86±0.20	1.88±0.21	1.80±0.21	1.87±0.20	0.186
Hypertension, *N* (%)	414 (67)	34 (62)	114 (70)	190 (67)	25 (71)	51 (63)	0.720
Hypercholesterolemia, *N* (%)	348 (57)	32 (58)	87 (53)	163 (58)	16 (46)	50 (62)	0.452
Diabetes mellitus, *N* (%)	150 (24)	12 (22)	35 (21)	70 (25)	6 (17)	27 (33)	0.233
Coronary artery disease, *N* (%)	311 (51)	22 (40)	75 (46)	143 (51)	15 (43)	56 (69)	**0.003**
Prior myocardial infarction, *N* (%)	126 (21)	9 (16)	26 (16)	57 (20)	9 (26)	25 (31)	0.069
History of smoking, *N* (%)	214 (35)	26 (47)	54 (33)	100 (36)	9 (26)	25 (31)	0.204
COPD, *N* (%)	101 (16)	8 (15)	7 (17)	36 (13)	12 (34)	18 (22)	**0.012**
History of atrial fibrillation, *N* (%)	169 (27)	5 (9)	16 (10)	83 (30)	17 (49)	48 (59)	**<0.001**
NYHA functional class ≥III, *N* (%)	254 (42)	21 (38)	40 (25)	117 (43)	24 (69)	52 (64)	**<0.001**
Symptoms, *N* (%)							
Angina	260 (42)	24 (44)	79 (49)	120 (43)	11 (31)	26 (32)	0.100
Dyspnea	478 (78)	40 (73)	111 (68)	220 (79)	33 (94)	74 (91)	**<0.001**
Syncope	67 (11)	5 (9)	25 (15)	33 (12)	0 (0)	4 (5)	**0.027**
Estimated GFR (ml/min/1.73 m^2)	62.2±20.6	66.1±21.5	64.7±21.8	63.5±19.8	50.5±19.9†‡§	55.4±17.7†‡§	**<0.001**
<60 ml/min/1.73 m^2, *N* (%)	287 (47)	22 (40)	72 (44)	121 (43)	23 (66)	49 (61)	**0.006**
Systolic BP (mmHg)	138.0±23.5	142.0±21.9	140.5±21.1	139.6±24.3	127.2±27.6†‡§	129.2±22.0†‡§	**<0.001**
Diastolic BP (mmHg)	73.8±13.4	76.6±13.6	76.0±12.4	72.8±13.1	69.2±16.1	72.7±14.0	**0.011**
Medication use, *N* (%)							
Beta-blocker	328 (53)	24 (44)	83 (51)	151 (54)	18 (51)	52 (64)	0.166
ACE-inhibitor/ARB	306 (50)	25 (46)	76 (46)	143 (51)	18 (51)	44 (54)	0.730
Aspirin/thienopyridines	280 (46)	26 (47)	84 (51)	122 (43)	13 (37)	35 (43)	0.422
Oral anticoagulation	173 (28)	10 (18)	20 (12)	82 (29)	16 (46)	45 (56)	**<0.001**
Statins	355 (58)	33 (60)	93 (57)	164 (58)	17 (49)	48 (59)	0.825
Calcium channel blocker	145 (24)	10 (18)	39 (24)	72 (26)	7 (20)	17 (21)	0.718
Diuretic agents	311 (51)	14 (26)	65 (40)	153 (54)	29 (83)	50 (62)	**<0.001**

Continuous variables are presented as mean±SD or median [interquartile range]. Categorical variables are expressed as number (percentage). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure, COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; NYHA, New York Heart Association. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. †*P* value <0.05 vs. Stage 0 with Bonferroni's post hoc analysis. ‡*P* value <0.05 vs. Stage 1 with Bonferroni's post hoc analysis. §*P* value <0.05 vs. Stage 2 with Bonferroni's post hoc analysis.

Table 2: Echocardiographic characteristics of total study population and per stage of cardiac damage classified according to proposed staging classification.

Variables	Total population (N = 616)	Stage 0 (N = 55)	Stage 1 (N = 164)	Stage 2 (N = 281)	Stage 3 (N = 35)	Stage 4 (N = 81)	*P* value*
Heart rate at TTE (bpm)	75.0±14.4	74.3±12.1	72.0±12.5	73.6±13.6	84.2±16.2†‡§	82.0±17.6†‡§	**<0.001**
Valve morphology, *N* (%)							
Tricuspid	555 (90)	47 (86)	135 (82)	261 (93)	34 (97)	78 (96)	
Bicuspid	61 (10)	8 (15)	29 (18)	20 (7)	1 (3)	3 (4)	
Atrial fibrillation at TTE, *N* (%)	72 (12)	0 (0)	0 (0)	34 (12)	10 (29)	28 (35)	**<0.001**
LV end-diastolic diameter (mm)	48.9±8.3	42.4±5.0	48.2±7.5†	49.3±8.3†	50.8±9.3†	52.0±8.8†‡	**<0.001**
LV end-systolic diameter (mm)	35.6±9.9	29.6±5.1	34.2±8.7†	35.3±9.7†	39.3±11.7†‡	41.8±11.0†‡§	**<0.001**
Septal wall thickness (mm)	12.9±2.3	11.3±1.6	12.5±1.9†	13.4±2.4†‡	12.7±2.4†	12.8±2.6†	**<0.001**
Posterior wall thickness (mm)	12.1±2.0	10.9±1.4	11.8±1.9	12.6±2.1†‡	11.9±1.9	11.8±2.2§	**<0.001**
LV mass index (g/m^2)	129.4±37.1	85.7±14.2	122.4±32.0†	138.0±37.6†‡	138.3±32.9†	138.6±34.5†‡	**<0.001**
LV end-diastolic volume (ml)	98 [76-130]	78 [60-95]	90 [74-114]	101 [80-133]	113 [71-139]	128 [92-161]	**<0.001**
LV end-systolic volume (ml)	45 [31-76]	31 [21-41]	38 [27-55]	47 [33-74]	58 [36-97]	83 [45-118]	
LV ejection fraction (%)	52.9±14.0	61.9±7.3	57.2±12.0	53.1±12.9†‡	45.3±14.4†‡§	40.6±15.1†‡§	**<0.001**
<50%, *N* (%)	203 (33)	0 (0)	33 (20)	90 (32)	21 (60)	59 (73)	**<0.001**
LV global longitudinal strain (%)	14.0±4.5	17.3±3.6	15.2±3.7†	14.2±4.2†	11.3±5.1†‡§	9.5±3.6†‡§	**<0.001**
Peak E-wave velocity (cm/s)	83.0±30.0	65.2±18.5	72.4±22.8	85.8±30.7†‡	104.4±26.1†‡§	98.1±34.3†‡§	**<0.001**
E' (cm/s)	5.1±2.1	6.0±1.5	4.4±1.5†	5.2±2.3‡	5.6±2.1‡	5.3±2.4‡	**<0.001**
E/e' ratio	16 [12-22]	11 [10-12]	17 [13-21]	17 [12-22]	20 [15-38]	20 [13-28]	**<0.001**
Left atrial volume index (ml/m^2)	41.0±17.5	23.9±5.8	25.1±6.8	48.8±14.4†‡	51.3±18.2†‡	52.3±16.7†‡	**<0.001**
Significant MR, *N* (%)	56 (9)	0 (0)	0 (0)	30 (11)	11 (31)	15 (19)	**<0.001**
Systolic PAP (mmHg)	33.0±12.4	24.9±8.4	28.7±7.5	31.9±9.5†‡	56.5±11.7†‡§	38.2±14.8†‡§‖	**<0.001**
Significant TR, *N* (%)	43 (7)	0 (0)	0 (0)	0 (0)	24 (69)	19 (24)	**<0.001**
TAPSE (mm)	20.2±3.9	21.9±2.5	21.5±3.0	21.3±3.0	19.0±3.0†‡§	13.5±1.5†‡§‖	**<0.001**
Mean AV gradient (mmHg)	42.3±16.6	41.0±13.8	43.4±15.3	45.0±17.7	37.7±14.9	33.3±14.4‡§	**<0.001**
Peak aortic jet velocity (m/s)	4.0±0.7	4.0±0.6	4.1±0.7	4.1±0.8	3.8±0.7	3.5±0.7†‡§	**<0.001**
AVA (cm^2)	0.77±0.19	0.85±0.22	0.78±0.17	0.76±0.19†	0.76±0.23	0.71±0.18†	**0.001**
Indexed AVA (cm^2/m^2)	0.41±0.10	0.46±0.11	0.42±0.09	0.41±0.10†	0.42±0.11	0.38±0.10†‡	**<0.001**
Low-flow low-gradient AS, *N* (%)	162 (26)	12 (22)	30 (18)	61 (22)	13 (37)	46 (57)	**<0.001**

Continuous variables are presented as mean±SD. Categorical variables are expressed as number (percentage). AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; bpm, beats per minute; LV, left ventricular; MR, mitral regurgitation; PAP, pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. †*P* value <0.05 vs. Stage 0 with Bonferroni's post hoc analysis. ‡*P* value <0.05 vs. Stage 1 with Bonferroni's post hoc analysis. §*P* value <0.05 vs. Stage 2 with Bonferroni's post hoc analysis. ‖*P* value <0.05 vs. Stage 3 with Bonferroni's post hoc analysis.

Table 3: Univariable and multivariable Cox proportional hazard analyses for all-cause mortality including proposed stages of cardiac damage.

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (per 1 year increase)	1.034 (1.020-1.048)	**<0.001**	1.023 (1.008-1.038)	**0.003**
Male gender (yes/no)	1.099 (0.845-1.429)	0.480	1.119 (0.846-1.480)	0.432
Coronary artery disease (yes/no)	1.566 (1.207-2.031)	**0.001**	1.035 (0.751-1.425)	0.835
Previous myocardial infarction (yes/no)	2.021 (1.521-2.685)	**<0.001**	1.490 (1.051-2.114)	**0.025**
Chronic obstructive pulmonary disease (yes/no)	1.191 (0.830-1.708)	0.343		
History of atrial fibrillation (yes/no)	1.455 (1.094-1.935)	**0.010**	0.948 (0.692-1.298)	0.737
Diabetes mellitus (yes/no)	1.598 (1.206-2.118)	**0.001**	1.552 (1.159-2.080)	**0.003**
NYHA functional class ≥III (yes/no)	1.455 (1.116-1.895)	**0.006**	1.165 (0.875-1.551)	0.297
Estimated GFR <60 ml/min/1.73 m^2 (yes/no)	2.422 (1.859-3.154)	**<0.001**	1.736 (1.312-2.295)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.998 (0.992-1.003)	0.430		
Diuretics (yes/no)	1.496 (1.155-1.938)	**0.002**	1.043 (0.787-1.381)	0.770
Peak aortic jet velocity (per 1 m/s increase)	0.645 (0.537-0.774)	**<0.001**	0.943 (0.761-1.169)	0.592
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.430 (0.386-5.291)	0.592	4.052 (0.910-18.05)	0.066
Surgical or transcatheter AVR (yes/no)	0.370 (0.269-0.509)	**<0.001**	0.384 (0.276-0.535)	**<0.001**
LV global longitudinal strain (per 1% increase)	0.911 (0.886-0.936)	<0.001	0.951 (0.919-0.983)	**0.004**
Stage of cardiac damage (per 1 stage increase)	1.541 (1.370-1.734)	**<0.001**	1.253 (1.087-1.445)	**0.002**
Stages according to cardiac damage				
Stage 0 (no cardiac damage)	Reference		Reference	
Stage 1 (LV damage)	1.108 (0.623-1.968)	0.727	1.138 (0.629-2.057)	0.669
Stage 2 (left atrial or mitral damage)	1.614 (0.938-2.776)	0.084	1.293 (0.730-2.290)	0.378
Stage 3 (pulmonary vasculature or tricuspid damage)	2.782 (1.387-5.578)	**0.004**	1.704 (0.786-3.696)	0.177
Stage 4 (right ventricular damage)	4.429 (2.471-7.938)	**<0.001**	2.327 (1.192-4.541)	**0.013**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio; GFR, glomerular filtration rate; LV, left ventricular; NYHA, New York Heart Association.

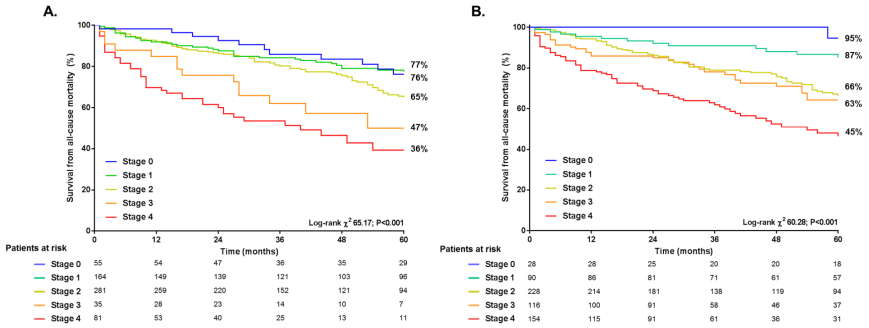


Figure 3: Kaplan-Meier survival curves for all-cause mortality per stage of cardiac damage according to the proposed staging classification (*panel A*) and after reclassification by incorporating LV GLS (*panel B*). GLS, global longitudinal strain; LV, left ventricular.

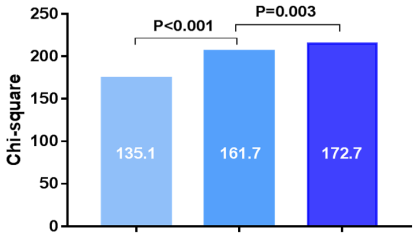
show a significant independent effect on prognosis (P>0.05). Importantly, LV GLS was associated with all-cause mortality, independent of stage of cardiac damage (HR: 0.95, 95% CI: 0.92-0.98; P=0.004).

INCORPORATION OF LV GLS IN STAGING CLASSIFICATION AND PROGNOSTIC IMPLICATIONS

To incorporate LV GLS in the proposed staging classification, LV GLS was divided by quintiles (i.e., >18%, 15.8 to 18%, 13.2 to 15.8%, 10 to 13.2% and <10%) and assigned to the stages of cardiac damage as shown in Figure 1. Using the same approach as with the proposed staging classification, patients were reclassified by taking into account LV GLS: 28 (4%) patients were categorized as Stage 0, 90 (15%) patients as Stage 1, 228 (37%) patients as Stage 2, 116 (19%) patients as Stage 3 and 154 (25%) patients as Stage 4 (Figure 2 *panel B*). Baseline and echocardiographic characteristics per reclassified stage of cardiac damage after incorporation of LV GLS are summarized in Supplemental Tables 5 and 6, respectively.

Kaplan-Meier survival curves for all-cause mortality per stage of cardiac damage reclassified after incorporating LV GLS are depicted in Figure 3 *panel B*. Cumulative 5-year survival rates decreased with increasing stages of cardiac damage (log-rank χ^2 60.3, P<0.001). Compared to the proposed staging classification, use of the staging classification incorporating LV GLS (Figure 3 *panel B*) resulted in better discrimination of cumulative survival in Stage ≥2 vs. Stage 0 and 1 (P<0.01 for all and P<0.02 for all, respectively). Kaplan-Meier analysis including the patients under medical therapy (i.e., censored at the moment of AVR) showed decreasing survival rates with increasing stages of cardiac damage (log-rank χ^2 11.50, P=0.022; Supplemental Figure 5).

Table 4 summarizes the Cox proportional hazard analyses for all-cause mortality, assessing the prognostic value of the staging classification after incorporation of LV GLS. On multivariable analysis, the stage of cardiac damage was independently associated with all-cause mortality (HR: 1.41, 95% CI: 1.22-1.62; P<0.001). Importantly, Stages 2-4 were all independent predictors of outcome: with each increasing stage, a gradually increasing risk for all-cause mortality was observed (Stage 2: HR 4.35 [95% CI: 1.35-14.10;



	Model 1	Model 2 + Stage of cardiac damage	Model 3 + LV GLS
Age (years)	1.03 (1.01-1.04)	1.02 (1.01-1.04)	1.02 (1.01-1.04)
Male gender	1.20 (0.91-1.59)	1.16 (0.88-1.53)	1.12 (0.85-1.48)
Coronary artery disease	1.02 (0.74-1.40)	0.99 (0.72-1.35)	1.04 (0.75-1.43)
Previous myocardial infarction	1.63 (1.15-2.30)	1.58 (1.12-2.23)	1.49 (1.05-2.11)
History of atrial fibrillation	1.15 (0.85-1.55)	0.95 (0.69-1.30)	0.95 (0.69-1.30)
Diabetes mellitus	1.54 (1.15-2.07)	1.54 (1.15-2.07)	1.55 (1.16-2.08)
NYHA functional class ≥ 3	1.31 (0.99-1.73)	1.27 (0.96-1.68)	1.17 (0.88-1.55)
Diuretics	1.14 (0.86-1.52)	1.06 (0.80-1.40)	1.04 (0.79-1.38)
Estimated GFR <60 ml/min/1.73m^2	1.82 (1.37-2.40)	1.77 (1.34-2.34)	1.74 (1.31-2.30)
Peak aortic jet velocity (m/s)	0.80 (0.65-0.98)	0.87 (0.70-1.07)	0.94 (0.76-1.17)
Indexed aortic valve area (cm^2/m^2)	1.39 (0.33-5.93)	2.19 (0.51-9.47)	4.05 (0.91-18.0)
Aortic valve replacement	0.39 (0.28-0.54)	0.37 (0.27-0.52)	0.38 (0.28-0.54)
Stage of cardiac damage		1.35 (1.18-1.54)	1.25 (1.09-1.45)
LV GLS (%)			0.95 (0.92-0.98)

Figure 4: Incremental value of LV GLS on top of the proposed staging classification of cardiac damage. The bar graphs depict the incremental prognostic value of LV GLS (Model 3) over the stages of cardiac damage and clinical parameters (Model 2) for all-cause mortality, as illustrated by a significant increase in χ^2 values on the y-axis. Data are presented as hazard ratios with corresponding 95% confidence intervals. GFR, glomerular filtration rate; GLS, global longitudinal strain; LV, left ventricular; NYHA, New York Heart Association.

P=0.014], Stage 3: HR 4.82 [95% CI: 1.45-16.00; *P*=0.010] and Stage 4: HR 8.08 [95% CI: 2.45-26.67; *P*<0.001]).

Incremental prognostic value of LV GLS over proposed staging classification

To assess the incremental prognostic value of LV GLS in addition to clinical parameters and the proposed staging classification, a likelihood ratio test was performed. As illustrated by Figure 4, the addition of stage of cardiac damage to a baseline model (Model 1) consisting of clinical characteristics associated with all-cause mortality in the univariable Cox regression analysis (Table 3) resulted in a significant increase in χ^2 (from 135 to 162; *P*<0.001). Adding LV GLS to the model including clinical parameters and stage of cardiac damage (Model 2) further improved the χ^2 value (*P*=0.003), thereby demonstrating the incremental prognostic value of LV GLS over stages of cardiac damage as classified by the proposed staging classification. For the subgroup of 162 patients with low-flow low-gradient severe AS, LV GLS showed incremental prognostic value over stages of cardiac damage (Supplemental Table 7 and Supplemental Figure 6).

Discussion

The present study demonstrated that, in a large single-center cohort of symptomatic severe AS patients, the extent of cardiac damage as classified by a recently proposed staging classification was independently associated with all-cause mortality. However,

Table 4: Univariable and multivariable Cox proportional hazard analyses for all-cause mortality including stages of cardiac damage after reclassification by incorporating LV GLS.

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (per 1 year increase)	1.034 (1.020-1.048)	**<0.001**	1.023 (1.009-1.038)	**0.002**
Male gender (yes/no)	1.099 (0.845-1.429)	0.480	1.111 (0.841-1.468)	0.459
Coronary artery disease (yes/no)	1.566 (1.207-2.031)	**0.001**	1.017 (0.740-1.399)	0.916
Previous myocardial infarction (yes/no)	2.021 (1.521-2.685)	**<0.001**	1.462 (1.031-2.073)	**0.033**
Chronic obstructive pulmonary disease (yes/no)	1.191 (0.830-1.708)	0.343		
History of atrial fibrillation (yes/no)	1.455 (1.094-1.935)	**0.010**	1.039 (0.767-1.407)	0.806
Diabetes mellitus (yes/no)	1.598 (1.206-2.118)	**0.001**	1.586 (1.182-2.127)	**0.002**
NYHA functional class ≥III (yes/no)	1.455 (1.116-1.895)	**0.006**	1.182 (0.890-1.568)	0.248
Estimated GFR <60 ml/min/1.73 m^2 (yes/no)	2.422 (1.859-3.154)	**<0.001**	1.746 (1.320-2.309)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.998 (0.992-1.003)	0.430		
Diuretics (yes/no)	1.496 (1.155-1.938)	**0.002**	0.994 (0.748-1.320)	0.966
Peak aortic jet velocity (per 1 m/s increase)	0.645 (0.537-0.774)	**<0.001**	0.924 (0.747-1.144)	0.468
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.430 (0.386-5.291)	0.592	4.115 (0.914-18.52)	0.065
Surgical or transcatheter AVR (yes/no)	0.370 (0.269-0.509)	**<0.001**	0.393 (0.282-0.546)	**<0.001**
Stage of cardiac damage (per 1 stage increase)	1.556 (1.380-1.754)	**<0.001**	1.406 (1.221-1.619)	**<0.001**
Stages according to cardiac damage				
Stage 0 (no cardiac damage)	Reference		Reference	
Stage 1 (LV damage)	2.259 (0.678-7.526)	0.184	3.199 (0.945-10.84)	0.062
Stage 2 (left atrial or mitral damage)	3.928 (1.242-12.43)	**0.020**	4.354 (1.345-14.10)	**0.014**
Stage 3 (pulmonary vasculature or tricuspid damage)	4.641 (1.438-14.98)	**0.010**	4.824 (1.454-16.00)	**0.010**
Stage 4 (right ventricular damage)	8.917 (2.814-28.26)	**<0.001**	8.082 (2.450-26.67)	**0.001**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio; GFR, glomerular filtration rate; LV, left ventricular; NYHA, New York Heart Association.

this seemed to be mainly determined by right ventricular damage (i.e., Stage 4). After incorporation of LV GLS divided by quintiles into the proposed staging classification for reclassification, Stages 2-4 were all independently associated with all-cause mortality. This suggests that incorporation of LV GLS improves the prognostic value of the staging classification by identifying patients with more advanced cardiac damage. LV GLS was demonstrated to have incremental prognostic value over clinical characteristics and over the originally proposed staging classification according to the extent of cardiac damage.

Cardiac damage and LV GLS in severe AS

Severe AS is currently regarded as a disease not limited to the aortic valve but also affecting the LV myocardium. Pressure overload caused by the stenotic aortic valve will ultimately lead to formation of myocardial fibrosis, resulting in LV systolic and diastolic dysfunction [1, 21]. However, hemodynamic consequences of severe AS often reach beyond the LV myocardium, as characterized by a high prevalence of concomitant mitral [2] and tricuspid regurgitation [3] and RV dysfunction [4–6] which negatively affect prognosis even after AVR. Généreux et al. [7] were the first to demonstrate the prognostic implications of classification of stages of symptomatic severe AS and their findings have recently been confirmed in more heterogenous populations of symptomatic [8] and asymptomatic [9] AS patients as well as in patients undergoing transcatheter AVR [10].

As a potential surrogate marker of myocardial fibrosis, LV myocardial longitudinal function as assessed by LV GLS using speckle tracking echocardiography has been shown to be an independent predictor of mortality and adverse outcomes in both symptomatic and asymptomatic severe AS patients [11, 12, 22–24]. Ng et al. [11] determined that severe AS patients with an LVEF ≥55% but impaired LV GLS (i.e., LV GLS >-14%) had a risk for all-cause mortality comparable to patients with impaired LVEF. This was corroborated by a recent meta-analysis showing a significant relationship between impaired LV GLS (i.e., absolute LV GLS <14.7%) and mortality in asymptomatic AS patients with LVEF ≥60% [25]. Interestingly, Cavalcante et al. [5] demonstrated that LV GLS was associated with all-cause mortality independent of the presence of significant tricuspid regurgitation and RV dysfunction in 65 low-flow low-gradient severe AS patients. The present study confirms and extends these findings by demonstrating that LV GLS is associated with all-cause mortality independently of stage of cardiac damage and has incremental prognostic value over clinical parameters and the originally proposed staging classification.

Risk stratification in severe AS

According to current guideline recommendations, a Class I indication for AVR is present in patients with severe AS with symptoms or evidence of LV systolic dysfunction defined by a LVEF <50% [14, 16]. The decision to intervene and the choice of type of intervention (i.e., surgical vs. transcatheter AVR) is made by the heart team based on an individual risk-benefit analysis and therefore, accurate risk assessment is paramount [14]. For preoperative risk stratification, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) [26] and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) [27] models are recommended and most frequently utilized [14, 16]. However, these algorithms derive from surgical populations and do not account for im-

provements in both surgical and transcatheter procedures [28]. Particularly in the field of transcatheter AVR, subsequent efforts have been made to develop transcatheter AVR-specific risk scores which include clinically relevant parameters of patient comorbidity [29] and frailty [30], but these are not routinely used.

Importantly, cardiac damage as assessed by conventional echocardiography remained a strong predictor for mortality after correcting for STS-PROM, comorbidities such as oxygen-dependent COPD and frailty [7, 10]. The presence of cardiac damage is underrepresented in current risk models: only atrial fibrillation, LV dysfunction and significant MR and TR are included in the STS-PROM and LV dysfunction and pulmonary hypertension in the logistic EuroSCORE, respectively. Importantly, both the present study and two recent studies did not find a relevant impact of the lower stages of cardiac damage (i.e., LV dysfunction and LA damage or significant MR) on prognosis [8, 10]. The presence of significant TR or pulmonary hypertension and RV dysfunction, however, was strongly associated with all-cause mortality, suggesting that incorporation of these parameters in current risk models may aid in future pre-procedural risk assessment [8, 10].

More advanced echocardiographic parameters such as LV GLS are not routinely assessed in clinical practice and are currently not included in risk stratification models. To modify the proposed staging scheme of cardiac injury, Tastet et al. [9] added impaired LV GLS (i.e., absolute value ≤15%) as a criterion for LV damage (Stage 1) and consequently reclassified patients from Stage 0 (i.e., no cardiac damage) to Stage 1. Although the authors concluded that the modified staging scheme resulted in better discrimination of mortality curves, the effect of the addition of LV GLS specifically was unclear, as LV GLS was only available in one-third of the study population (250/735 patients). The present study extends these findings by demonstrating in a much larger population that LV GLS has incremental prognostic value over cardiac damage assessed by more conventional means. Incorporation of LV GLS by quintiles in the proposed staging classification reclassifies patients in lower stages to more advanced stages of cardiac damage. This results in better discrimination of prognostic impact of the separate stages, especially of LA or mitral valve damage (Stage 2), when compared to the original staging classification. These findings confirm the relevance of using both conventional and advanced echocardiographic parameters for the assessment of cardiac injury in clinical practice, which may aid in future risk stratification. Future prospective studies are needed for validation of this extended staging classification before implementation in clinical practice is feasible.

STUDY LIMITATIONS

The current study is limited by its retrospective design and was performed in a single referral center. This may have introduced selection and referral bias as patients underwent AVR based on the decision of the heart team as recommended by current guidelines [14]. Frailty index could not be taken into account in the analyses, as the components comprising frailty index (e.g., gait speed, weight loss, cognitive assessment) were not routinely assessed and reported in hospital records. In the current study, the study population consisted of symptomatic severe AS patients and findings cannot be extrapolated to asymptomatic AS patients. Future research on the staging of cardiac damage

using incorporation of LV GLS in this population could provide insight in the role of this extended staging classification in therapeutic decision making by identifying patients (in particular with preserved [>50%] or supranormal [≥60%] LVEF and impaired LV GLS) who might benefit from early intervention. Coronary artery disease and previous myocardial infarction were not regarded as exclusion criteria, which may have influenced LV GLS measurements. However, an earlier study on LV GLS in AS found no significant difference in LV GLS between patients with and without obstructive coronary artery disease that required coronary artery bypass grafting [12]. Other comorbidities such as chronic obstructive pulmonary disease and atrial fibrillation may have contributed to pulmonary hypertension and RV dysfunction. However, on multivariable analysis in the present study, LV GLS was independently associated with all-cause mortality after correcting for coronary artery disease, previous myocardial infarction and atrial fibrillation (COPD was not associated with outcome in the univariable Cox regression analysis). Furthermore, as comorbidities such as coronary artery disease are prevalent findings in severe AS patients, inclusion of these patients depicts a true representation of the severe AS population in daily practice. For correct assessment of cardiac damage, comprehensive echocardiographic evaluation is necessary, preferably using standard protocols. This may not be always be feasible in clinical practice, although the included criteria for the staging classification were selected based on broad acceptance and simplicity in acquisition [7]. In the present study, LV GLS was measured using vendor-dependent software and therefore, the results may not be generalizable across other imaging platforms. However, recent studies have reported good feasibility and inter- and intra-observer variability and only limited differences between vendors, especially compared to conventional parameters such as LVEF [31, 32]. Finally, LV GLS has been reported to be a load-dependent parameter, influenced particularly by afterload [33, 34]. In AS, afterload is increased due to pressure overload and this may have affected LV GLS measurements in the current study. Importantly, impaired LV GLS has been suggested to reflect true depression of myocardial contractility [35], and has been shown to be an independent predictor of outcome in load-dependent conditions such as acute heart failure [36] and secondary mitral regurgitation [37].

Conclusions

This large single-center cohort of symptomatic severe AS patients demonstrates that LV GLS has incremental prognostic value over a recently proposed staging classification based on cardiac damage. Incorporation of ranges of LV GLS in the staging classification results in the identification of patients with more advanced cardiac damage among those classified within the less advanced cardiac damage stages and reclassification of these patients to more advanced stages, improving the prognostic value of the originally proposed staging classification. These findings suggest that the addition of LV GLS to the currently proposed staging classification may enhance risk stratification, especially when staging of cardiac damage based on conventional echocardiography suggests limited cardiac damage. In addition, it may provide better pre-procedural risk assessment if implemented in currently used risk prediction algorithms and therefore improve timing of intervention in severe AS patients.

REFERENCES

[1] Carabello BA, Paulus WJ. Aortic stenosis. Lancet. 2009;373(9667):956-66.

[2] Barbanti M, Webb JG, Hahn RT, Feldman T, Boone RH, Smith CR, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement insight from the placement of aortic transcatheter valve (PARTNER) trial cohort A. Circulation. 2013;128(25):2776-84.

[3] Amano M, Izumi C, Taniguchi T, Morimoto T, Miyake M, Nishimura S, et al. Impact of concomitant tricuspid regurgitation on long-termoutcomes in severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2019;20(3):353-60.

[4] Galli E, Guirette Y, Feneon D, Daudin M, Fournet M, Leguerrier A, et al. Prevalence and prognostic value of right ventricular dysfunction in severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2015;16(5):531-8.

[5] Cavalcante JL, Rijal S, Althouse AD, Delgado-Montero A, Katz WE, Schindler JT, et al. Right Ventricular Function and Prognosis in Patients with Low-Flow, Low-Gradient Severe Aortic Stenosis. J Am Soc Echocardiogr. 2016;29(4):325-33.

[6] Asami M, Stortecky S, Praz F, Lanz J, Räber L, Franzone A, et al. Prognostic Value of Right Ventricular Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Img. 2019;12(4):577-87.

[7] Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J. 2017;38(45):3351-8.

[8] Vollema EM, Amanullah MR, Ng ACT, van der Bijl P, Prevedello F, Sin YK, et al. Staging Cardiac Damage in Patients With Symptomatic Aortic Valve Stenosis. J Am Coll Cardiol. 2019;74(4):538-49.

[9] Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, et al. Staging Cardiac Damage in Patients With Asymptomatic Aortic Valve Stenosis. J Am Coll Cardiol. 2019;74(4):550-63.

[10] Fukui M, Gupta A, Abdelkarim I, Sharbaugh MS, Althouse AD, Elzomor H, et al. Association of Structural and Functional Cardiac Changes with Transcatheter Aortic Valve Replacement Outcomes in Patients with Aortic Stenosis. JAMA Cardiology. 2019;4(3):215-22.

[11] Ng ACT, Prihadi EA, Antoni ML, Bertini M, Ewe SH, Marsan NA, et al. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. Eur Heart J Cardiovasc Imaging. 2018;19(8):859-67.

[12] Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circ Cardiovasc Imaging. 2014;7(6):938-45.

[13] Klaeboe LG, Haland TF, Leren IS, ter Bekke RMA, Brekke PH, Røsjø H, et al. Prognostic Value of Left Ventricular Deformation Parameters in Patients with Severe Aortic Stenosis: A Pilot Study of the Usefulness of Strain Echocardiography. J Am Soc Echocardiogr. 2017;30(8):727-35.e1.

[14] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[15] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[16] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

[17] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[18] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321-60.

[19] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013;14(7):611-44.

[20] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and. J Am Soc Echocardiogr. 2010;23(7):685-713.

[21] Asami M, Lanz J, Stortecky S, Räber L, Franzone A, Heg D, et al. The Impact of Left Ventricular Diastolic Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv. 2018;11(6):593-601.

[22] Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Maller JE. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging. 2012;5(5):613-20.

[23] Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2012;13(10):827-33.

[24] Vollema EM, Sugimoto T, Shen M, Tastet L, Ng ACT, Abou R, et al. Association of left ventricular global longitudinal strain with asymptomatic severe aortic stenosis natural course and prognostic value. JAMA Cardiology. 2018;3(9):839-47.

[25] Magne J, Cosyns B, Popescu BA, Carstensen HG, Dahl J, Desai MY, et al. Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis: An Individual Participant Data Meta-Analysis. J Am Coll Cardiol Img. 2019;12(1):84-92.

[26] Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg. 2008;135(1):180-7.

[27] Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13.

[28] Tarantini G, Lefèvre T, Terkelsen CJ, Frerker C, Ohlmann P, Mojoli M, et al. One-year outcomes of a European transcatheter aortic valve implantation cohort according to surgical risk sub-analysis of the SOURCE 3 registry. Circ Cardiovasc Interv. 2019;12(1):1-10.

[29] Edwards FH, Cohen DJ, O'Brien SM, Peterson ED, Mack MJ, Shahian DM, et al. Development and validation of a risk prediction model for in-hospital mortality after transcatheter aortic valve replacement. JAMA Cardiology. 2016;1(1):46-52.

[30] Hermiller JB, Yakubov SJ, Reardon MJ, Deeb GM, Adams DH, Afilalo J, et al. Predicting Early and Late Mortality After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;68(4):343-52.

[31] Negishi T, Negishi K, Thavendiranathan P, Cho GY, Popescu BA, Vinereanu D, et al. Effect of Experience and Training on the Concordance and Precision of Strain Measurements. J Am Coll Cardiol Img. 2017;10(5):518-22.

[32] Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr. 2015;28(10):1171-81.

[33] Yotti R, Bermejo J, Benito Y, Sanz-Ruiz R, Ripoll C, Martínez-Legazpi P, et al. Validation of noninvasive indices of global systolic function in patients with normal and abnormal loading conditions a simultaneous echocardiography pressure-volume catheterization study. Circ Cardiovasc Imaging. 2014;7(1):164-72.

[34] Reant P, Metras A, Detaille D, Reynaud A, Diolez P, Jaspard-Vinassa B, et al. Impact of Afterload Increase on Left Ventricular Myocardial Deformation Indices. J Am Soc Echocardiogr. 2016;29(12):1217-28.

[35] Ng ACT, Delgado V, Bertini M, Antoni ML, Van Bommel RJ, Van Rijnsoever EPM, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: A two-dimensional speckle tracking analysis. Eur Heart J. 2011;32(12):1542-50.

[36] Park JJ, Park JB, Park JH, Cho GY. Global Longitudinal Strain to Predict Mortality in Patients With Acute Heart Failure. Journal of the American College of Cardiology. 2018;71(18):1947-57.

[37] Namazi F, van der Bijl P, Hirasawa K, Kamperidis V, van Wijngaarden SE, Mertens B, et al. Prognostic Value of Left Ventricular Global Longitudinal Strain in Patients With Secondary Mitral Regurgitation. J Am Coll Cardiol. 2020;75(7):750-8.

SUPPLEMENTARY MATERIAL

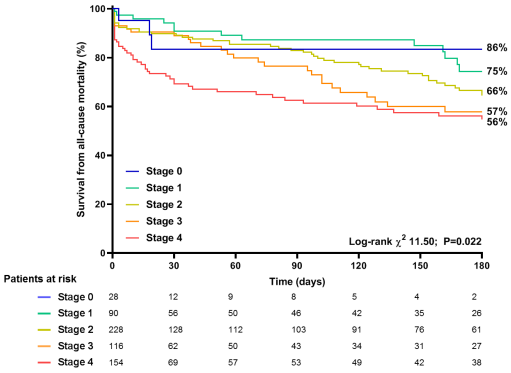
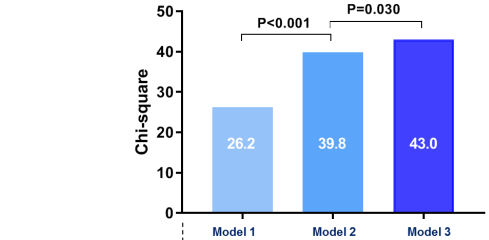


Figure 5: Kaplan-Meier survival curves for all-cause mortality per stage of cardiac damage after reclassification by incorporating LV GLS for patients censored at moment of aortic valve replacement (N = 616). GLS, global longitudinal strain; LV, left ventricular.



Previous myocardial infarction	1.88 (1.19-2.97)	1.95 (1.23-3.08)	1.77 (1.11-2.82)
Diabetes mellitus	1.77 (1.11-2.83)	1.83 (1.14-2.92)	1.95 (1.21-3.15)
Estimated GFR <60 ml/min/1.73m²	1.76 (1.07-2.90)	1.70 (1.03-2.80)	1.70 (1.04-2.80)
Stroke volume index	0.99 (0.95-1.03)	1.01 (0.97-1.06)	1.03 (0.98-1.08)
Aortic valve replacement	0.57 (0.33-1.01)	0.56 (0.32-0.99)	0.63 (0.36-1.13)
Stage of cardiac damage		1.44 (1.18-1.75)	1.32 (1.07-1.62)
LV GLS (%)			0.93 (0.88-0.99)

Figure 6: Incremental value of LV GLS on top of the proposed staging classification of cardiac damage in low-flow low-gradient severe AS patients (N = 162). The bar graphs depict the incremental prognostic value of LV GLS (Model 3) over the stages of cardiac damage and clinical parameters (Model 2) for all-cause mortality, as illustrated by a significant increase in χ^2 values on the y-axis. Data are presented as hazard ratios with corresponding 95% confidence intervals. AS, aortic stenosis; GFR, glomerular filtration rate; GLS, global longitudinal strain; LV, left ventricular.

Table 5: Clinical characteristics of total study population and per stage of cardiac damage after reclassification by incorporating LV GLS.

Variables	Total population (N = 616)	Stage 0 (N = 28)	Stage 1 (N = 90)	Stage 2 (N = 228)	Stage 3 (N = 116)	Stage 4 (N = 154)	*P* value*
Age (years)	74.4±10.7	73.1±9.9	71.2±13.6	75.9±10.0‡	76.4±10.3‡	76.6±9.5‡	**0.001**
Male gender, *N* (%)	359 (58)	17 (61)	41 (46)	127 (56)	71 (61)	103 (67)	**0.019**
Body mass index (kg/m^2)	26.3±4.4	27.8±4.7	25.9±3.3	26.8±4.7	26.1±4.5	25.7±4.5	0.059
Body surface area (m^2)	1.87±0.21	1.89±0.20	1.84±0.20	1.88±0.21	1.87±0.20	1.87±0.21	0.604
Hypertension, *N* (%)	414 (67)	18 (64)	59 (66)	162 (71)	82 (71)	93 (60)	0.228
Hypercholesterolemia, *N* (%)	348 (57)	19 (68)	49 (54)	126 (55)	69 (60)	85 (55)	0.682
Diabetes mellitus, *N* (%)	150 (24)	7 (25)	14 (16)	59 (26)	29 (25)	41 (27)	0.339
Coronary artery disease, *N* (%)	311 (51)	11 (39)	32 (36)	114 (50)	57 (49)	97 (63)	**0.001**
Previous MI, *N* (%)	126 (21)	3 (11)	9 (10)	36 (16)	27 (23)	51 (33)	**<0.001**
History of smoking, *N* (%)	214 (35)	13 (46)	30 (33)	76 (33)	43 (37)	52 (34)	0.680
COPD, *N* (%)	101 (16)	5 (18)	13 (14)	34 (15)	18 (16)	31 (20)	0.682
History of atrial fibrillation, *N* (%)	169 (27)	3 (11)	4 (4)	61 (27)	35 (30)	66 (43)	**<0.001**
NYHA functional class ≥III, *N* (%)	254 (42)	13 (46)	13 (15)	77 (35)	60 (52)	91 (59)	**<0.001**
Symptoms, *N* (%)							
Angina	260 (42)	13 (46)	43 (48)	100 (44)	54 (47)	50 (33)	0.070
Dyspnea	478 (78)	21 (75)	58 (64)	168 (74)	92 (79)	139 (90)	**<0.001**
Syncope	67 (11)	1 (4)	13 (14)	32 (14)	10 (9)	11 (7)	0.088
Estimated GFR (ml/min/1.73m^2)	62.2±20.6	68.7±17.7	67.6±22.6	65.5±19.5	58.8±20.4‡	55.7±19.5†‡§	**<0.001**
<60 ml/min/1.73m^2, *N* (%)	287 (47)	10 (36)	32 (36)	95 (42)	61 (53)	89 (58)	**0.002**
Systolic BP (mmHg)	138.0±23.5	143.8±21.8	142.8±19.8	143.8±23.0	138.6±23.3	125.2±22.1	**<0.001**
Diastolic BP (mmHg)	73.8±13.4	74.5±13.7	75.5±9.8	75.4±14.0	72.6±13.4	71.2±13.8	**0.020**
Medication, *N* (%)							
Beta blocker	328 (53)	10 (36)	46 (51)	121 (53)	65 (56)	86 (56)	0.354
ACE inhibitor/ARB	306 (50)	15 (54)	35 (39)	124 (54)	51 (44)	81 (53)	0.077
Aspirin/thienopyridines	280 (46)	15 (54)	40 (44)	107 (47)	56 (48)	62 (40)	0.553
Oral anticoagulant	173 (28)	3 (11)	9 (10)	52 (23)	36 (31)	73 (47)	**<0.001**
Statin	355 (58)	18 (64)	54 (60)	131 (58)	67 (58)	85 (55)	0.895
Calcium channel blocker	145 (24)	6 (21)	20 (22)	63 (28)	24 (21)	32 (21)	0.485
Diuretics	311 (51)	6 (21)	21 (23)	107 (47)	74 (64)	103 (67)	**<0.001**

Continuous variables are presented as mean±SD or median [interquartile range]. Categorical variables are expressed as number (percentage). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. ‡*P* value <0.05 vs. Stage 1 with Bonferroni's post hoc analysis. §*P* value <0.05 vs. Stage 2 with Bonferroni's post hoc analysis.

Table 6: Echocardiographic characteristics of total study population and per stage of cardiac damage after reclassification by incorporating LV GLS.

Variables	Total population (N = 616)	Stage 0 (N = 28)	Stage 1 (N = 90)	Stage 2 (N = 228)	Stage 3 (N = 116)	Stage 4 (N = 154)	*P* value*
Heart rate at TTE (bpm)	75.0±14.4	72.6±12.0	71.2±11.4	72.1±13.3	75.4±13.5	81.4±16.6†‡§‖	**<0.001**
Valve morphology, *N* (%)							**<0.001**
Tricuspid	555 (90)	24 (86)	70 (78)	208 (91)	110 (95)	143 (93)	
Bicuspid	61 (10)	4 (14)	20 (22)	20 (9)	6 (5)	11 (7)	
Atrial fibrillation at TTE, *N* (%)	72 (12)	0(0)	0 (0)	19 (8)	17 (15)	36 (23)	**<0.001**
LV end-diastolic diameter (mm)	48.9±8.3	41.5±4.1	45.4±6.4	47.4±6.4†	48.8±7.7†‡	54.5±9.6†‡§‖	**<0.001**
LV end-systolic diameter (mm)	35.6±9.9	28.6±4.8	31.1±6.4	32.2±6.8	35.9±8.5†‡§	44.4±11.4†‡§‖	**<0.001**
Septal wall thickness (mm)	12.9±2.3	11.3±1.5	12.4±1.8	13.2±2.2†‡	13.3±2.5†	12.6±2.5	**<0.001**
Posterior wall thickness (mm)	12.1±2.0	11.1±1.5	11.6±1.7	12.5±1.9†‡	12.4±2.3†‡	11.7±2.1§‖	**<0.001**
LV mass index (g/m^2)	129.4±37.1	84.2±14.2	110.5±26.3†	128.1±31.1†‡	135.0±40.4†‡	146.9±39.2†‡§‖	**<0.001**
LV end-diastolic volume (ml)	109.8±54.3	79.9±23.0	85.9±25.6	94.7±34.1	110.7±44.2†‡§	151.2±75.1†‡§‖	**<0.001**
LV end-systolic volume (ml)	59.9±46.1	29.7±13.1	36.9±22.0	42.9±20.3	60.2±31.6†‡§	103.9±63.4†‡§‖	**<0.001**
LV ejection fraction (%)	52.9±14.0	63.0±7.7	62.8±8.1	59.1±8.0‡	50.6±10.8†‡§	37.7±13.7†‡§‖	**<0.001**
<50%, *N* (%)	203 (33)	0 (0)	4 (4)	25 (11)	51 (44)	123 (80)	**<0.001**
LV global longitudinal strain (%)	14.0±4.5	20.0±2.0	18.0±1.4†	16.3±2.2†‡	12.3±2.1†‡§	8.3±3.1†‡§‖	**<0.001**
Peak E-wave velocity (cm/s)	83.0±30.0	69.4±18.6	73.1±21.0	82.6±29.7	83.8±31.7	91.3±32.9†‡	**<0.001**
E' (cm/s)	5.1±2.1	6.4±1.5	4.7±1.5†	5.2±2.1	5.0±1.9†	5.0±2.6†	**0.009**
E/e' ratio	18.5±9.9	11.1±1.8	17.3±7.7†	17.9±9.8†	18.6±9.1†	21.4±11.6†‡§	**<0.001**
Left atrial volume index (ml/m^2)	41.0±17.5	22.9±5.3	24.6±6.3	43.3±17.2†‡	42.2±15.1†‡	50.0±17.1†‡§‖	**<0.001**
Significant MR, *N* (%)	56 (9)	0 (0)	0 (0)	17 (8)	11 (10)	28 (18)	**<0.001**
Systolic PAP (mmHg)	33.0±12.4	23.5±6.1	27.6±7.7	32.0±9.0†	33.7±12.8†‡	38.9±15.8†‡§‖	**<0.001**
Significant TR, *N* (%)	43 (7)	0 (0)	0 (0)	0 (0)	14 (12)	29 (19)	**<0.001**
TAPSE (mm)	20.2±3.9	22.3±2.2	21.8±2.9	21.9±3.1	20.6±2.8‡§	16.2±3.5†‡§‖	**<0.001**
Mean AV gradient (mmHg)	42.3±16.6	39.5±13.3	44.0±13.6	46.0±16.7	45.6±17.0	33.6±15.1‡§‖	**<0.001**
Peak aortic jet velocity (m/s)	4.0±0.7	3.9±0.6	4.1±0.6	4.2±0.7	4.2±0.7	3.6±0.8‡§‖	**<0.001**
AVA (cm^2)	0.77±0.19	0.89±0.23	0.81±0.18	0.78±0.17†	0.74±0.20†‡	0.72±0.20†‡§	**<0.001**
Indexed AVA (cm^2/m^2)	0.41±0.10	0.48±0.13	0.45±0.09	0.42±0.09†	0.40±0.10†‡	0.39±0.10†‡§	**<0.001**
Low-flow low-gradient AS, *N* (%)	162 (26)	7 (25)	11 (12)	35 (15)	27 (23)	82 (53)	**<0.001**

Continuous variables are presented as mean±SD. Categorical variables are expressed as number (percentage). AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; bpm, beats per minute; LV, left ventricular; MR, mitral regurgitation; PAP, pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. †*P* value <0.05 vs. Stage 0 with Bonferroni's post hoc analysis. ‡*P* value <0.05 vs. Stage 1 with Bonferroni's post hoc analysis. §*P* value <0.05 vs. Stage 2 with Bonferroni's post hoc analysis. ‖*P* value <0.05 vs. Stage 3 with Bonferroni's post hoc analysis.

Table 7: Univariable and multivariable Cox proportional hazard analyses for all-cause mortality in patients with low-flow low-gradient severe AS (N = 162).

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (per 1 year increase)	1.021 (0.995-1.048)	0.112		
Male gender (yes/no)	1.534 (0.941-2.501)	0.086		
Coronary artery disease (yes/no)	1.534 (0.953-2.471)	0.078		
Previous myocardial infarction (yes/no)	1.914 (1.216-3.012)	**0.005**	1.766 (1.105-2.821)	**0.017**
History of atrial fibrillation (yes/no)	1.325 (0.843-2.082)	0.223		
Diabetes mellitus (yes/no)	1.772 (1.116-2.813)	**0.015**	1.953 (1.210-3.152)	**0.006**
NYHA functional class ≥III (yes/no)	1.390 (0.885-2.183)	0.153		
Estimated GFR <60 ml/min/1.73m^2 (yes/no)	2.108 (1.311-3.390)	**0.002**	1.703 (1.035-2.802)	**0.036**
Diuretics (yes/no)	1.356 (0.841-2.187)	0.212		
Stroke volume index (per 1 ml/m^2 increase)	0.994 (0.953-1.037)	0.782	1.027 (0.979-1.078)	0.280
Indexed AVA (per 0.01 cm^2/m^2 increase)	3.414 (0.248-46.9)	0.359		
Surgical or transcatheter AVR (yes/no)	0.533 (0.311-0.912)	**0.022**	0.632 (0.355-1.127)	0.120
LV global longitudinal strain (per 1% increase)	1.096 (1.043-1.152)	**<0.001**	0.933 (0.875-0.993)	**0.030**
Stage of cardiac damage (per 1 stage increase)	1.400 (1.162-1.687)	**<0.001**	1.315 (1.067-1.621)	**0.010**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; GFR, glomerular filtration rate; NYHA, New York Heart Association; LV, left ventricular.

4

ASSOCIATION OF LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN WITH ASYMPTOMATIC SEVERE AORTIC STENOSIS: NATURAL COURSE AND PROGNOSTIC VALUE

E. Mara Vollema, Tadafumi Sugimoto, Mylène Shen,
Lionel Tastet, Arnold C.T. Ng, Rachid Abou,
Nina Ajmone Marsan, Bart Mertens, Raluca Dulgheru,
Patrizio Lancellotti, Marie-Annick Clavel, Philippe Pibarot,
Philippe Généreux, Martin B. Leon, Victoria Delgado, Jeroen J. Bax

Published in JAMA Cardiol. 2018; 3(9): 839-847.

ABSTRACT

IMPORTANCE

The optimal timing to operate in patients with asymptomatic severe aortic stenosis (AS) remains controversial. Left ventricular global longitudinal strain (LV GLS) may help to identify patients who might benefit from undergoing earlier aortic valve replacement.

OBJECTIVE

To investigate the prevalence of impaired LV GLS, the natural course of LV GLS, and its prognostic implications in patients with asymptomatic severe AS with preserved left ventricular ejection fraction (LVEF).

DESIGN, SETTING, AND PARTICIPANTS

This registry-based study included the institutional registries of 3 large tertiary referral centers and 220 patients with asymptomatic severe AS and preserved LVEF (>50%) who were matched for age and sex with 220 controls without structural heart disease. The echocardiograms of patients and controls were performed between 1998 and 2017.

EXPOSURES

Both clinical and echocardiographic data were assessed retrospectively. Severe AS was defined by an indexed aortic valve area <0.6 cm^2/m^2. Left ventricular global longitudinal strain was evaluated on transthoracic echocardiography using speckle tracking imaging.

MAIN OUTCOMES AND MEASURES

The prevalence of impaired LV GLS, the natural course of LV GLS, and the association of impaired LV GLS with symptom onset and the need for aortic valve intervention.

RESULTS

Two-hundred twenty patients (mean age 68±13 years; 126 men [57%]) were included. Despite comparable LVEF, LV GLS was significantly impaired in patients with asymptomatic severe AS compared with age- and sex-matched controls without AS (mean LV GLS, -17.9±2.5% vs. -19.6±2.1%; P<0.001). After a median follow-up of 12 (interquartile range [IQR]: 7 to 23) months, mean LV GLS significantly deteriorated (-18.0±2.6% to -16.3±2.8%; P<0.001) while LVEF remained unchanged. Patients with impaired LV GLS at baseline (>-18.2%) showed a higher risk for developing symptoms (P=0.02) and needing aortic valve intervention (P=0.03) at follow-up compared with patients with more preserved LV GLS (≤-18.2%).

CONCLUSIONS AND RELEVANCE

Subclinical myocardial dysfunction that is characterized by impaired LV GLS is often present in patients with asymptomatic severe AS with preserved LVEF. Left ventricular global longitudinal strain further deteriorates over time and impaired LV GLS at baseline is associated with an increased risk for progression to the symptomatic stage and the need for aortic valve intervention.

Introduction

In patients with asymptomatic severe aortic stenosis (AS), the current guidelines recommend a watchful waiting strategy until symptoms or left ventricular (LV) systolic dysfunction (i.e., LV ejection fraction [LVEF] <50%) develop [1, 2]. The optimal timing for intervention in these patients remains controversial [3–6]. To determine whether the patients are truly asymptomatic, exercise testing is animportant diagnostic tool [7]. However, in patients who are unable to perform this test, additional measurements are needed to better define the timing of the intervention. The assessment of LV systolic function by means of global longitudinal strain (GLS) by speckle tracking echocardiography has demonstrated that a significant proportion of patients with severe AS have impaired LV GLS despite having normal LVEF [8–13]. Impaired LV GLS has been associated with worse outcomes in patients with symptomatic severe AS [14]. However, to our knowledge, the prevalence of impaired LV GLS among patients with asymptomatic severe AS and normal LVEF and the natural course and prognostic value of LVGLS in this subgroup of patients has not been extensively elucidated. Accordingly, this study aimed to investigate the prevalence of impaired LV GLS, as well as describing the natural course of serial changes in LV GLS and its prognostic implications, in asymptomatic patients with severe AS and preserved LVEF.

Methods

Study population and data collection

From a multicenter international registry of patients with AS (Leiden University Medical Center [Leiden, The Netherlands], HeartValve Clinic [Liège, Belgium], and Institut Universitaire de Cardiologie et de Pneumologie de Québec [Quebec, Canada]), 220 patients with asymptomatic severe AS and preserved LV ejection fraction (LVEF >50%) were selected and included in this retrospective study. Patients were selected based on available echocardiographic data at baseline (defined as the date of the first diagnosis of severe AS) with a feasible speckle tracking analysis. The definition of severe AS was based on an indexed aortic valve area (AVA) <0.6 cm^2/m^2 and/or a mean aortic valve gradient of ≥40 mmHg and/or a peak aortic jet velocity ≥4 m/s [2, 15, 16]. When available, the last transthoracic echocardiogram performed at the outpatient clinic or before aortic intervention was analyzed to evaluate the changes in valve hemodynamics, LV structure, and systolic function (including LV GLS). Measurements of the echocardiographic data were performed at each institution by experienced observers. Aortic valve intervention was defined as a surgical or transcatheter aortic valve replacement (AVR) or balloon valvuloplasty. The exclusion criteria were AS-related symptoms at baseline (e.g., angina, syncope, or dyspnea), nonsevere AS, LVEF <50%, having undergone prior aortic or mitral valve intervention, acute endocarditis at baseline, or the inability to measure LV GLS.

In addition, an age- and sex-matched control group of 220 individuals without structural heart disease was included and used as a reference for measuring LV GLS. The transthoracic echocardiograms of this group of individuals were performed at the Leiden University Medical Center. The referral reasons to perform echocardiography in this group were atypical chest pain, palpitations, or syncope without the presence of a murmur.

Baseline patient demographics and clinical follow-up data were gathered and analyzed retrospectively using the departmental patient information systems and hospital records. This retrospective analysis of clinically acquired data was approved by the respective institutional review boards of each participating center, and consent was waived due to the retrospective nature of the study.

TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed in all patients at rest in the left decubitus position using commercially available ultrasonography systems. Conventional LV dimensions and function as well as AVA were measured following current recommendations [17]. Additionally, LV GLS was measured with a 2-dimensional speckle tracking analysis on apical 2-, 3-, and 4-chamber views using commercially available software (Leiden University Medical Center: EchoPac, version 113; General Electric; Vingmed Ultrasound; Heart Valve Clinic Liège and Institut Universitaire de Cardiologie et de Pneumologie de Québec: 2D Cardiac Performance Analysis; TomTec Imaging Systems) [17]. The frame rate of the 2-dimensional echocardiographic data was ≥40 frames per second. Left ventricular GLS measures the shortening of the myocardial fibers in the longitudinal direction and is conventionally presented as a negative value. Therefore, a less negative LV GLS (i.e., closer to 0) represents worse LV systolic function.

CLINICAL AND ECHOCARDIOGRAPHIC FOLLOW-UP AND ENDPOINTS

Patients were routinely followed up at the outpatient clinic according to guideline recommendations [16]. The onset of AS-related symptoms was recorded. The medical treatment and timing for AVR was left at the discretion of the treating physician of each institution. The time to symptom development and AVR, as well as the date of all-cause mortality, were recorded as clinical end points for assessing the prognosis.

STATISTICAL ANALYSIS

Categorical variables were presented as numbers (percentage) and continuous variables as mean±SD if normally distributed or medians (interquartile range [IQR]) if otherwise. Histograms were used to evaluate if a Gaussian distribution was present. Comparisons between the total asymptomatic severe AS group and the control group were performed using the *t* test or Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables as appropriate. The group of patients with asymptomatic severe AS was divided according to the symptom status at the last echocardiogram performed: symptomatic vs. asymptomatic. Changes within and between these 2 groups were assessed using linear mixed models, with correction for age, sex, and time to follow-up. To further examine the prognostic value of LV GLS, the study population was divided according to the median baseline LV GLS value. Cumulative event rates were calculated with the Kaplan-Meier method. Two end points were defined: new onset of symptoms and AVR. Comparisons between the 2 groups were performed using log-rank tests. To assess the association between baseline LV GLS and the end points, Cox proportional hazards modeling was used. Spline models were fitted with overlaying confidence intervals for each end point vs. LV GLS on the log-hazards scale, adjusting for age, sex, coronary artery disease, atrial fibrillation, and LV mass index. SPSS, version 23.0 (IBM,

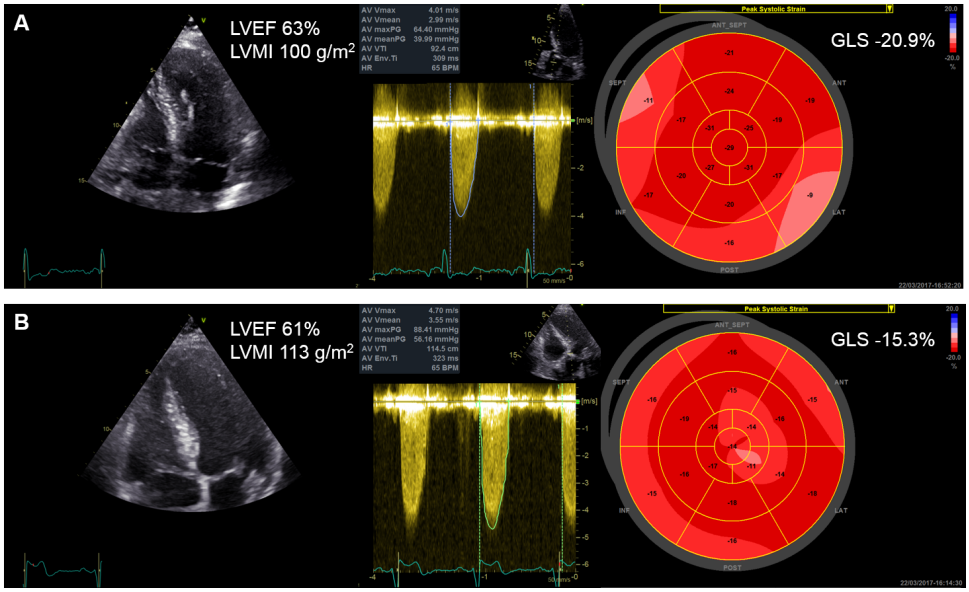


Figure 1: Example of a patient with asymptomatic severe aortic stenosis and preserved left ventricular (LV) ejection fraction (LVEF) at baseline (*panel A*) and at follow-up (*panel B*). Over time, the aortic stenosis severity and LV hypertrophy progressed and LV systolic function as assessed with LV global longitudinal strain (GLS) deteriorated, whereas LVEF remained unchanged. LVMI, left ventricular mass index.

Armonk, New York) was used for the statistical analyses. A *P* value of <0.05 was considered statistically significant.

Results

Characteristics of patients with asymptomatic severe AS vs. controls

In total, 220 patients with asymptomatic severe AS and preserved LVEF (mean age 68±13 years; 126 men [57%]) were evaluated in this study (Table 1). Despite comparable LVEF, LV GLS was significantly impaired in the patients with asymptomatic severe AS compared with controls, suggesting that asymptomatic patients with severe AS can harbor subtle myocardial dysfunction. When using the mean LV GLS value of the control group as a reference to define normal (≤-19.6%) or impaired LV longitudinal systolic function (>-19.6%), 153 patients (70%) with asymptomatic severe AS had impaired LV GLS. Left ventricular global longitudinal strain was not significantly different across the centers (Leiden, -18.2±2.3%; Québec, -18.0±1.8%; Liège, -17.4±3.1%]; analysis of variance *P*=0.15). In addition, there were no differences across the centers in the proportion of patients with impaired LV GLS (Leiden, 65%; Québec, 81%; Liège, 73%; *P*=0.20).

Table 1: Baseline clinical and echocardiographic characteristics of asymptomatic severe aortic stenosis patients and an age- and sex-matched cohort of individuals without structural heart disease.

Variables	Patients with asymptomatic severe AS (N = 220)	Age- and sex-matched cohort (N = 220)	*P* value
Clinical characteristics			
Age, years	67.9±13.0	65.7±13.3	0.08
Male gender, *N* (%)	126 (57)	126 (57)	1.00
Body surface area, m^2	1.87±0.2	1.93±0.2	**0.002**
Hypertension, *N* (%)	128 (59)	103(48)	**0.02**
Hypercholesterolemia, *N* (%)	103 (47)	54 (25)	**<0.001**
Diabetes, *N* (%)	34 (16)	24 (11)	0.16
History of smoking, *N* (%)	73 (38)	17 (11)	**<0.001**
Coronary artery disease, *N* (%)	47 (22)	0 (0)	**<0.001**
Prior myocardial infarction, *N* (%)	15 (7)	0 (0)	**<0.001**
Medication use, *N* (%)			
Beta-blocker	78 (36)	49 (23)	**0.002**
ACE-inhibitor/ARB	88 (40)	65 (30)	**0.02**
Calcium antagonist	48 (22)	23 (11)	**0.001**
Diuretic agents	52 (24)	44 (20)	0.34
Statins	112 (51)	56 (26)	**<0.001**
Aspirin and/or clopidogrel	93 (43)	48 (22)	**<0.001**
Vitamin K antagonist or NOAC	31 (14)	3 (1)	**<0.001**
Creatinin level, µmol/l	80 [70-97]	80 [69-93]	0.56
Estimated GFR, ml/min/1.73 m^2	76 [61-89]	80 [65-89]	0.48
Baseline echocardiography			
Valve anatomy, *N* (%)			**<0.001**
Tricuspid	170 (77)	220 (100)	
Bicuspid	50 (23)	0 (0)	
Aortic valve mean gradient (mmHg)*	39.4±12.6	N/A	N/A
Aortic valve peak velocity (m/s)*	4.0±0.6	N/A	N/A
Aortic valve area (cm^2)*	0.86±0.1	N/A	N/A
Aortic valve area index (cm^2/m^2)*	0.46±0.1	N/A	N/A
Stroke volume (ml)*	81.4±17.1	N/A	N/A
Stroke volume index (ml/m^2)*	43.8±9.1	N/A	N/A
LV end-diastolic diameter (mm)	45.4±5.8	48.5±6.4	**<0.001**
LV end-systolic diameter (mm)	28.2±5.0	30.5±6.5	**<0.001**
Intraventricular septal thickness (mm)	12.9±2.3	10.3±1.7	**<0.001**
Posterior wall thickness (mm)	11.6±1.9	10.0±2.0	**<0.001**
LV mass index (g/m^2)	112.0±27.7	92.5±21.4	**<0.001**
LV ejection fraction (%)	61.5±5.9	62.1±6.3	0.27
LV global longitudinal strain (%)	-17.9±2.5	-19.6±2.1	**<0.001**

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AS, aortic stenosis; GFR, glomerular filtration rate estimated using CKD-EPI formula; LV, left ventricular; N/A, not applicable; NOAC, novel oral anti-coagulants. *Aortic valve gradients, aortic valve area, and stroke volume were only measured for patients with AS.

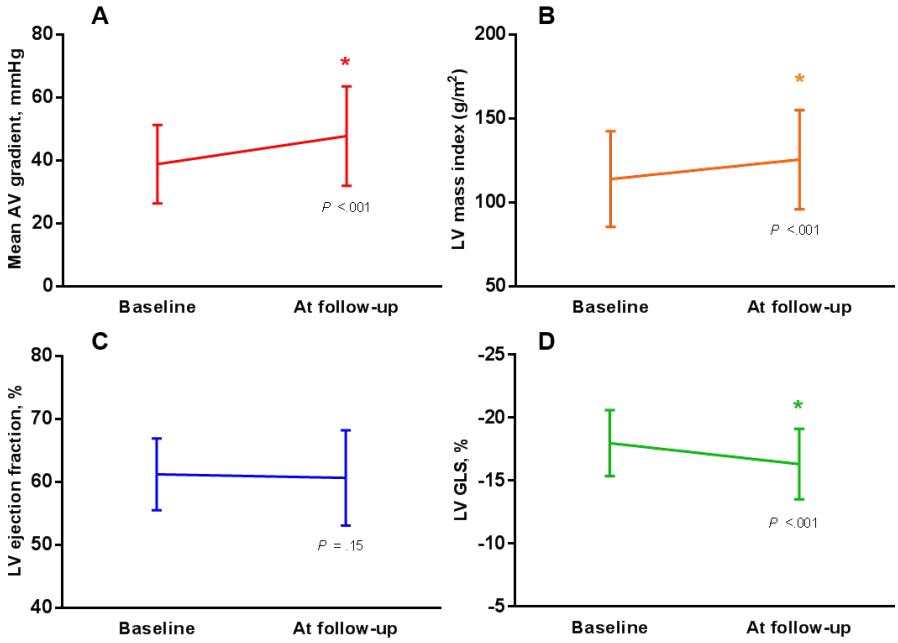


Figure 2: Time course of valve hemodynamics and left ventricular systolic function in 150 patients with asymptomatic severe aortic stenosis at baseline vs. follow-up echocardiography by aortic valve (AV) mean gradient (*panel A*), left ventricular (LV) hypertrophy (*panel B*) and LV systolic function by LV ejection fraction (*panel C*) and LV global longitudinal strain (GLS)(*panel D*). *Indicates *P*<0.001.

Changes in LV GLS over time in patients with AS

To evaluate the changes in LV GLS in patients with asymptomatic severe AS, a subgroup of 150 patients (68.2%) with severe AS with an available second transthoracic echocardiogram result (at the last clinical follow-up or before AVR) and a feasible speckle tracking analysis result was evaluated. The median time interval between the 2 echocardiograms was 12 (IQR: 7 to 23) months. The changes in valve hemodynamics and LV systolic function are displayed in Supplemental Table 3. Over time, there were significant increases in mean transvalvular gradients and LV mass index, whereas the AVA decreased. While the LVEF remained unchanged (61.2±5.7% to 60.6±7.6%; *P*=0.15), LV GLS showed significant impairment over time (-18.0±2.6% to -16.3±2.8%; *P*<0.001) (Figures 1 and 2), demonstrating increasing subclinical LV dysfunction over time.

Of the 150 patients with echocardiographic follow-up and feasible speckle tracking analysis, 78 (52%) were symptomatic at follow-up echocardiography and 72 patients (48%) remained asymptomatic. The median time from baseline to follow-up echocardiography was similar between these 2 groups (symptomatic, 13 [IQR: 8 to 28] months vs. asymptomatic, 12 [IQR: 6 to 20] months; *P*=0.09). Compared with asymptomatic patients, patients who developed symptoms at follow-up showed a higher prevalence of atrial fibrillation (22% vs. 10%, respectively; *P*=0.05) and had more frequent coronary

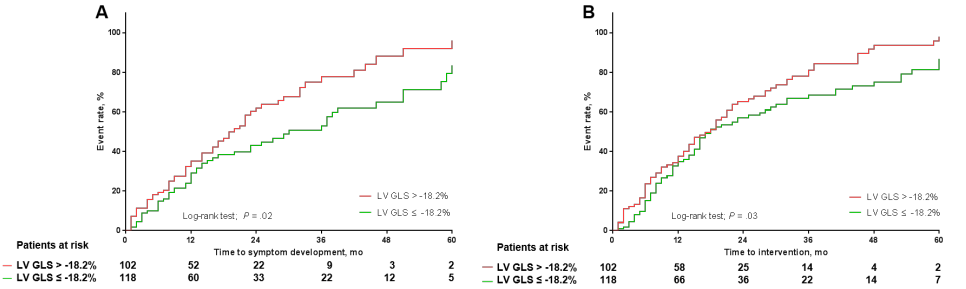


Figure 3: Kaplan-Meier estimates for event rates for symptom development (*panel A*) and intervention (*panel B*) in patients with asymptomatic aortic stenosis. Cumulative event rates were compared with the study population divided according to left ventricular (LV) global longitudinal strain (GLS) at baseline >-18.2% (more impaired, red line) vs. ≤-18.2% (more preserved, green line).

artery disease (27% vs. 16%, respectively; *P*=0.09). Table 2 outlines the changes in valve hemodynamics and LV systolic function over time in these patients divided by symptom status at follow-up. Within both groups, the progression of AS was observed over time with a concomitant increase in LV mass index and impairment in LV GLS without changes in LVEF. Between both groups, no significant differences were observed in valve hemodynamics and LV systolic function, although LV mass index at follow-up was higher in patients with AS who developed symptoms.

PROGNOSTIC VALUE OF LV GLS IN SYMPTOM DEVELOPMENT AND AVR

Of the 220 patients with asymptomatic severe AS, 118 (54%) developed symptoms during a median follow-up of 12 months (IQR, 5-24). After a median follow-up period of 13 (IQR: 6 to 25) months, 162 patients (74%) received an aortic valve intervention (28 [17%] received transcatheter aortic valve implantation, 130 [80%] underwent surgical AVR, and 4 [3%] underwent balloon valvuloplasty). Most of these patients underwent aortic valve intervention because of symptom development (104 [64%]) or progression of AS severity (40 [25%]); only 18 patients (11%) received an AVR because of other reasons, such as an indication for coronary artery bypass grafting. During follow-up, 28 patients (13%) died; 8 patients (4%) died while scheduled for AVR or when receiving conservative treatment.

To evaluate the prognostic value of baseline LV GLS, the study population was divided into 2 groups according to the median value of baseline LV GLS (more preserved, ≤-18.2% vs. more impaired, >-18.2%) Supplemental Table 4). Compared with patients with more preserved LV GLS, patients with more impaired LV GLS had a higher prevalence of coronary artery disease (30% vs. 15%, *P*=0.01) and atrial fibrillation (26% vs. 12%, *P*=0.01). On transthoracic echocardiography, patients with more impaired LV GLS had a larger LV mass index and lower LVEF than patients with more preserved LV GLS, although mean LVEF was >60% in both groups (Supplemental Table 4).

The cumulative event rates for developing symptoms were significantly higher in patients with a baseline LV GLS >-18.2% compared with patients with an LV GLS ≤-18.2% (59% vs. 45% at 2-year follow-up, respectively, and 91% vs. 79% at 5-year follow-up, respectively; log-rank *P*=0.02) (Figure 3, *panel A*). Similarly, for AVR, the cumulative

Table 2: Echocardiographic parameters in 150 patients with asymptomatic severe aortic stenosis at baseline vs. follow-up divided by symptom status at follow-up echocardiography.

	Symptomatic at follow-up (N = 78)			**Asymptomatic at follow-up (N = 72)**			***P* value intergroup**	
Variable	**Baseline**	**Follow-up**	***P* value**	**Baseline**	**Follow-up**	***P* value**	**Baseline**	**Follow-up**
Aortic valve								
Mean gradient (mmHg)	38.4±11.6	49.0±15.8	**<0.001**	39.4±13.5	46.6±15.8	**<0.001**	0.71	0.31
Peak velocity (m/s)	3.9±0.6	4.4±0.6	**<0.001**	4.0±0.6	4.3±0.6	**<0.001**	0.36	0.25
Area (cm^2)	0.88±0.1	0.76±0.1	**<0.001**	0.85±0.1	0.79±0.1	0.05	0.12	0.30
Area index (cm^2/m^2)	0.48±0.1	0.41±0.1	**<0.001**	0.46±0.1	0.42±0.1	**0.02**	0.08	0.41
Stroke volume (ml)	81.1±14.6	80.6±14.8	0.17	81.7±19.5	82.1±19.2	0.71	0.97	0.91
Stroke volume index (ml/m^2)	44.6±9.0	43.7±8.5	0.34	43.6±10.1	43.5±8.3	0.94	0.55	0.84
Left ventricular								
Mass index (g/m^2)	114.0±27.1	129.6±29.2	**<0.001**	113.7±30.6	121.0±29.6	0.009	0.76	0.06
Ejection fraction (%)	61.4±6.3	61.6±6.9	0.25	61.0±5.0	59.5±8.2	0.28	0.65	0.06
GLS (%)	-17.7±2.6	-16.3±2.9	**<0.001**	-18.2±2.6	-16.4±2.6	**<0.001**	0.21	0.83

AVR, aortic valve replacement; GLS, global longitudinal strain; LV, left ventricular.

event rates were significantly higher in patients with impaired baseline LV GLS (>-18.2%) compared with patients with more preserved baseline LV GLS (≤-18.2%) after 2 years (66% vs. 57%, respectively) and 5 years of follow-up (96% vs. 82%, respectively; log-rank *P*=0.03) (Figure 3, *panel B*). The spline curves to assess the association between symptom development and aortic valve intervention across a range of LV GLS are shown in Supplemental Figure 4. For both symptom development and aortic valve intervention, the linearity assumption was not violated (χ^2, 0.83; *P*=0.67, and χ^2, 1.86; *P*=0.41, respectively). For symptom development, a plateau can be seen (Supplemental Figure 4). For aortic valve intervention, a clear increase in hazard ratios can be observed for more impaired LV GLS (Supplemental Figure 4).

DISCUSSION

THIS study demonstrated that in patients with asymptomatic severe AS and preserved LVEF, LV GLS assessed by speckle tracking imaging is impaired as compared with age- and sex matched controls without structural heart disease. Over time, patients with asymptomatic severe AS showed a progression of AS severity accompanied by increasing LV hypertrophy and further impairment of LV GLS, while LVEF remained relatively unchanged. Patients with impaired LV GLS at baseline showed a higher risk for developing symptoms and for needing aortic valve intervention at follow-up as compared with patients with more preserved LV GLS. These findings suggest that LV GLS is a more sensitive marker for early myocardial damage than LVEF in this patient group and may help identify the patients who may benefit from earlier AVR.

LV GLS AS A MARKER FOR SUBTLE LV DYSFUNCTION IN ASYMPTOMATIC SEVERE AS

Symptom development and LV systolic dysfunction are the main factors that determine the timing of AVR in patients with severe AS [1, 2]. However, decreased physical activity in the aging AS population may result in the underrecognition or late reporting of symptoms [18]. Zilberszac et al. [19] demonstrated that 43% of elderly patients with asymptomatic severe AS who developed symptoms presented with severe heart failure symptoms (New York Heart Association class ≥III). The deterioration of LV systolic function defined by an LVEF <50% can be regarded as a more objective parameter that indicates the need for AVR. However, this will only occur when the concentric remodeled left ventricle fails to maintain normal wall stress because of significant afterload mismatch [20]. At this stage, LV remodeling is characterized by progressive myocardial fibrosis, which is not reversible after an intervention [21, 22]. Therefore, more sensitive markers of LV systolic dysfunction are needed at an earlier stage to identify patients with severe AS who are at risk for irreversible myocardial damage. Recently, Stokke et al. [12] showed that by inducing concentric LV remodelling with an increase in wall thickness and a reduction in diameter of the LV cavity, the LVEF can remain preserved, whereas LV GLS will be impaired. While the presence of impaired LV GLS with preserved LVEF has been described in symptomatic severe AS [8, 9, 23], the prevalence of impaired LV GLS in asymptomatic severe AS has been less studied. Lafitte et al. [24] reported significantly impaired LV GLS in 65 patients with asymptomatic severe AS compared with 60 healthy participants (-

17.8±3.5% vs. -21.1±1.8%, respectively; P <0.05), while no differences were observed in LVEF (64±7% vs. 66±5%, respectively) [24]. This study extends these findings in a larger population. However, the mean value of LV GLS in this study was more preserved than that reported in previous studies (-18.0% vs. -15% to -16.6%) [25–29]. This discrepancy could be explained by the inclusion of older patients in those studies. Furthermore, to our knowledge, this study is the first to report sequential measurements of LV GLS in the period between the initial AS diagnosis and intervention and to demonstrate a clear deterioration of LV GLS without a decline in LVEF.

Prognostic value of LV GLS in patients with asymptomatic severe AS

Multiple echocardiographic predictors of mortality and other adverse cardiac events have been identified in asymptomatic severe AS with preserved LVEF (i.e., peak aortic jet velocity >5.0 m/s [4, 19, 30, 31], aortic valve calcification [27, 32], small AVA [33], inappropriate LV hypertrophy [34], and increased valvuloarterial impedance [35]. Data demonstrating the prognostic effect of LV GLS in severe AS and its incremental value over these determinants are accumulating. In a cohort of 395 patients with AS, including 302 patients with severe AS, Kusunose et al. [10] demonstrated that LV GLS was an independent predictor of all-cause mortality and had incremental prognostic value on top of known echocardiographic predictors and symptom status. However, only 21% of these patients with severe AS were asymptomatic, and mortality rates were high (25%). Lancellotti et al. [25] showed in 163 exclusively asymptomatic patients with severe AS that LV GLS was independently associated with the occurrence of cardiac events (i.e., symptom development, eventual AVR, and death). Other studies have investigated the prognostic effect of LV GLS in asymptomatic AS, but these often had small patient samples, included moderate AS, or did not report symptom development as an end point [6, 26–29]. In contrast, this study included a larger study population of 220 patients with asymptomatic severe AS with low mortality rates at follow-up (28 patients [13%]) and a more preserved LV GLS at baseline, thus representing a lower-risk study population in an earlier disease stage of severe AS. In addition, this study demonstrated that the natural course of LV GLS is characterized by further deterioration over time. These results provide further insights into the currently available literature by confirming that LV GLS is a sensitive marker for subclinical myocardial dysfunction and might aid in identifying patients who are at risk for symptom development and the need for intervention. Therefore, the present evaluation corroborates that LV GLS holds promise in the pre-operative assessment of patients with asymptomatic severe AS without overt signs of LV dysfunction, although further prospective research is needed to determine the exact role of LV GLS in predicting AS progression and severity.

Clinical implications

In patients with symptomatic severe AS, it has been demonstrated that myocardial fibrosis can be present and persist after AVR [21]. Diffuse myocardial fibrosis that was noninvasively assessed by native T1 mapping on cardiac magnetic resonance imaging was present in asymptomatic patients with severe AS and was associated with LV GLS that was measured by speckle tracking echocardiography [36]. This study shows that LV

GLS is often impaired in asymptomatic severe AS and will further deteriorate if left untreated, while LVEF remains unchanged. This suggests that patients with impaired LV GLS at baseline have subclinical myocardial dysfunction that is probably secondary to diffuse fibrosis, which is not detected by the conventional echocardiographic parameters of LV systolic function. Therefore, the evaluation of LV GLS and consideration of objective signs of AS-related cardiac damage in patients with asymptomatic severe AS with preserved LVEF (as recently suggested in a new AS staging classification [37]) may help to define the optimal timing for AVR (before symptom development and irreversible myocardial damage occur).

LIMITATIONS

This study was limited by its retrospective design, which could have introduced a selection bias. Left ventricular GLS was measured using different platforms, which can lead to slight variations in the quantification of LV systolic dysfunction when considering the current variability in LV GLS measurements across vendors. Although intervendor differences in LV GLS measurements have been reported to be statistically significant, this bias was only moderate and the interobserver and intraobserver reproducibility of LV GLS were comparable with or superior to conventional echocardiographic parameters, such as LVEF [38, 39]. Furthermore, the precision of LV GLS has been shown to be high even in observers with low experience levels [39]. The differences in mean LV GLS values or in the prevalence of LV systolic dysfunction based on an LV GLS value >-19.6% were not observed across the participating centers. Finally, as the participating centers are tertiary referral hospitals for AVR, referral bias could be present, with subsequent increased rates of AVR. The decision of referral for AVR was left to the discretion of the treating cardiologist.

CONCLUSIONS

IN asymptomatic severe AS, most patients have impaired LV GLS at the initial diagnosis despite preserved LVEF. Furthermore, during follow-up and before intervention, a further deterioration of LV GLS occurred without a change in LVEF, whereas AS severity progressed and LV hypertrophy increased. Impaired LV GLS at baseline was associated with a higher risk of symptom development and need for aortic valve intervention. Therefore, assessing LV GLS holds promise in the risk assessment of asymptomatic severe AS, although further prospective studies in larger patient populations are warranted to establish the exact role of LV GLS, integrated with other markers of AS severity and progression, in identifying patients who might benefit from earlier aortic valve intervention.

REFERENCES

[1] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[2] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

[3] Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005;111(24):3290-5.

[4] Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. Circulation. 2010;121(1):151-6.

[5] Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al. Initial Surgical Versus Conservative Strategies in Patients with Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2015;66(25):2827-38.

[6] Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, et al. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients with Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2016;67(19):2263-88.

[7] Redfors B, Pibarot P, Gillam LD, Burkhoff D, Bax JJ, Lindman BR, et al. Stress testing in asymptomatic aortic stenosis. Circulation. 2017;135(20):1956-76.

[8] Ng ACT, Delgado V, Bertini M, Antoni ML, Van Bommel RJ, Van Rijnsoever EPM, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J. 2011;32(12):1542-50.

[9] Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2012;13(10):827-33.

[10] Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circ Cardiovasc Imaging. 2014;7(6):938-45.

[11] Klaeboe LG, Haland TF, Leren IS, ter Bekke RMA, Brekke PH, Røsjø H, et al. Prognostic Value of Left Ventricular Deformation Parameters in Patients with Severe Aortic Stenosis: A Pilot Study of the Usefulness of Strain Echocardiography. J Am Soc Echocardiogr. 2017;30(8):727-35.e1.

[12] Stokke TM, Hasselberg NE, Smedsrud MK, Sarvari SI, Haugaa KH, Smiseth OA, et al. Geometry as a Confounder When Assessing Ventricular Systolic Function: Comparison Between Ejection Fraction and Strain. J Am Coll Cardiol. 2017;70(8):942-54.

[13] Ng ACT, Prihadi EA, Antoni ML, Bertini M, Ewe SH, Ajmone Marsan N, et al. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. Eur Heart J Cardiovasc Imaging. 2018;19(8):859-67.

[14] Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global Strain in Severe Aortic Valve Stenosis: Relation to Clinical Outcome After Aortic Valve Replacement Jordi. Circ Cardiovasc Imaging. 2012 sep;5(5):613-20.

[15] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[16] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451-96.

[17] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[18] Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, Lereun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.

[19] Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic Severe Aortic Stenosis in the Elderly. J Am Coll Cardiol Img. 2017;10(1):43-50.

[20] Carabello BA. Aortic regurgitation: a lesion with similarities to both aortic stenosis and mitral regurgitation. Circulation. 1990;82(3):1051-3.

[21] Weidemann F, Herrmann S, Störk S, Niemann M, Frantz S, Lange V, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation. 2009;120(7):577-84.

[22] Treibel TA, López B, González A, Menacho K, Schofield RS, Ravassa S, et al. Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients. Eur Heart J. 2018;39(8):699-709.

[23] Delgado V, Tops LF, Van Bommel RJ, Van Der Kley F, Marsan NA, Klautz RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J. 2009;30(24):3037-47.

[24] Lafitte S, Perlant M, Reant P, Serri K, Douard H, Demaria A, et al. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. Eur J Echocardiogr. 2009;10(3):414-9.

[25] Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart. 2010;96(17):1364-71.

[26] Zito C, Salvia J, Cusm-Piccione M, Antonini-Canterin F, Lentini S, Oreto G, et al. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. Am J Cardiol. 2011;108(10):1463-9.

[27] Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging. 2012;5(6):719-25.

[28] Nagata Y, Takeuchi M, Wu VCC, Izumo M, Suzuki K, Sato K, et al. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. J Am Coll Cardiol Img. 2015;8(3):232-45.

[29] Carstensen HG, Larsen LH, Hassager C, Kofoed KF, Jensen JS, Mogelvang R. Basal longitudinal strain predicts future aortic valve replacement in asymptomatic patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2016;17(3):283-92.

[30] Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation. 2010;121(13):1502-9.

[31] Bohbot Y, Rusinaru D, Delpierre Q, Marechaux S, Tribouilloy C. Risk Stratification of Severe Aortic Stenosis With Preserved Left Ventricular Ejection Fraction Using Peak Aortic Jet Velocity: An Outcome Study. Circ Cardiovasc Imaging. 2017;10(10):e006760.

[32] Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of Outcome in Severe, Asymptomatic Aortic Stenosis. N Engl J Med. 2000;343(9):611-7.

[33] Maréchaux S, Ringle A, Rusinaru D, Debry N, Bohbot Y, Tribouilloy C. Prognostic Value of Aortic Valve Area by Doppler Echocardiography in Patients With Severe Asymptomatic Aortic Stenosis. J Am Heart Assoc. 2016;5(5):e003146.

[34] Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart. 2011;97(4):301-7.

[35] Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the Valvuloarterial Impedance to Predict Adverse Outcome in Asymptomatic Aortic Stenosis. J Am Coll Cardiol. 2009;54(11):1003-11.

[36] Lee SP, Lee W, Lee JM, Park EA, Kim HK, Kim YJ, et al. Assessment of Diffuse Myocardial Fibrosis by Using MR Imaging in Asymptomatic Patients with Aortic Stenosis. Radiology. 2015;274(2):359-69.

[37] Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J. 2017;38(45):3351-8.

[38] Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr. 2015;28(10):1171-81.

[39] Negishi T, Negishi K, Thavendiranathan P, Cho GY, Popescu BA, Vinereanu D, et al. Effect of Experience and Training on the Concordance and Precision of Strain Measurements. J Am Coll Cardiol Img. 2017;10(5):518-22.

SUPPLEMENTARY MATERIAL

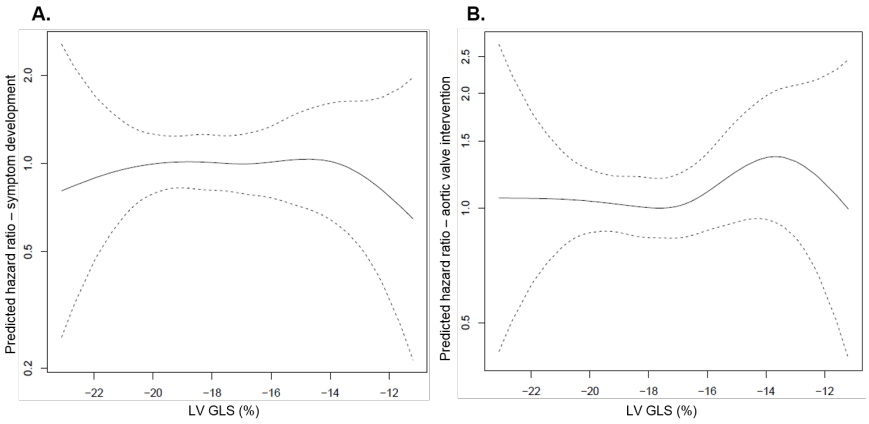


Figure 4: Predicted outcomes of asymptomatic severe aortic stenosis across a range of left ventricular (LV) global longitudinal strain (GLS). Fitted Cox spline models, including overlaying confidence intervals, for symptom development (*panel A*) and aortic valve intervention (*panel B*) vs. LV GLS after adjustment for age, sex, coronary artery disease, atrial fibrillation and LV mass index.

Table 3: Changes in valve hemodynamics and left ventricular (LV) systolic function in 150 patients with asymptomatic severe aortic stenosis from baseline to follow-up (second transthoracic echocardiogram at last follow-up or prior to aortic valve replacement).

Variables	**Baseline (N = 150)**	**Follow-up (N = 150)**	***P* value**
Aortic valve mean gradient (mmHg)	38.9±12.5	47.8±15.8	**<0.001**
Aortic valve peak velocity (m/s)	3.9±0.6	4.4±0.6	**<0.001**
Aortic valve area (cm^2)	0.87±0.1	0.78±0.1	**<0.001**
Aortic valve area index (cm^2/m^2)	0.47±0.1	0.42±0.1	**<0.001**
Stroke volume (ml)	81.4±17.1	81.3±17.0	0.16
Stroke volume index (ml/m^2)	44.1±9.5	43.6±8.4	0.37
LV mass index (g/m^2)	113.9±28.7	125.4±29.6	**<0.001**
LV ejection fraction (%)	61.2±5.7	60.6±7.6	0.15
LV global longitudinal strain (%)	-18.0±2.6	-16.3±2.8	**<0.001**

LV, left ventricular.

Table 4: Baseline clinical and echocardiographic characteristics of asymptomatic severe aortic stenosis patients divided according to the median value of LV GLS at baseline ≤ −18.2% (more preserved) vs. >-18.2% (more impaired).

Variables	Total population of AS patients (N = 220)	Preserved LV GLS (≤-18.2%) (N = 118)	Impaired LV GLS (>-18.2%) (N = 102)	*P* value
Clinical characteristics				
Age (years)	67.9±13.0	66.8±14.4	69.2±11.2	0.16
Male gender, *N* (%)	126 (57)	61 (52)	65 (64)	0.07
Body surface area (m^2)	1.87±0.2	1.85±0.2	1.89±0.2	0.14
Hypertension, *N* (%)	128 (59)	64 (55)	64 (63)	0.20
Hypercholesterolemia, *N* (%)	103 (47)	49 (42)	54 (54)	0.09
Diabetes, *N* (%)	34 (16)	19 (16)	15 (15)	0.78
History of smoking, *N* (%)	73 (38)	40 (36)	33 (41)	0.49
Coronary artery disease, *N* (%)	47 (22)	17 (15)	30 (30)	**0.007**
Prior myocardial infarction, *N* (%)	15 (7)	5 (4)	10 (10)	0.10
History of atrial fibrillation, *N* (%)	40 (18)	14 (12)	26 (26)	**0.009**
Medication use, *N* (%)				
Beta-blocker	78 (36)	35 (30)	43 (43)	0.05
ACE-inhibitor/ARB	88 (40)	43 (37)	45 (45)	0.24
Calcium antagonist	48 (22)	26 (22)	22 (22)	0.94
Diuretic agents	52 (24)	29 (25)	23 (23)	0.70
Statins	112 (51)	54 (46)	58 (57)	0.10
Aspirin and/or clopidogrel	93 (43)	46 (39)	47 (47)	0.28
Vitamin K antagonist or NOAC	31 (14)	17 (15)	14 (14)	0.89
Creatinin level (µmol/l)	80 [70-97]	76 [69-93]	85 [73-104]	**0.006**
Estimated GFR (ml/min/1.73 m^2)	76 [61-89]	79 [68-91]	72 [55-88]	**0.04**

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AS, aortic stenosis; GFR, glomerular filtration rate estimated using CKD-EPI formula; GLS, global longitudinal strain; LV, left ventricular; NOAC, novel oral anti-coagulants.

Table 4: Baseline clinical and echocardiographic characteristics of asymptomatic severe aortic stenosis patients divided according to the median value of LV GLS at baseline ≤ −18.2% (more preserved) vs. >-18.2% (more impaired) (*continued*).

Variables	Total population of AS patients (N = 220)	Preserved LV GLS (≤-18.2%) (N = 118)	Impaired LV GLS (>-18.2%) (N = 102)	*P* value
Baseline echocardiography				
Valve anatomy, *N* (%)				0.18
Tricuspid	170 (77)	87 (74)	83 (81)	
Bicuspid	50 (23)	31 (26)	19 (19)	
Aortic valve mean gradient (mmHg)	39.4±12.6	38.2±12.3	40.8±12.9	0.13
Aortic valve peak velocity (m/s)	4.0±0.6	3.9±0.6	4.0±0.6	0.39
Aortic valve area (cm^2)	0.86±0.1	0.87±0.1	0.85±0.1	0.21
Aortic valve area index (cm^2/m^2)	0.46±0.1	0.47±0.1	0.45±0.1	**0.008**
Stroke volume (ml)	81.4±17.1	80.9±16.0	82.0±18.4	0.64
Stroke volume index (ml/m^2)	43.8±9.1	44.4±9.6	43.1±8.6	0.31
LV end-diastolic diameter (mm)	45.4±5.8	44.6±5.5	46.5±6.0	0.02
LV end-systolic diameter (mm)	28.2±5.0	27.1±4.4	29.5±5.5	**0.001**
Intraventricular septal thickness (mm)	12.9±2.3	12.7±2.1	13.1±2.5	0.23
Posterior wall thickness (mm)	11.6±1.9	11.4±1.8	11.8±1.9	0.10
LV mass index (g/m^2)	112.0±27.7	107.1±25.9	117.7±28.7	**0.006**
LV ejection fraction (%)	61.5±5.9	62.5±5.5	60.4±6.3	**0.008**
LV global longitudinal strain (%)	-17.9±2.5	-19.8±1.1	-15.8±1.8	**<0.001**

AS, aortic stenosis; GLS, global longitudinal strain; LV, left ventricular.

5

PROGNOSTIC IMPLICATIONS OF RENAL DYSFUNCTION IN PATIENTS WITH AORTIC STENOSIS

E. Mara Vollema, Edgard A. Prihadi, Arnold C.T. Ng,
Tea Gegeneva, Nina Ajmone Marsan, Jeroen J. Bax, Victoria Delgado

Published in Am J Cardiol. 2020;125(7):1108-1114.

ABSTRACT

AORTIC stenosis (AS) and renal dysfunction share risk factors and often occur simultaneously. The influence of renal dysfunction on the prognosis of patients with various grades of AS has not been extensively described.

The present study aimed to assess the prognostic implications of renal dysfunction in a large cohort of patients with aortic sclerosis and AS grades ranging from mild to severe AS. Patients diagnosed with various grades of AS by transthoracic echocardiography were assessed and divided according to renal function by estimated glomerular filtration rate (eGFR). The occurrence of all-cause mortality (primary endpoint) and aortic valve replacement (AVR) was noted.

Of 1178 patients (mean age 70±13 years, 60% male), 327 (28%) had aortic sclerosis, 86 (7%) had mild AS, 285 (24%) had moderate AS and 480 (41%) had severe AS. Renal dysfunction (eGFR <60 ml/min/1.73 m^2) was present in 440 (37%) patients, and moderate to severe AS was observed more often in these patients compared to patients without (70 vs. 62%, respectively; P=0.008). After a median follow-up of 95 [31-149] months, 626 (53%) patients underwent AVR and 549 (47%) patients died. Severely impaired renal function (eGFR <30 ml/min/1.73 m^2) and AVR were independently associated with all-cause mortality after correcting for AS severity.

In conclusion, renal dysfunction is highly prevalent in patients with various grades of AS. After correcting for AS severity and AVR, severely impaired renal function (eGFR <30 ml/min/1.73 m^2) was independently associated with all-cause mortality. Independent of renal function, AVR was associated with improved survival.

Introduction

Aortic stenosis (AS) and renal dysfunction share several risk factors (e.g., hypertension and diabetes) and often occur simultaneously and with a complex interaction [1]. In patients with end-stage kidney disease, aortic valve calcification has been observed in 28 to 55% of patients, occurs 10 to 20 years earlier and has a faster progression as compared to the general population [1, 2]. Similarly, in patients with milder grades of renal dysfunction, an association between stage of renal dysfunction and grade of aortic valve calcification has been demonstrated and has prognostic implications [3, 4]: moderate and severe AS are present more often in these patients [5, 6] and this has been associated with significantly lower survival as compared to patients with normal renal function [5] or to patients with renal dysfunction without AS [6]. Inversely, renal dysfunction is a frequent finding in severe AS patients undergoing either surgical or transcatheter aortic valve replacement (AVR) and has been associated with poor short- and mid-term outcomes after intervention [7–12]. The influence of renal dysfunction on the prognosis of patients with various grades of AS has not been extensively described. The present study aimed to assess the prognostic implications of renal dysfunction in a large cohort of patients with aortic sclerosis and patients with various grades of AS.

Methods

From an ongoing registry at the Leiden University Medical Center (Leiden, the Netherlands), 1178 patients diagnosed with various grades of AS between May 1994 and June 2017 were included in this retrospective study. Patients were selected based on available baseline echocardiographic data for assessment of AS severity (defined as the first available echocardiographic study performed) and renal function measurement. As currently recommended by international guidelines, the grade of AS severity was determined based on mean aortic valve gradient, peak aortic jet velocity and calculated aortic valve area [13]. Patients were divided according to the following AS severity categories: aortic sclerosis, mild AS, moderate AS and severe AS [13]. Clinical history, physical examination and transthoracic echocardiography were performed at the time of first AS diagnosis for each patient. Clinical data were collected by review of the patient files at the departmental cardiology information system (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands) and hospital electronic medical records (HiX; ChipSoft, Amsterdam, the Netherlands). Baseline clinical data included patient demographics, cardiovascular risk factors, use of cardiovascular medication and laboratory results such as hemoglobin and creatinine level. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated glomerular filtration rate (eGFR) [14]. Patients were divided into four groups according to the eGFR as recommended by the current guidelines: normal renal function (eGFR ≥90 ml/min/1.73 m^2), mildly impaired renal function (eGFR 60-89 ml/min/1.73 m^2), moderately impaired renal function (eGFR 30-59 ml/min/1.73 m^2) and severely impaired renal function (eGFR <30 ml/min/1.73 m^2) [15]. Exclusion criteria included subvalvular or supravalvular AS, dynamic subaortic obstruction, active endocarditis and previous AVR. For this retrospective analysis of clinically acquired data, the institutional review board waived the need for patient written informed consent.

Transthoracic echocardiography was performed using commercially available ultrasound systems (System 5, Vivid 7 or E9, General Electric Vingmed, Horten, Norway) equipped with 3.5MHz or M5S transducers with the patient in the left lateral decubitus position. Images were stored digitally on hard disk and analysed offline (EchoPac version BT13; GE Medical Systems). Measurements of the echocardiographic data were performed de novo by experienced observers. Two-dimensional, colour, continuous and pulsed-wave Doppler data from the parasternal and apical views were acquired. Left ventricular (LV) dimensions were measured on the parasternal long-axis view and the LV mass was calculated and indexed for body surface area [16]. The end-diastolic and end-systolic LV volumes were measured on the apical 2- and 4-chamber views using the Simpson's biplane method and the LV ejection fraction was calculate [16]. Continuous-wave Doppler recordings of the 3- or 5-chamber apical views were obtained for estimation of the peak aortic jet velocity [13]. Using the simplified Bernoulli equation, the peak and mean gradients of the aortic valve were calculated [13]. On the 3- or 5-chamber apical views, pulsed-wave Doppler recordings of the flow through the LV outflow tract were obtained to derive the velocity-time integral and the aortic valve area (AVA) was calculated according to the continuity equation [13]. AS severity was classified according to the current recommendations: aortic sclerosis was defined as calcification and thickening of the aortic valve with a peak aortic jet velocity ≤2.5 m/s; mild AS was defined as a peak aortic jet velocity of 2.6-2.9 m/s, a mean gradient <20 mmHg or an AVA >1.5 cm^2; moderate AS was defined as a peak aortic jet velocity of 3.0-4.0 m/s, a mean gradient of 20-40 mmHg or an AVA of 1.0-1.5 cm^2; and severe AS was defined as a peak aortic jet velocity ≥4.0 m/s, a mean gradient ≥40 mmHg or an AVA <1.0 cm^2 [13].

Occurrence of surgical or transcatheter AVR and all-cause death from the moment of the first diagnosis of AS at baseline echocardiography to the last follow-up was noted for all patients. The primary endpoint of all-cause mortality was assessed through individual patient record review, linked to the governmental death registry database.

Continuous variables are presented as mean±standard deviation when normally distributed and compared across patient groups divided according to the renal function category using the analysis of variance (ANOVA) test. When not normally distributed, continuous variables were presented as median and interquartile range (IQR) and compared across groups using the Kruskal-Wallis test. Categorical variables were presented as numbers and percentages and compared using χ^2 tests. Cumulative event-free survival from all-cause mortality was calculated using the Kaplan Meier method and log-rank tests were performed for comparison across groups. For the identification of clinical and echocardiographic parameters associated with all-cause mortality, univariable Cox proportional hazard regression analyses were performed. Significant univariable variables (P <0.05) were then introduced as covariates in a multivariable Cox proportional hazards regression model to identify demographic, clinical and echocardiographic variables independently associated with all-cause mortality. The occurrence of surgical or transcatheter AVR was entered as a time-dependent covariate and was forced into the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CI) were presented. The validity of the assumption of proportional hazards for the Cox regression analyses was confirmed for all categorical variables using log minus log plots. For continuous variables, the proportional hazard assumption was confirmed using partial

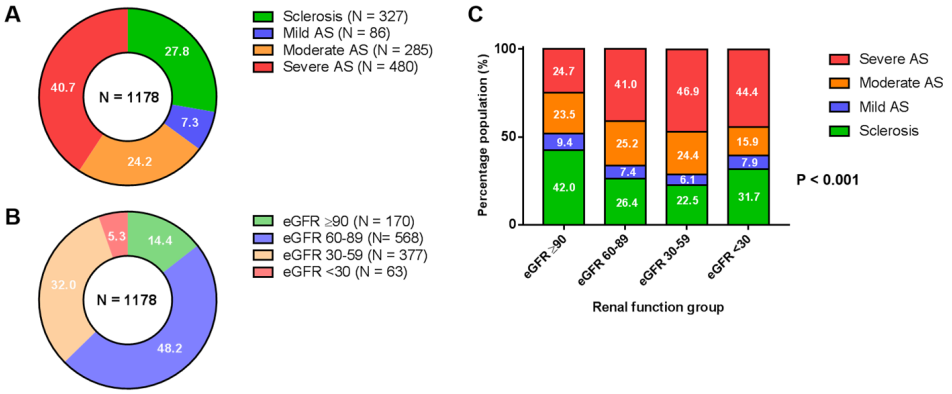


Figure 1: Distribution of grade of aortic stenosis (*panel A*) and renal function (*panel B*) in total study population and of various grades of aortic stenosis across renal function groups (*panel C*). AS, aortic stenosis; eGFR, estimated glomerular filtration rate.

residuals (i.e., Schoenfeld residuals). SPSS software (version 23.0; IBM, Armonk, NY) was used for the statistical analyses. A two-sided P value <0.05 was considered statistically significant.

Results

The total study population consisted of 1178 patients (mean age 70.1±13.0 years, 60% male) diagnosed with aortic sclerosis and various grades of AS: 327 (27.8%) patients had aortic sclerosis, 86 (7.3%) patients had mild AS, 285 (24.2%) patients had moderate AS and 480 (40.7%) patients had severe AS (Figure 1 *panel A*). The population was divided into four groups based on the renal function: normal renal function (eGFR ≥90 ml/min/1.73 m^2) was present in 170 (14.4%) patients, mildly impaired renal function (eGFR 60-89 ml/min/1.73 m^2) in 568 (48.2%) patients, moderately impaired renal function (eGFR 30-59 ml/min/1.73 m^2) in 377 (32.0%) patients and severely impaired renal function (eGFR <30 ml/min/1.73 m^2) in 63 (5.3%) patients (Figure 1 *panel B*). The distribution of the various grades of AS across the renal function groups is depicted in Figure 1 *panel C*: there was a higher prevalence of moderate to severe AS in patients with moderately to severely impaired renal function (eGFR <60 ml/min/1.73 m^2) compared to normal to mildly impaired renal function (eGFR ≥60 ml/min/1.73 m^2) patients (69.8% vs. 62.1%, respectively; P=0.008).

Baseline clinical and echocardiographic characteristics for the total study population and according to renal function groups are listed in Table 1 and Table 2. Compared to patients with normal to mildly impaired renal function, patients with moderately to severely impaired renal function were older, more often had New York Heart Association class ≥III symptoms, more often had cardiovascular risk factors and comorbidities such as diabetes, coronary artery disease, previous myocardial infarction and atrial fibrillation and therefore more often used cardiovascular medication (Table 1). On echo-

Table 1: Baseline clinical characteristics of the total study population and according to renal function group.

Variables	Total population (N = 1178)	eGFR ≥90 ml/min/1.73 m^2 (N = 170)	eGFR 60-89 ml/min/1.73 m^2 (N = 568)	eGFR 30-59 ml/min/1.73 m^2 (N = 377)	eGFR <30 ml/min/1.73 m^2 (N = 63)	*P* value
Male gender	706 (60%)	114 (67%)	334 (59%)	219 (58%)	39 (62%)	0.209
Age (years)	70.1±13.0	55.2±15.3	70.7±10.7	75.7±9.1	70.8±13.9	**<0.001**
Body surface area (m^2)	1.88±0.20	1.90±0.21	1.88±0.20	1.86±0.20	1.87±0.18	0.214
Systolic blood pressure (mmHg)	143±29	140±22	144±26	144±28	143±29	0.323
Diastolic blood pressure (mmHg)	78±14	79±13	78±13	77±14	78±15	0.492
Heart rate (beats per minute)	74±15	73±14	74±15	73±15	76±16	0.613
NYHA class III-IV symptoms	295 (26%)	18 (11%)	138 (25%)	124 (34%)	15 (24%)	**<0.001**
Hypertension	629 (55%)	63 (38%)	293 (53%)	238 (65%)	35 (56%)	**<0.001**
Hypercholesterolemia	376 (34%)	40 (24%)	195 (37%)	126 (36%)	15 (25%)	**0.011**
Diabetes mellitus	232 (20%)	29 (17%)	97 (18%)	92 (25%)	14 (22%)	**0.040**
Previous myocardial infarction	199 (17%)	17 (10%)	93 (17%)	73 (19%)	16 (25%)	**0.015**
Atrial fibrillation	205 (18%)	17 (10%)	97 (18%)	73 (20%)	18 (29%)	**0.005**
COPD	155 (13%)	14 (8%)	77 (14%)	59 (16%)	5 (8%)	0.061
Creatinin level (μmol/L)	89 [74-109]	67 [57-76]	81 [72-93]	115 [100-132]	255 [181-528]	**<0.001**
eGFR CKD-EPI (ml/min/1.73 m^2)	66.6±22.6	100.0±10.7	74.4±8.5	47.6±8.3	18.8±12.3	**<0.001**
Hemoglobin (mmol/L)	8.2±1.2	8.3±1.3	8.4±1.1	8.2±1.1	7.0±1.1	**<0.001**
Urea (mmol/L)	6.9 [5.4-9.0]	5.1 [4.2-6.1]	6.5 [5.4-7.9]	9.1 [7.2-11.5]	19.2 [13.4-25.8]	**<0.001**
Medication use						
Beta blocker	499 (44%)	55 (33%)	234 (43%)	179 (48%)	31 (51%)	**0.006**
ACE inhibitor/ARB	507 (44%)	52 (31%)	236 (43%)	188 (51%)	31 (51%)	**<0.001**
Diuretics	417 (36%)	33 (20%)	171 (31%)	183 (49%)	30 (49%)	**<0.001**
Calcium antagonists	257 (22%)	29 (17%)	111 (20%)	99 (27%)	18 (30%)	**0.023**
Statin	508 (44%)	54 (32%)	250 (46%)	172 (46%)	32 (53%)	**0.006**
Anticoagulation/antiplatelet	598 (52%)	54 (32%)	289 (53%)	220 (59%)	35 (57%)	**<0.001**

Continuous variables are presented as mean±SD or median [25th -75th percentile]. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

Table 2: Echocardiographic parameters of the total study population and according to renal function group.

Variables	Total population (N = 1178)	eGFR ≥90 ml/min/1.73 m^2 (N = 170)	eGFR 60-89 ml/min/1.73 m^2 (N = 568)	eGFR 30-59 ml/min/1.73 m^2 (N = 377)	eGFR <30 ml/min/1.73 m^2 (N = 63)	*P* value
Aortic valve morphology						**<0.001**
Tricuspid	1079 (92%)	132 (78%)	524 (92%)	363 (96%)	60 (95%)	
Bicuspid	99 (8%)	38 (22%)	44 (8%)	14 (4%)	3 (5%)	
Significant aortic regurgitation	10 (1%)	0 (0%)	5 (1%)	4 (1%)	1 (2%)	0.558
Significant mitral regurgitation	42 (4%)	2 (1%)	20 (4%)	19 (5%)	1 (2%)	0.115
LV end-diastolic diameter (mm)	48.5±7.6	48.5±6.4	48.3±7.5	48.7±8.5	49.2±6.4	0.807
Septal wall thickness (mm)	12.2±2.3	11.7±2.3	12.1±2.2	12.5±2.3	12.4±2.2	**0.002**
Posterior wall thickness (mm)	11.8±2.0	11.4±2.0	11.8±2.0	12.0±2.1	12.3±2.5	**0.013**
LV mass index (g/m^2)	121.4±36.6	113.5±35.4	119.7±34.8	126.0±38.2	130.0±39.9	**<0.001**
LV ejection fraction (%)	55.7±12.0	59.4±8.3	55.9±11.9	54.5±13.1	53.1±13.1	**<0.001**
Stroke volume index (ml/m^2)	41.9±12.8	44.8±11.7	42.2±12.9	40.3±12.7	40.8±13.3	**0.002**
Peak aortic jet velocity (m/s)	3.1±1.1	2.8±1.2	3.2±1.1	3.2±1.1	3.0±1.2	**0.001**
Mean aortic valve gradient (mmHg)	27.4±19.3	23.2±19.8	27.7±18.6	29.2±19.6	25.6±20.2	**0.007**
Aortic valve area (cm^2)	1.29±0.65	1.58±0.74	1.27±0.63	1.18±0.58	1.31±0.78	**<0.001**

Continuous variables are presented as mean±SD or median [25th -75th percentile]. eGFR, estimated glomerular filtration rate; LV, left ventricular.

cardiography, patients with moderately to severely impaired renal function had a larger LV mass index, lower LV ejection fraction and higher mean aortic valve gradient than patients with less than moderately impaired renal function (Table 2).

After a median follow-up of 95 [IQR: 31-149] months, 626 (53%) patients underwent AVR (63% had a surgical AVR and 37% a transcatheter AVR) and 549 (47%) patients died. The distribution of all-cause mortality across the renal function groups is shown in Table 3.

Figure 2 *panel A* shows the Kaplan-Meier curves of cumulative event-free survival for the various renal function groups. At 10 years, the cumulative survival rates were significantly lower for patients with moderately and severely impaired renal function compared to patients with mildly impaired and normal renal function (43% and 19% vs. 61% and 76%, respectively, log-rank *P*<0.001). To determine the prognostic effect of AS severity grade, the study population was divided by the presence of moderate to severe AS and renal dysfunction (defined as eGFR <60 ml/min/1.73 m^2)(Figure 2 *panel B*). Amongst patients without renal dysfunction, patients with moderate to severe AS had lower 10-year cumulative event-free survival rates than patients with less than moderate AS (61% vs. 70%, respectively; log-rank *P*=0.015). However, amongst patients with renal dysfunction, no additional effect of AS severity on 10-year cumulative event-free survival rates was observed (39% for less than moderate AS vs. 40% for moderate to severe AS, log-rank *P*=0.636).

For the evaluation of the independent associates of all-cause mortality, a multivariable Cox proportional hazards regression model was constructed (Table 4). To take into account the effect of AVR on survival, AVR was introduced as a time-dependent covariate and forced into the multivariable model. In the univariable analysis, multiple parameters were significantly associated with all-cause mortality: renal function, age, hypertension, diabetes, previous myocardial infarction, atrial fibrillation, LV ejection fraction, LV mass index and AVA. On multivariable analysis, renal function (HR: 0.99; 95% CI 0.98-0.99; *P*<0.001) and surgical or transcatheter AVR (HR: 0.67; 95% CI 0.54-0.85; *P*=0.001) were independently associated with all-cause mortality, together with age, diabetes, previous myocardial infarction and LV ejection fraction (Table 4). When regarded as a categorical variable, only severely impaired renal function was independently associated with all-cause mortality (HR: 3.24; 95% CI 2.02-5.21; *P*<0.001).

Table 3: Outcomes of the total study population and according to renal function group.

Population	**All-cause mortality, *N* (%)**	***P* value**
Total population (N = 1178)	549 (47)	
According to renal function group		**<0.001**
eGFR ≥90 ml/min/1.73 m^2 (N = 170)	45 (27)	
eGFR 60-89 ml/min/1.73 m^2 (N = 568)	242 (43)	
eGFR 30-59 ml/min/1.73 m^2 (N = 377)	211 (56)	
eGFR <30 ml/min/1.73 m^2 (N = 63)	51 (81)	

eGFR, estimated glomerular filtration rate

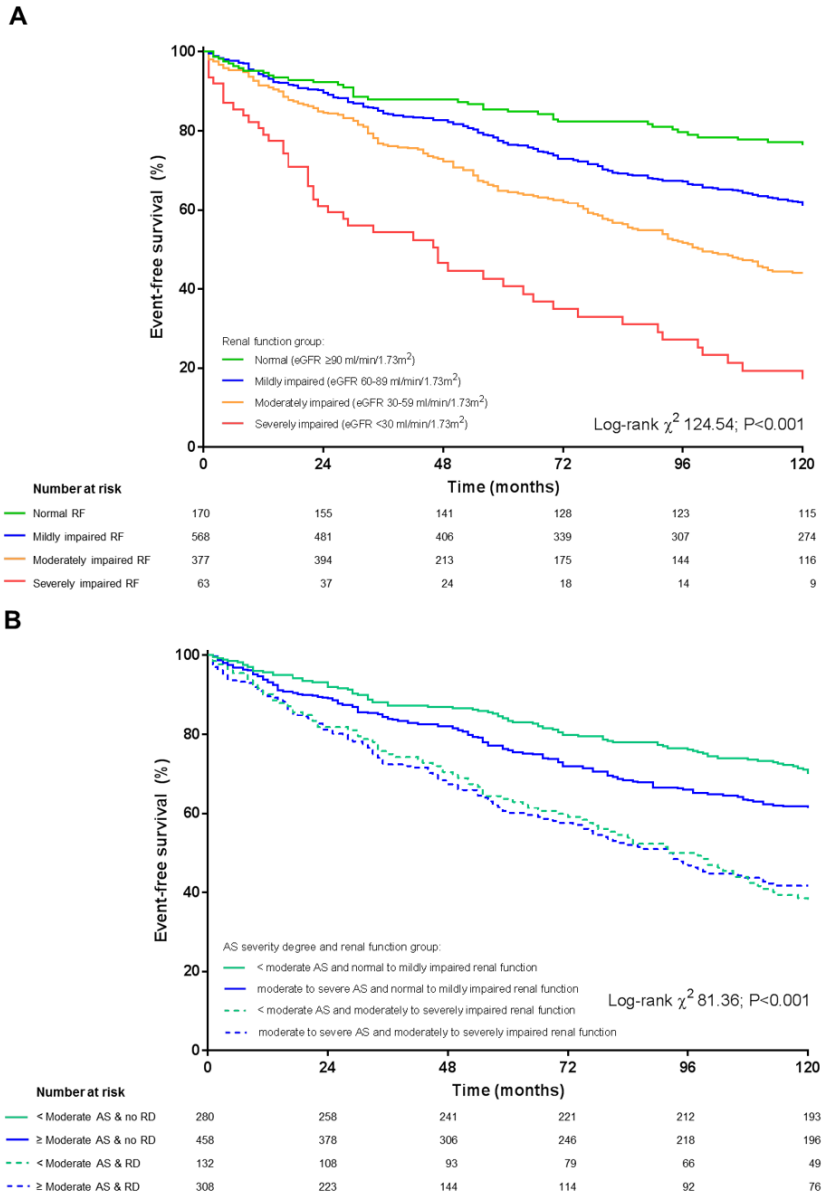


Figure 2: Kaplan-Meier estimates of cumulative event-free survival of study population stratified by (*panel A*) renal function group and (*panel B*) grade of aortic stenosis and presence of renal dysfunction (eGFR <60 ml/min/1.73 m^2). AS, aortic stenosis; eGFR, estimated glomerular filtration rate; RD, renal dysfunction; RF, renal function.

Table 4: Univariable and multivariable Cox regression analyses to identify independent associates of all-cause mortality.

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (years)	1.05 (1.04-1.06)	**<0.001**	1.05 (1.04-1.06)	**<0.001**
Male gender	1.10 (0.93-1.31)	0.261		
NYHA class III-IV symptoms	1.15 (0.95-1.41)	0.159		
Hypertension	1.21 (1.02-1.43)	**0.031**	0.98 (0.81-1.19)	0.854
Hypercholesterolemia	0.84 (0.69-1.02)	0.072		
Diabetes mellitus	1.56 (1.29-1.90)	**<0.001**	1.50 (1.21-1.86)	**<0.001**
Previous myocardial infarction	1.80 (1.47-2.19)	**<0.001**	1.45 (1.16-1.80)	**0.001**
Atrial fibrillation	1.38 (1.11-1.71)	**0.003**	0.97 (0.76-1.23)	0.796
LV ejection fraction (%)	0.98 (0.97-0.98)	**<0.001**	0.99 (0.98-0.99)	**0.003**
LV mass index (g/m^2)	1.01 (1.00-1.01)	**<0.001**	1.00 (1.00-1.00)	0.230
Peak aortic jet velocity (m/s)	0.99 (0.91-1.07)	0.723		
Mean aortic valve gradient (mmHg)	1.00 (0.99-1.00)	0.566		
Aortic valve area (cm^2)	0.79 (0.69-0.91)	**0.001**	0.85 (0.71-1.03)	0.096
Aortic valve replacement (surgical or transcatheter)	0.89 (0.74-1.06)	0.189	0.67 (0.54-0.85)	**0.001**
Estimated GFR (ml/min/1.73 m^2)	0.98 (0.98-0.98)	**<0.001**	0.99 (0.98-0.99)	**<0.001**
According to renal function group				
Estimated GFR ≥90 ml/min/1.73 m^2	Reference		Reference	
Estimated GFR 60-89 ml/min/1.73 m^2	1.97 (1.44-2.72)	**<0.001**	1.02 (0.70-1.47)	0.933
Estimated GFR 30-59 ml/min/1.73 m^2	3.23 (2.34-4.46)	**<0.001**	1.22 (0.83-1.81)	0.313
Estimated GFR <30 ml/min/1.73 m^2	6.65 (4.43-9.95)	**<0.001**	3.24 (2.02-5.21)	**<0.001**

CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association.

Discussion

The present study showed that renal dysfunction (eGFR <60 ml/min/1.73 m^2) is highly prevalent in a large cohort of patients with various grades of AS. Even after correcting for AS severity and surgical or transcatheter AVR, severely impaired renal function (eGFR <30 ml/min/1.73 m^2) was independently associated with all-cause mortality. Surgical or transcatheter AVR was associated with improved survival, independent of renal function. This suggests that patients undergoing AVR have a survival benefit, even in the presence of severely impaired renal function.

Renal dysfunction and aortic stenosis share several risk factors (e.g., hypertension, diabetes mellitus, hypercholesterolemia and smoking) and often coexist [1]. However, the bidirectional interaction between renal dysfunction and AS is complex and not completely understood. It is increasingly recognized that an active process very similar to atherosclerosis underlies aortic valve calcification (AVC), the precursory phase of AS [17, 18].

An increased prevalence and more rapid progression of AVC and AS has been observed in end-stage renal disease patients: AVC has been observed in 28 to 55% of these patients with a 10-20 year earlier onset as compared to patients without renal disease [1, 2, 19]. Studies on the prevalence of AVC and AS in patients with less severe renal disease have reported conflicting results: although Guerraty et al. [3] reported an independent and dose-dependent association of eGFR with AVC, the majority of studies did not find a significant association [20–22]. Focussing on AS, renal disease was shown to be associated with a doubling of yearly AS progression rate in moderate AS patients [23]. Vavilis et al. recently demonstrated that in 1,121,875 patients (of which 66,949 [6.0%] patients had renal dysfunction), the risk for development of AS was associated with eGFR in a dose-dependent manner [4]. Furthermore, Samad et al. evaluated 78,059 patients (including 23,727 [30%] patients with eGFR <60 ml/min/1.73 m^2), and described that patients with renal dysfunction had higher odds of having mild and moderate AS compared to patients without (odds ratio [OR] 1.30 (95% CI 1.18-1.43) and OR 1.22 (95% CI 1.07-1.40), respectively; P<0.001) [5]. In patients with renal dysfunction and at least mild AS, the presence of AS was associated with worse survival as compared to renal dysfunction patients without AS (P<0.001) and lower eGFR was associated with an increased risk for all-cause mortality (HR: 1.18 [95% CI 1.08–1.29]) [6]. Inversely, renal dysfunction is commonly reported in severe AS patients undergoing AVR, with prevalence rates of 25 to 34% in surgical AVR [7, 24] and of 38 to 70% in transcatheter AVR patients [8, 10–12, 25]. The prevalence of renal dysfunction in more varying grades of AS has not been well described. The present study corroborates and extends earlier findings by showing that renal dysfunction is prevalent in a population with aortic sclerosis and AS grades ranging from mild to severe AS.

Preoperative renal dysfunction has been demonstrated to negatively influence both short- and long-term survival of severe AS patients undergoing either surgical or transcatheter AVR [7, 9–11, 24]. Importantly, the Euro Heart Survey reported that renal dysfunction was an important reason for denying intervention when indicated [26]. The prognostic value of renal dysfunction has not been extensively evaluated in less than severe AS patients. The present study demonstrates and corroborates earlier findings that severely impaired renal function is significantly associated with all-cause mortality, in-

dependent of AS severity [6]. Furthermore, AVR was shown to have a positive effect on outcome, independent of renal function [6]. This suggests that patients with severely impaired renal function may have survival benefit undergoing AVR, although this needs to be corroborated by future studies.

The present study has limitations inherent to its retrospective design and was performed in a single centre, which is a referral centre for cardiac surgery. This may have introduced selection bias. A considerable part of the study population underwent AVR, which may have a positive impact on prognosis. Although these patients were not equally distributed over the renal function groups, AVR was introduced in the Cox regression analyses as a time-dependent covariate to correct for this potential effect. There can be residual biases due to additional confounders influencing prognosis which have not been taken into account in the analyses (e.g., serum values of calcium and phosphate, systolic pulmonary artery pressure, significant tricuspid regurgitation and right ventricular function) due to lack of systematic recording of these parameters in the database. Classification of patient into renal function groups was based on a single measurement of eGFR, this may have led to misclassification and precluded differentiation between acute and chronic renal dysfunction. Low flow-low gradient severe AS was present in 99 of 480 severe AS patients (20.6%). Data on dobutamine stress echocardiography was unavailable in these patients, and misclassification of AS severity could have occurred. In a small proportion of patients (4%), calculation of AVA was not possible due to missing data on velocity-time integral of the LV outflow tract and AS severity classification was based solely on mean gradient and peak aortic jet velocity [13]. Albuminuria, an important marker for kidney damage [15], was not taken in to account due to lack of systematic determination of these data. For similar reasons, renal replacement therapy and causes of renal dysfunction were not considered in the analyses.

CONCLUSIONS

IN this large single-center study of patients with aortic sclerosis and AS grades ranging from mild to severe AS, renal dysfunction (defined as eGFR <60 ml/min/1.73 m^2) is a prevalent finding. Severely impaired renal function (i.e., eGFR <30 ml/min/1.73 m^2) was independently associated with all-cause mortality (HR: 3.24; 95% CI 2.01-5.20; P<0.001).

REFERENCES

[1] Kahn MR, Robbins MJ, Kim MC, Fuster V. Management of cardiovascular disease in patients with kidney disease. Nat Rev Cardiol. 2013;10(5):261-73.

[2] London GM, Pannier B, Marchais SJ, Guerin AP. Calcification of the aortic valve in the dialyzed patient. J Am Soc Nephrol. 2000;11(4):778-83.

[3] Guerraty MA, Chai B, Hsu JY, Ojo AO, Gao Y, Yang W, et al. Relation of aortic valve calcium to chronic kidney disease (from the Chronic Renal Insufficiency Cohort Study). Am J Cardiol. 2015;115(9):1281-6.

[4] Vavilis G, Bäck M, Occhino G, Trevisan M, Bellocco R, Evans M, et al. Kidney Dysfunction and the Risk of Developing Aortic Stenosis. J Am Coll Cardiol. 2019;73(3):305-14.

[5] Samad Z, Sivak JA, Phelan M, Schulte PJ, Patel U, Velazquez EJ. Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. J Am Heart Assoc. 2017;6(10):1-15.

[6] Patel KK, Shah SY, Arrigain S, Jolly S, Schold JD, Navaneethan SD, et al. Characteristics and Outcomes of Patients With Aortic Stenosis and Chronic Kidney Disease. J Am Heart Assoc. 2019;8(3):e009980.

[7] Thourani VH, Keeling WB, Sarin EL, Guyton RA, Kilgo PD, Dara AB, et al. Impact of Preoperative Renal Dysfunction on Long-Term Survival for Patients Undergoing Aortic Valve Replacement. Ann Thorac Surg. 2011;91(6):1798-807.

[8] Thourani VH, Forcillo J, Beohar N, Doshi D, Parvataneni R, Ayele GM, et al. Impact of Preoperative Chronic Kidney Disease in 2,531 High-Risk and Inoperable Patients Undergoing Transcatheter Aortic Valve Replacement in the PARTNER Trial. Ann Thorac Surg. 2016;102(4):1172-80.

[9] Gargiulo G, Capodanno D, Sannino A, Perrino C, Capranzano P, Stabile E, et al. Moderate and Severe Preoperative Chronic Kidney Disease Worsen Clinical Outcomes After Transcatheter Aortic Valve Implantation: Meta-Analysis of 4992 Patients. Circulation: Cardiovascular Interventions. 2015;8(2):e002220.

[10] Gupta T, Goel K, Kolte D, Khera S, Villablanca PA, Aronow WS, et al. Association of Chronic Kidney Disease With In-Hospital Outcomes of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv. 2017;10(20):2050-60.

[11] Lüders F, Kaier K, Kaleschke G, Gebauer K, Meyborg M, Malyar NM, et al. Association of CKD with outcomes among patients undergoing transcatheter aortic valve implantation. Clin J Am Soc Nephrol. 2017;12(5):718-26.

[12] Mohananey D, Griffin BP, Svensson LG, Popovic ZB, Tuzcu EM, Rodriguez LL, et al. Comparative Outcomes of Patients With Advanced Renal Dysfunction Undergoing Transcatheter Aortic Valve Replacement in the United States From 2011 to 2014. Circ Cardiovasc Interv. 2017;10(10):e005477.

[13] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[14] Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

[15] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):136-50.

[16] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[17] Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. J Am Coll Cardiol. 2015;66(5):561-77.

[18] Linefsky JP, OBrien KD, Katz R, De Boer IH, Barasch E, Jenny NS, et al. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. J Am Coll Cardiol. 2011;58(3):291-7.

[19] Kim D, Shim CY, Hong GR, Cho IJ, Chang HJ, Ha JW, et al. Effect of End-Stage Renal Disease on Rate of Progression of Aortic Stenosis. Am J Cardiol. 2016;117(12):1972-7.

[20] Ix JH, Shlipak MG, Katz R, Budoff MJ, Shavelle DM, Probstfield JL, et al. Kidney function and aortic valve and mitral annular calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 2007;50(3):412-20.

[21] Fox CS, Larson MG, Vasan RS, Guo CY, Parise H, Levy D, et al. Cross-Sectional Association of Kidney Function with Valvular and Annular Calcification: The Framingham Heart Study. J Am Soc Nephrol. 2006;17(2):521-7.

[22] Hensen LCR, el Mahdiui M, van Rosendael AR, Smit JM, Jukema JW, Bax JJ, et al. Prevalence and Prognostic Implications of Mitral and Aortic Valve Calcium in Patients With Chronic Kidney Disease. Am J Cardiol. 2018;122(10):1732-7.

[23] Ersboll M, Schulte PJ, Al Enezi F, Shaw L, Køber L, Kisslo J, et al. Predictors and progression of aortic stenosis in patients with preserved left ventricular ejection fraction. Am J Cardiol. 2015;115(1):86-92.

[24] Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Late survival after aortic valve replacement in patients with moderately reduced kidney function. J Am Heart Assoc. 2016;5(12):1-11.

[25] Allende R, Webb JG, Munoz-Garcia AJ, De Jaegere P, Tamburino C, Dager AE, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. Eur Heart J. 2014;35(38):2685-96.

[26] Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. Eur Heart J. 2003;24(13):1231-43.

6

AORTIC VALVE CALCIUM LOAD: DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS IN AORTIC STENOSIS

E. Mara Vollema, Victoria Delgado, Jeroen J. Bax

Published in Circ Cardiovasc Imaging. 2018; 11(3): e007643.

In aortic stenosis (AS), patient management is highly dependent on the accurate evaluation of AS severity. A mean transvalvular pressure gradient ≥40 mmHg, peak aortic jet velocity ≥4 m/s, and an aortic valve area <1.0 cm^2 measured with echocardiography reflect severe AS [1–3]. In the majority of patients with severe AS, these criteria are always present. However, up to 30% of patients with severe AS may show an aortic valve area <1.0 cm^2 despite a low mean transvalvular pressure gradient (<40 mmHg) [4]. This low-gradient severe AS is often the consequence of a low-flow state that may be a result of impaired left ventricular (LV) systolic function (ejection fraction <50%, so-called classical low-flow low-gradient severe AS) or in the setting of severe LV hypertrophy with normal LV ejection fraction (≥50%) and a small LV cavity (paradoxical low-flow low-gradient severe AS) [4]. In patients with classical low-flow low-gradient severe AS, the question is whether the aortic valve does not open because of degenerative (calcific) changes (true severe AS) or because the dysfunctional LV is unable to generate enough stroke volume to open the valve (pseudosevere AS). By increasing LV contractility with low-dose dobutamine infusion, Doppler echocardiography can demonstrate a >20% increase in stroke volume (so-called flow reserve). If the mean pressure gradient increases >40 mmHg and the aortic valve area remains narrow, the diagnosis of true severe AS can be established [5]. However, if the aortic valve area increases to >1.0 cm^2, the underlying problem is likely the LV dysfunction, and the diagnosis is pseudosevere AS. Nevertheless, normalization of the flow cannot be achieved in a considerable number of patients [6]. In patients with paradoxical low-flow low-gradient severe AS, the use of low dose dobutamine stress echocardiography is suboptimal. Assessment of the morphology and calcification burden of the aortic valve can help to identify the patients with true severe AS who may benefit from intervention. Computed tomography is a high spatial resolution imaging technique that clearly displays the morphology of the valve and permits estimation of the aortic valve calcium score (computed tomography aortic valve calcium scoring [CT-AVC]), which has shown good correlation with hemodynamic AS severity and clinical outcomes [7–9]. It is important to note the sex differences in aortic valve calcification burden shown in previous CT-AVC studies [10, 11]. Women have lower aortic valve calcium load than men despite similar hemodynamic AS severity, and therefore, sex-specific thresholds have been proposed (1275 arbitrary units in women and 2065 arbitrary units in men) [9].

In this issue of Circulation: Cardiovascular Imaging, Pawade et al. [12], using data from an international multicenter registry of 918 patients with at least mild AS, aimed to validate those cutoff values and demonstrate the additive clinical value of CT-AVC, in identifying patients with true severe AS among those with low-gradient AS and also to assess the association with clinical outcomes. Patients were divided into (1) concordant nonsevere or severe AS group (N = 708), (2) discordant low-flow AS group (N = 79), and (3) discordant normal-flow AS group (N = 131). In the concordant AS group, 437 (62%) patients had severe AS. Based on these patients, the sex-specific CT-AVC thresholds that provided optimal discrimination of severe AS were 1377 arbitrary units in women and 2062 arbitrary units in men. Among patients with discordant flow AS, 49% presented with a CT-AVC score equal or higher than these thresholds and could have been diagnosed with true severe AS. Specifically, 56% of patients with paradoxical low-flow low-gradient severe AS and 50% of patients with classical low-flow low-gradient severe AS

had CT-AVC values above the proposed thresholds. Interestingly, among patients with high-flow and an aortic valve area >1.0 cm^2, 74% had CT-AVC values exceeding the proposed thresholds.

These findings question the accuracy of CT-AVC to identify the patients with true severe AS based on hemodynamic criteria. The management of patients with AS is not solely based on an isolated number (CT-AVC, aortic valve area, or peak aortic jet velocity) but on an integrated approach that includes symptoms, hemodynamic consequences on the LV, and various morphological and hemodynamic aortic valve variables, all well-known predictors of outcome [2].

The present study also provides prognostic information. The association between these sex-specific CT-AVC thresholds and clinical outcomes was evaluated in only 215 (23%) patients of the concordant nonsevere or severe AS group. During a median follow-up of ≈3 years, 79 patients underwent aortic valve replacement (AVR; N = 59) or died (N = 20). CT-AVC was independently associated with outcomes (hazard ratio [HR]: 1.04; P<0.001).

In the groups of discordant low or normal flow, 17 of 41 patients with follow-up underwent AVR or died. CT-AVC was independently associated with outcomes in these groups (HR: 3.31; P=0.03). Although the number of patients with follow-up was relatively limited, these findings contribute to the existing evidence showing the association between aortic valve calcification load and adverse events. In patients with concordant severe AS and symptoms or impaired LV ejection fraction, assessment of CT-AVC will not be of help because current guidelines recommend AVR (class I)[2, 3]. However, in patients with concordant severe AS who are asymptomatic and have an LV ejection fraction >50% and in patients with paradoxical low-flow low-gradient severe AS, the assessment of CT-AVC may help in the decision making because current recommendations for AVR in these groups of patients are not strong (class IIa) [2, 3]. Whether such an approach will impact on the outcomes of these patients will require randomized clinical trials. The ongoing EARLY-TAVR trial (Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients With AsYmptomatic Severe Aortic Stenosis, URL: https://clinicaltrials.gov. Unique identifier: NCT03042104), for example, randomizing asymptomatic patients with severe AS to transcatheter AVR versus medical therapy may help to better understand the impact of CT-AVC quantification on outcome.

REFERENCES

[1] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[2] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[3] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

[4] Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. Eur Heart J. 2016;37(34):2645-57.

[5] Monin JL, Quéré JP, Monchi M, Petit H, Baleynaud S, Chauvel C, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation. 2003;108(3):319-24.

[6] Annabi MS, Touboul E, Dahou A, Burwash IG, Bergler-Klein J, Enriquez-Sarano M, et al. Dobutamine Stress Echocardiography for Management of Low-Flow, Low-Gradient Aortic Stenosis. J Am Coll Cardiol. 2018;71(5):475-85.

[7] Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart. 2011;97(9):721-6.

[8] Messika-Zeitoun D, Aubry MC, Detaint D, Bielak LF, Peyser PA, Sheedy PF, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation. 2004;110(3):356-62.

[9] Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013;62(24):2329-38.

[10] Aggarwal SR, Clavel MA, Messika-Zeitoun D, Cueff C, Malouf J, Araoz PA, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging. 2013;6(1):40-7.

[11] Simard L, Côté N, Dagenais F, Mathieu P, Couture C, Trahan S, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? Circ Res. 2017;120(4):681-91.

[12] Pawade T, Clavel MA, Tribouilloy C, Dreyfus J, Mathieu T, Tastet L, et al. Computed Tomography Aortic Valve Calcium Scoring in Patients with Aortic Stenosis. Circ Cardiovasc Imaging. 2018;11(3):1-11.

Part II

EVALUATION OF THERAPY

7

ECHOCARDIOGRAPHY IN TRANSCATHETER AORTIC VALVE REPLACEMENT

E. Mara Vollema, Victoria Delgado, Jeroen J. Bax

Published in Heart Lung Circ. 2019; 28: 1354-1399

ABSTRACT

TRANSCATHETER aortic valve replacement (TAVR) is a safe and efficient alternative for surgical valve aortic replacement in patients with symptomatic severe aortic stenosis who are inoperable or have a high risk for surgery. Randomized clinical trials have shown that TAVR is not inferior to surgical aortic valve replacement in intermediate-risk patients and ongoing trials will demonstrate the effects of TAVR in asymptomatic severe aortic stenosis patients and in patients with heart failure and pseudosevere aortic stenosis. Continuous developments in procedural and post-procedural management along with increased operator experience and technical improvements and ongoing advances in imaging modalities (particularly in 3-dimensional techniques), have reduced the procedural risks and the incidence of complications such as paravalvular aortic regurgitation. Importantly, proper selection of both patient and prosthesis, procedural guidance and follow-up of prosthesis performance remain paramount for the success of the TAVR. In all these steps, echocardiography plays a crucial role. An overview of the clinical applications and current role of echocardiographic techniques in patient selection, prosthesis sizing, periprocedural guidance and post-procedural follow-up will be provided in this review article.

Introduction

Transcatheter aortic valve replacement (TAVR) has become a feasible alternative to surgical aortic valve replacement (SAVR) in the treatment of inoperable or high-risk symptomatic severe aortic stenosis (AS) patients. At mid-term follow-up, TAVR portends similar outcomes to SAVR and good valve durability has been demonstrated [1–3]. For this specific group of patients, TAVR has received a class I recommendation in recently updated guidelines [4, 5]. In addition, TAVR has extended to intermediate-risk patients, in whom studies demonstrate promising outcomes [6–8]. Currently, ongoing large trials are assessing the safety and efficacy of TAVR in low-risk and in asymptomatic severe AS patients [9]. Continuous technical developments in TAVR systems, increased operator experience and developments in procedural (e.g., use of minimalist strategy) and post-procedural (e.g., early discharge) management, careful risk evaluation and proper patient selection remain paramount for successful TAVR.

Echocardiography is the imaging technique of first choice to evaluate patients with severe AS who may be treated with TAVR, particularly for the assessment of aortic valve morphology and AS severity. When the diagnostic accuracy of two-dimensional (2D) transthoracic echocardiography is insufficient, three-dimensional (3D) visualization of the aortic valve or aortic valve calcium scoring using computed tomography (CT) provides incremental diagnostic value. For the proper selection of the transcatheter prosthesis size, CT is considered the preferred imaging tool. However, 3D transesophageal echocardiography is a valid alternative to CT in the presence of contra-indications (e.g., renal dysfunction). Furthermore, echocardiography (transthoracic, transesophageal and, less common, intracardiac echocardiography) is an important imaging technique to assist the TAVR procedure. At follow-up, evaluation of the hemodynamic performance of the transcatheter valve is usually performed with echocardiography.

The present review article provides an overview of the clinical applications and current role of echocardiographic techniques in TAVR for (i) patient selection, (ii) prosthesis sizing, (iii) periprocedural guidance, and (iv) postprocedural follow-up.

Echocardiography in patient selection prior to TAVR

Two-dimensional and Doppler transthoracic echocardiography (TTE) is the imaging technique of first choice to diagnose AS severity. Furthermore, it provides information on aortic root dimensions, left ventricular (LV) dimensions and function (e.g., presence of LV hypertrophy), pulmonary arterial pressure and associated valve disease (mitral and tricuspid regurgitation), which are important factors to take into consideration in the clinical decision making of patients with severe AS [10].

Aortic valve morphology

The first step in the evaluation of patients with severe AS is to define the aortic valve morphology. Conventional 2D TTE permits visualization of the number and position of cusps and qualitative assessment of calcium deposition and the movement of the cusps. However, in severely calcified aortic valves, 2D TTE may not be accurate enough to define the morphology of the valve (tricuspid vs. bicuspid). Transoesophageal echocardiography and CT provide better accuracy to identify the valve morphology

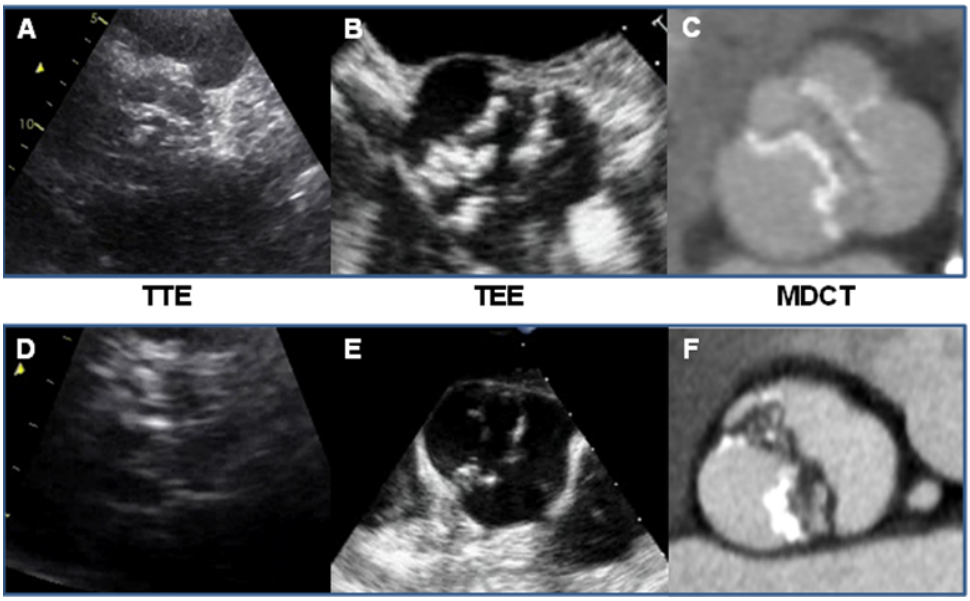


Figure 1: Comparison of transthoracic echocardiography (TTE), transoesophageal echocardiography (TEE) and multi-detector row computed tomography (MDCT) for the detection of bicuspid aortic valve (BAV) stenosis. Examples of BAV with a fusion raphe (*panels A-C*) and BAV without a fusion raphe (*panel D-F*) are shown. For both examples, TTE (*panels A and D*) has insufficient accuracy to correctly detect the presence of BAV and its specific morphology. TEE (*panels B and E*) shows a better accuracy for BAV diagnosis. MDCT (*panels C and F*) allows for optimal detection of BAV and the presence and location of raphes, especially when leaflet calcification is present.

(Figure 1) [10, 11].

Bicuspid aortic valve (BAV) is diagnosed in systole by the presence of 2 commissures. However, the phenotype of BAV is highly variable depending on the presence and location of a fusion raphe between cusps. According to the classification of Sievers [12], BAV can be classified into type 0, when there are 2 commissures and 2 cusps without a raphe; type 1, when there are 2 commissures and 3 cusps with 2 of them fused by one raphe; and type 2, when there is 1 commissure with 3 cusps and 2 of them fused by two raphes. These BAV types can be further classified according to the orientation of the commissures and location of the raphe (Figure 2) [12].

Landmark randomized controlled trials on TAVR excluded BAV patients [6, 7]. However, several registries have reported the feasibility of TAVR in patients with BAV. A higher incidence of significant paravalvular leakage has been reported in bicuspid AS patients treated with early-generation TAVR devices as compared to tricuspid AS patients [13, 14]. However, new-generation TAVR devices showed device success rate and incidence of significant paravalvular leakage in BAV patients similar to those reported in tricuspid AS patients [15–17].

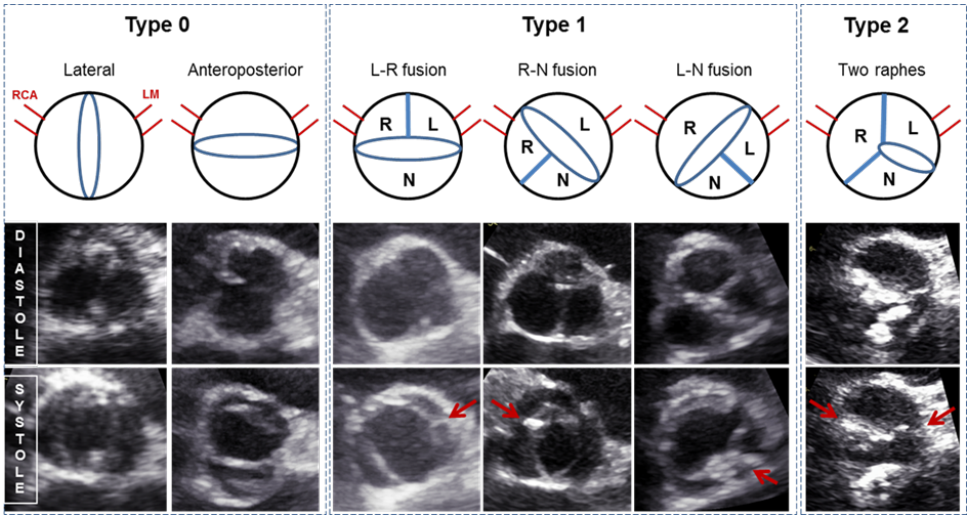


Figure 2: Schematic overview and two-dimensional transthoracic echocardiographic views of the bicuspid aortic valve (BAV) morphologies according to the classification of Sievers [12]. The aortic valves are depicted from the short-axis views from the left ventricular view in both the diastolic and systolic phase. The raphe (commissural fusion) is represented by the blue bands and red arrows. The origins of the left main (LM) and right coronary artery (RCA) are depicted with red lines. Type 0 denotes BAV without a fusion raphe with a lateral or anteroposterior orientation of the commissures and type 1 and 2 denote BAV with one or two fusion raphes, respectively. LM, left main coronary artery; L-N; left and non-coronary cusp; L-R, left and right coronary cusp; RCA, right coronary artery; R-N, right and non-coronary cusp.

AORTIC STENOSIS SEVERITY

Secondly, assessment of AS severity relies on the following echocardiographic parameters: peak aortic jet velocity, mean transvalvular pressure gradient and the aortic valve area (AVA) by continuity equation. Severe AS is conventionally defined as an aortic jet velocity ≥4 m/s, a mean gradient ≥40 mmHg and/or an AVA <1.0 cm^2 [4, 18]. Although the majority of patients with severe AS meet all these criteria, around one third of the patients show discordant grading: an AVA <1.0 cm^2 with a mean gradient <40 mmHg (so called low-gradient severe AS) [19]. Low-gradient severe AS is frequently observed when the LV ejection fraction (LVEF) is reduced, as this results in a low outflow status [19]. The presence of low flow through the aortic valve, defined as a stroke volume (SV) index <35 ml/m^2 [4, 18], may result in underestimation of the mean gradient (which is the squared function of flow) [10].

In this clinical scenario, differentiation between true severe AS and pseudosevere AS is crucial to provide the most appropriate treatment to the patient. To differentiate between these two entities, low-dose (up to 20 μg/kg/min) dobutamine stress echocardiography (DSE) is utilized to increase LV contractility and subsequently increase flow rate. In true severe AS, the increased flow (defined as an >20% increase in SV) will cause an increase in mean gradient (>40 mmHg) while the AVA remains <1.0 cm^2 (Figure 3), whereas in pseudosevere AS, the mean gradient will remain <40 mmHg and the increased SV will result in an AVA >1.0 cm^2 [10]. In patients without contractile reserve or in whom nor-

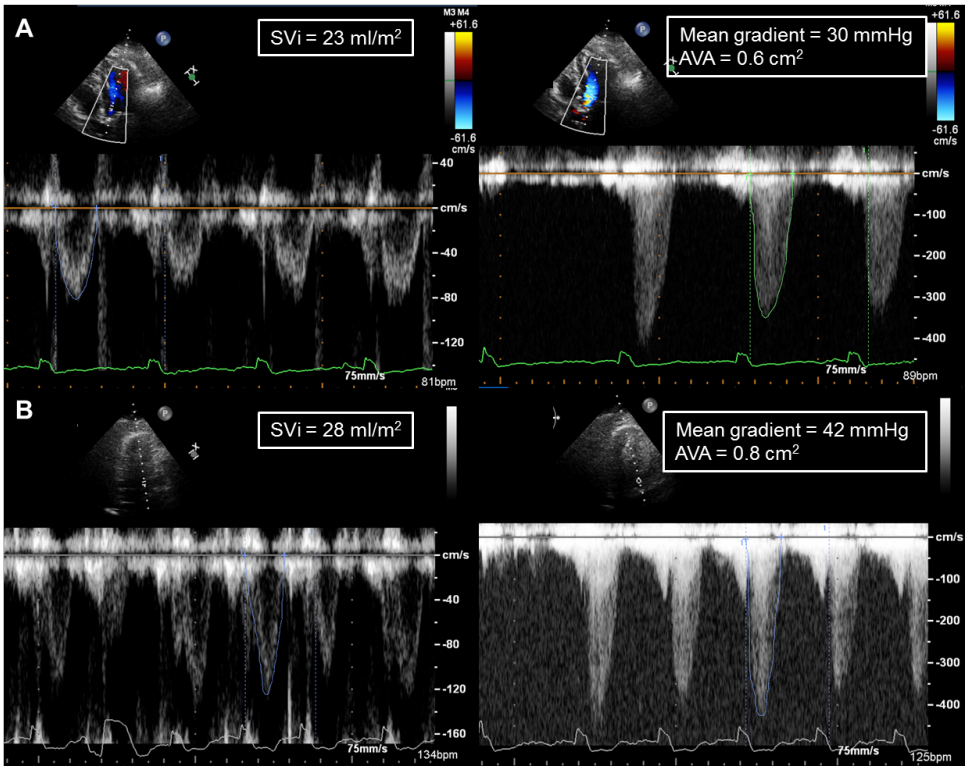


Figure 3: Evaluation of low-flow low-gradient severe aortic stenosis (AS) with reduced left ventricular ejection fraction using low-dose dobutamine stress echocardiography. At baseline, discordant grading of AS severity was apparent: the mean gradient was 30 mmHg and the aortic valve area (AVA) was 0.6 cm^2. The stroke volume index (SVi) was 23 ml/m^2, corresponding with low-flow low-gradient AS (*panel A*). Low-dose dobutamine stress echocardiography was performed to differentiate between true severe AS and pseudosevere AS. This resulted in an increase of the mean gradient to 42 mmHg and of the SVi by 22% to 28 ml/m^2 while the AVA remained <1.0 cm^2, consistent with classical low-flow low-gradient true severe AS and the presence of flow reserve (i.e., increase of SVi > 20%)(*panel B*).

malization of flow rate cannot be achieved, quantification of aortic valve calcification with CT can be helpful [20]. Current recommendations indicate that severe AS is likely when the calcium score of the aortic valve is ≥1200 arbitrary units in women and ≥2000 arbitrary units in men [4].

Recently, transaortic flow rate (defined as SV divided by the systolic ejection period) has emerged as a potentially useful parameter for the assessment of true severe AS in patients with low-gradient severe AS [21–23]. Chahal et al. demonstrated that, in 67 low-gradient severe AS patients with either low flow or LV systolic dysfunction, normal resting transaortic flow rate (i.e., ≥200 ml/s) was independently associated with the presence of true severe AS on DSE and suggested that DSE may only be required for the evaluation of AS severity in patients with a resting flow rate <200 ml/s [21]. In a small study of 42 low-flow low-gradient severe AS patients, use of normalized transaortic flow rate (i.e.,

increase up to ≥200 ml/s) during DSE as a criterium for the assessment of true severe AS instead of the presence of flow reserve (defined as ≥20% SV increase) resulted in more conclusive tests (82% vs. 36.4%, *P*=0.13)[22]. Furthermore, low transaortic flow rate was shown to be an independent predictor of mortality and provided incremental information over SV index in low-gradient severe AS patients undergoing aortic valve intervention, although these findings need to be confirmed in larger prospective studies [23].

Paradoxical low-flow low-gradient severe AS, defined by a mean gradient >40 mmHg, AVA <1.0 cm^2 and SV index <35 ml/min with preserved LVEF (≥50%), is often characterized by pronounced LV concentric hypertrophy contributing to a small LV cavity with impaired LV filling, resulting in low SV [24]. To correctly diagnose paradoxical low-flow low-gradient severe AS, it is paramount to exclude measurement errors such as underestimation of the LV outflow tract (LVOT) diameter or misalignment of the sample volume resulting in underestimation of the aortic jet velocity and transvalvular gradients. In addition, it is recommended to use indexed AVA (AVAi) [10].

The optimal method to differentiate patients with true severe AS from those with probably moderate AS among paradoxical low-flow low-gradient severe AS patients remains unclear, as the feasibility and safety of DSE in these patients with restrictive physiology is uncertain [25]. Assessment of the degree of aortic valve calcification with CT or calculation of the AVA by combining 3D planimetered LVOT area (on CT or 3D transoesofageal echocardiography [TEE]) with Doppler TTE data can be helpful [26, 27]. Kamperidis et al. showed that by incorporating a CT-derived LVOT-area into the continuity equation formula combined with hemodynamic echocardiographic data as assessed by Doppler TTE, resulted in larger AVA index than that calculated conventionally with 2D TTE (Figure 4) [27]. Accordingly, the use of CT to calculate the AVA resulted in reclassification of a significant proportion of paradoxical low-flow low-gradient severe AS into moderate AS [27]. In a subanalysis of the Placement of Aortic Transcatheter Valves (PARTNER) trial, treatment with TAVR was associated with reduced mortality compared to medical management at 2 year follow-up in both classical (47% vs. 80%, respectively, *P*=0.039) and paradoxical low-flow low-gradient severe AS (57% vs. 77%, respectively; *P*=0.047) [28]. Therefore, accurate assessment of AS severity is crucial to provide the best treatment and improve outcomes.

The role of 3D TEE in prosthesis sizing

Measurement of the dimensions of the aortic valve annulus and prosthesis size selection are crucial steps in TAVR. Over- or undersizing of the TAVR prosthesis might result in aortic root rupture, valve embolization or paravalvular aortic leakage. The aortic annulus is an oval-shaped virtual ring which dimensions are better measured with 3D imaging techniques [29–31], with CT providing the highest spatial resolution [32]. However, in patients with renal dysfunction in whom associated comorbidities such as heart failure may increase the risk of acute kidney injury, the use of iodinated contrast should be kept at a minimum [33]. Three-dimensional TEE is a valid alternative to CT to measure the aortic annulus. Several studies have reported a moderate to high correlation for cross-sectional dimensions of the aortic annulus (area and perimeter) measured with CT and 3D TEE [34–36]. However, cross-sectional 3D TEE measurements of the aortic annulus were significantly smaller than dimensions obtained by CT, thus potentially resulting

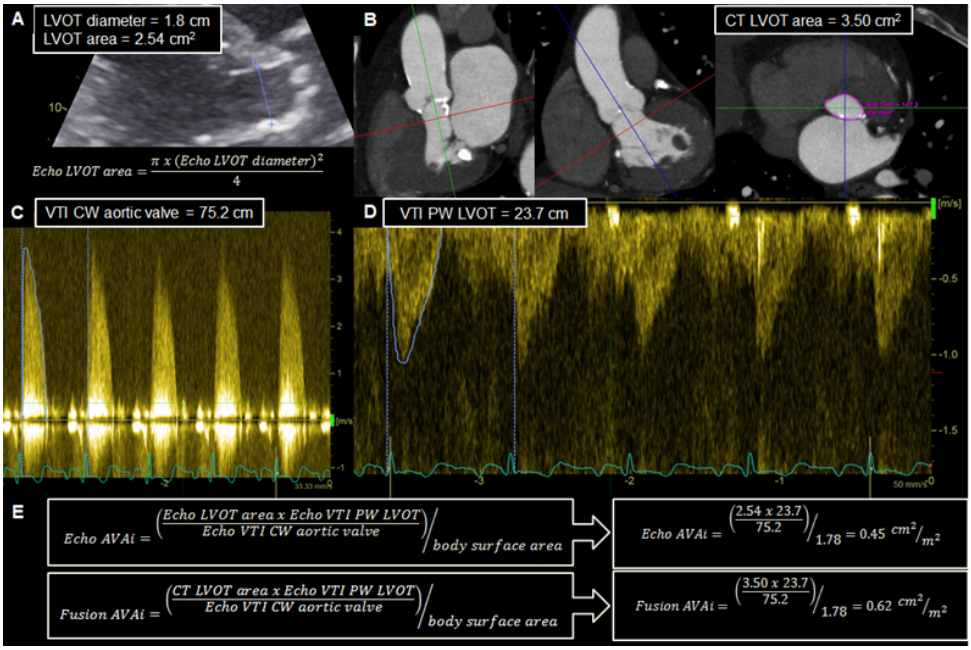


Figure 4: Evaluation of the aortic valve area index (AVAi) by two-dimensional Doppler echocardiography (Echo) and by fusion of multi-detector row computed tomography (CT)-derived and echocardiographic measurements. Using echocardiography, the left ventricular outflow tract (LVOT) diameter was measured 5 mm below the aortic annulus in the parasternal long-axis view and the LVOT area was calculated (*panel A*). Using CT, the LVOT area was located 5 mm below the aortic annulus and planimetered in the reconstructed double oblique transverse view in systole (*panel B*). Continuous-wave (CW) Doppler on the apical 5-chamber view was performed to measure the velocity time integral (VTI) of the aortic valve (*panel C*). Pulsed-wave (PW) Doppler recordings of the LVOT were obtained by placing the sample volume 5 mm below the aortic annulus and the VTI of the flow at the LVOT was measured (*panel D*). By utilizing the continuity equation, the Echo AVAi and fusion AVAi were calculated incorporating the echocardiographically estimated LVOT area and CT-derived LVOT area, respectively. In both calculations, the VTI of the LVOT and the aortic valve area were used (*panel E*). In this example, reclassification to moderate AS was possible by calculating the fusion AVAi.

in prosthesis undersizing when implemented in the sizing algorithms recommended by manufacturers [35, 36].

The advent of semi-automated quantitative software for direct planimetry of the aortic annulus has allowed a more systematic approach minimizing the influence of the observer (Figure 5). Studies comparing semi-automated or automated software by different vendors have demonstrated good to excellent agreement between 3D TEE and CT for the measurements of the annular area, mean diameter and perimeter with low interobserver and intraobserver variability [37–41].

The limitations of 3D TEE include the semi-invasive approach and the acoustic shadowing due to bulky calcification of the aortic valve or annulus which can challenge the visualization of the annulus [38, 40]. By acquiring the 3D TEE data of the aortic root in an off-axis plane, the acoustic shadowing created by the aortic valve calcification can be minimized resulting in improved agreement between CT and 3D TEE measurements of

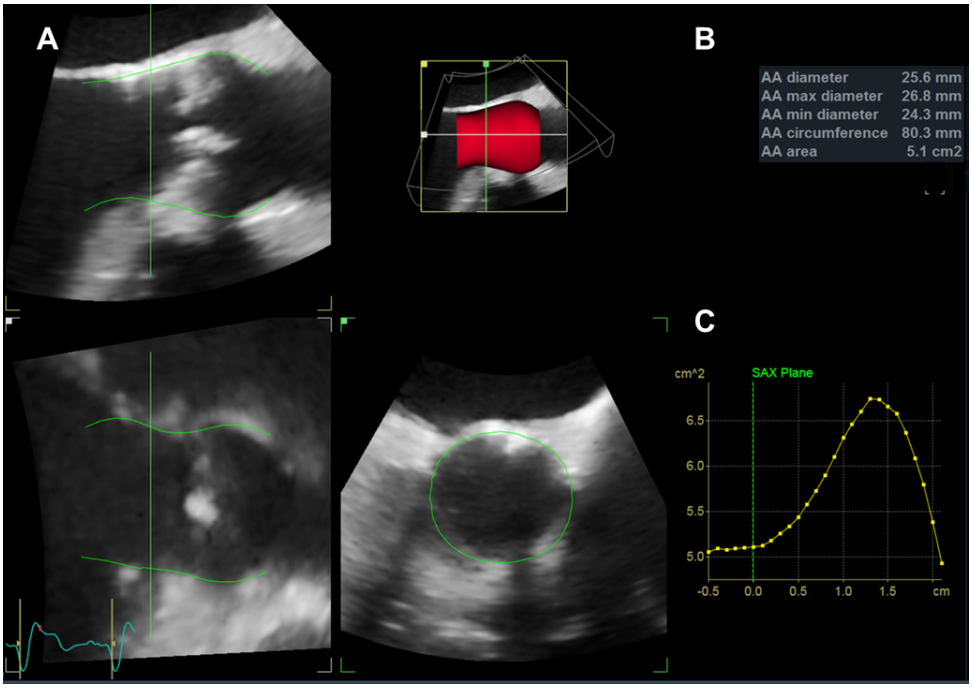


Figure 5: Evaluation of the aortic annulus by three-dimensional transoesophageal echocardiography using automated software (4D Automated Aortic Valve Quantification (4D Auto AVQ); EchoPAC, version 201, GE-Vingmed). First, a multiplanar reconstruction of the aortic valve is constructed in mid-systole by aligning the two long-axis orthogonal planes through the aortic valve and moving the transverse plane toward the hinge points of the aortic valve leaflet insertions. Automatic delineation of the left ventricular outflow tract and aortic root is then performed by the 4D Auto AVQ program and, if needed, manual adjustments can be made (*panel A*). After approval of the contouring of the aortic annulus (AA) and aortic root, the automatic software computes the annular dimensions: average diameter (calculated based on the perimeter), maximum and minimum diameters, circumference (perimeter) and area (*panel B*). The software generates a graph representing the cross-sectional area along the aortic root and left ventricular outflow tract (*panel C*).

the aortic annulus dimensions (Figure 6) [42].

With the prospect that future TAVR procedures will be performed in younger patients with low operative risk in whom radiation needs to be minimized, 3D TEE may be a good alternative to CT for aortic annulus sizing.

Echocardiographic guidance during TAVR procedure

Procedural guidance during TAVR is routinely performed using fluoroscopy [43]. Transoesofageal echocardiography is used as an adjunct to fluoroscopy and offers multiple advantages: it reduces the amount of nephrotoxic iodine contrast and radiation exposure and allows for early assessment of potential intra-procedural or immediate post-procedural complications [44, 45]. As TEE offers real-time and continuous monitoring, it is useful for all aspects of the TAVR procedure.

Although manipulation and positioning of wires is usually monitored by fluoroscopy,

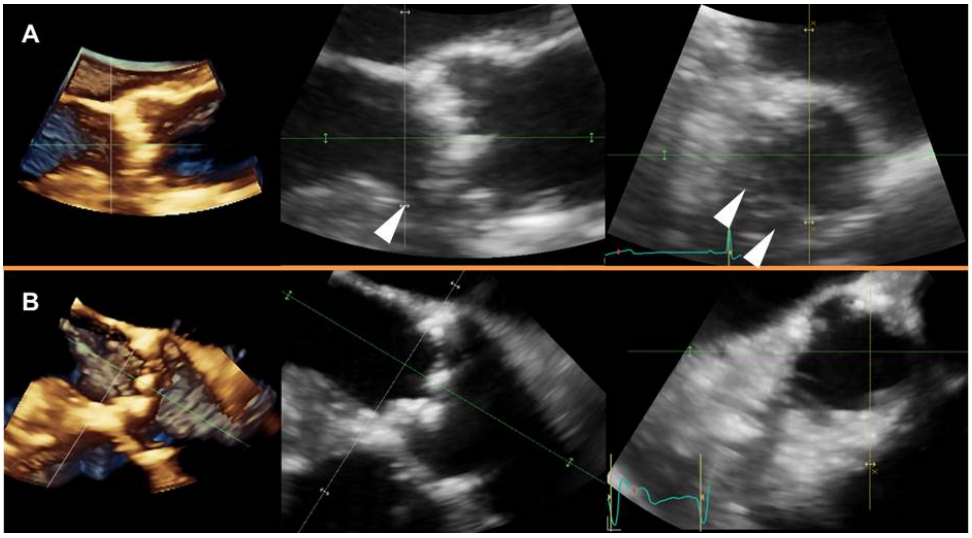


Figure 6: Assessment of the aortic valve and annulus using three-dimensional transoesophageal echocardiography. From the three-dimensional full volume, the two-dimensional long-axis multiplanar reconstruction (middle) and the short-axis multiplanar reconstruction at the level of the aortic annulus (right) are displayed. In *panel A*, the ultrasound beam is angled parallel to the calcified aortic valve causing considerable acoustic shadowing over the aortic annulus, which challenges accurate assessment of the aortic annulus (white arrows). In *panel B*, the three-dimensional echocardiographic data were acquired in an off-axis plane, causing the acoustic shadowing to be projected over the sinus of Valsalva and providing a more clear view of the aortic annulus and more accurate measurements of the aortic annulus dimensions.

TEE can help to confirm the correct positioning the pacing wire in the right ventricular apex as well as the position of the retrograde stiff wire in the left ventricle. TEE also permits rapid assessment of potential pericardial effusion in the event of ventricular perforation. During positioning of the wire, entrapment of the guidewire within the mitral apparatus causing mitral regurgitation can be detected at an early stage [45].

If balloon aortic valvuloplasty is deemed necessary, TEE can be used to guide the balloon positioning relative to the valve and to ensure a stable position. Furthermore, it may aid in visualizing how calcified aortic valve cusps will displace relative to the coronary ostia and predict whether occlusion of coronary ostia might occur. For the correct positioning of both balloon- and self-expandable prostheses prior to deployment, fluoroscopy plays a pivotal role. However, fluoroscopy can prove challenging in the setting of limited calcification of the aortic valve / annulus, in which case TEE can be particularly useful. Although the simultaneous use of TEE can cause an obstruction of the fluoroscopic view, changing the echocardiographic window or fluoroscopic angle may overcome this disadvantage [45].

Immediately after the valve is deployed, appropriate valve position and function can be confirmed by TEE. Importantly, the presence and severity of paravalvular aortic regurgitation should be assessed. Correct assessment of the severity of paravalvular aortic regurgitation is challenging as multiple paravalvular jets with an eccentric and irregular appearance can be present [43]. Aortography provides a qualitative assessment of the

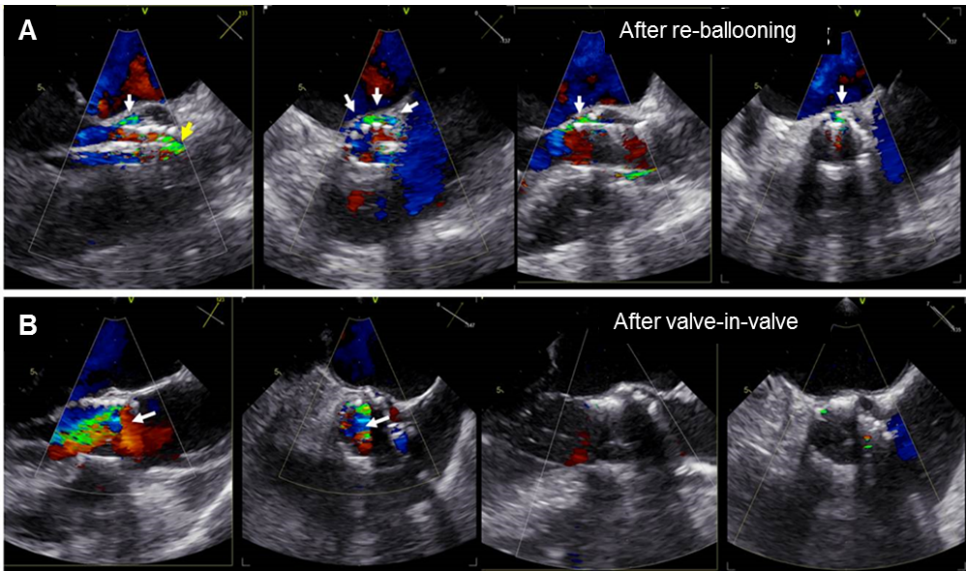


Figure 7: Evaluation of transcatheter aortic valve replacement results: differentiating paravalvular from transvalvular regurgitation. *Panel A* shows a patient who received a self-expanding valve prosthesis. The images on the left show the presence of paravalvular regurgitation (white arrow) and transvalvular regurgitation caused by the presence of the wire (yellow arrow). The orthogonal simultaneous view shows the short-axis of the transcatheter valve with paravalvular regurgitation along >25% of the prosthesis frame circumference (arrows). After re-ballooning of the valve, the paravalvular regurgitation significantly reduced to trace. *Panel B* shows a patient who received a balloon-expandable prosthesis with a frozen (i.e., not deployed) leaflet resulting in severe transvalvular regurgitation (arrow) and hemodynamic instability of the patient. The orthogonal short-axis view shows the regurgitant jet covering 50% of the internal area of the transcatheter valve (arrow). In this situation, valve-in-valve implantation is needed to hemodynamically stabilize the patient and treat the regurgitation.

residual aortic regurgitation, but it does not provide information on the mechanism of regurgitation (paravalvular versus transvalvular), which is important to decide whether re-ballooning of the transcatheter valve is needed to ensure good sealing of the annulus and reduce paravalvular regurgitation, or if rescue valve-in-valve is needed to reduce transvalvular regurgitation (Figure 7).

The importance of using the recommended multi-window and multi-parametric echo-cardiographic approach, incorporating both qualitative (i.e., jet features) and semiquantitative (i.e., jet width at origin as percentage of LVOT diameter and circumferential extent of the jet(s)) parameters [43, 46], was recently illustrated by Hahn et al. [47]. In this study, 15.9% of patients who were graded as moderate paravalvular aortic regurgitation by a method using the circumferential extent of the regurgitant jet, were reclassified as mild paravalvular aortic regurgitation when the multiparametric approach was used [47].

Growing operator experience and the development of smaller delivery systems has increased the feasibility of transfemoral TAVR with local anaesthesia or conscious sedation (also called monitored anaesthesia care) rather than general anaesthesia [48, 49], resulting in the increased use of TTE to evaluate the results of TAVR. This less invasive

strategy has been associated with a shorter duration of hospitalization and improved post-procedural outcomes without safety issues [49–52]. In addition to using TTE for intraprocedural guidance, transnasal TEE and intracardiac echocardiography have been suggested as alternative imaging methods in procedures with monitored anaesthesia care [43]. Compared to conventional TEE, transnasal TEE does not have the capability for 3D assessment and the image quality is considerably less [43]. Intracardiac echocardiography provides better image quality than transnasal TEE and uninterrupted monitoring without fluoroscopic interference [53]. This is achieved by using a steerable catheter, which is introduced into the femoral vein and advanced via the inferior vena cava and right atrium towards the superior cavo-atrial junction [53]. In this position, the aortic valve and root can be continuously monitored. Real time 3D imaging, with a 22 x 90° volume image, allows for the postprocedural assessment of paravalvular aortic regurgitation and potential complications [53]. Major disadvantages of this technique are the lesser image quality (particularly in 3D due to the small image volume), the possible interference of the device with the pacemaker lead with subsequent risk of lead displacement and loss of capture, lack of experience and especially the high costs of the device [53].

ECHOCARDIOGRAPHY DURING FOLLOW-UP AFTER TAVR: WHAT TO LOOK FOR?

FOR the assessment of prosthesis function and durability after TAVR and detection of possible late complications, TTE is the mainstay imaging modality. According to current guidelines, echocardiographic follow-up of TAVR should be performed prior to discharge or within 30 days after implantation, after 6 months and 1 year and yearly thereafter [32, 54]. Importantly, if new symptoms and signs of valve dysfunction appear, echocardiography should be performed and the frequency of follow-up visits should be increased when deterioration of LV function and valve hemodynamics are noted. Using TTE, the position of the TAVR stent and the morphology of the prosthesis leaflets, in particular cusp thickness and mobility, and the presence of valve stenosis or regurgitation should be assessed.

STENT POSITION AND LEAFLET MORPHOLOGY

Deployment of the TAVR prosthesis lower than recommended can result in protruding native valve leaflets above the aortic edge of the frame and limited anchoring, increasing the risk of delayed migration of the prosthetic valve into the LVOT or LV [43, 55]. This can cause either prosthetic regurgitation or native valve restenosis or result in mitral regurgitation due to interaction with the mitral apparatus [55]. Structural valve deterioration (SVD), i.e., acquired and permanent intrinsic deterioration of the prosthetic valve, typically manifests as prosthesis stenosis caused by thickening and calcification of the prosthesis leaflets (Figure 8). Less often, flailing or tearing of a leaflet can be observed causing new onset of transvalvular regurgitation (Figure 8).

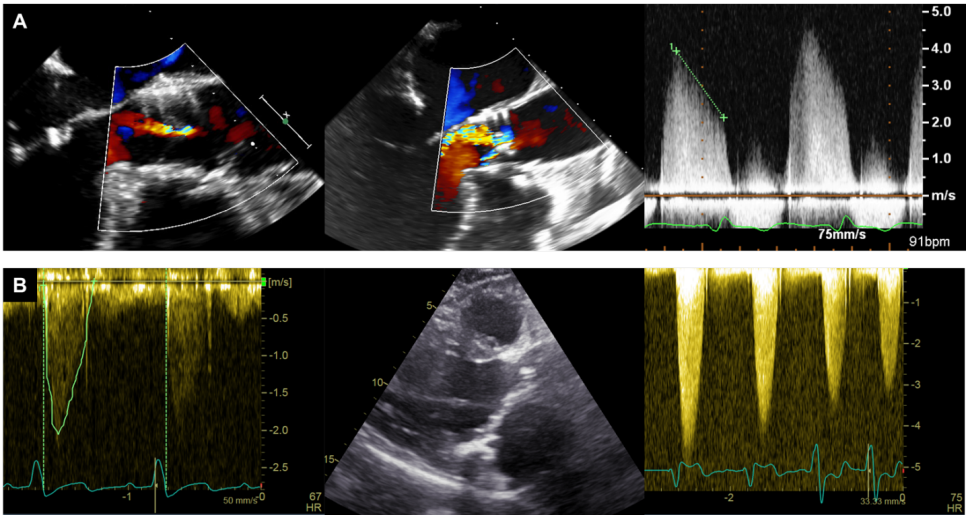


Figure 8: Structural valve deterioration after transcatheter aortic valve replacement showing severe transvalvular aortic regurgitation (*panel A*) or severe prosthetic valve stenosis (*panel B*). *Panel A* shows a patient receiving a balloon-expandable valve with periprocedural transoesophageal echocardiography demonstrating mild paravalvular regurgitation on color Doppler (left panel). After 4 years follow-up, transoesophageal echocardiography showed severe transvalvular aortic regurgitation on the color Doppler image (middle panel), confirmed by continuous wave Doppler recordings with steep downsloping of the regurgitant flow (right panel). *Panel B* shows a patient receiving a balloon-expandable valve with periprocedural transoesophageal echocardiography demonstrating low transprosthetic gradients (left panel). After 6 years of follow-up, transthoracic echocardiography showed thickened and calcified prosthetic valve leaflets on the long-axis view (middle panel). Increased transprosthetic gradients were observed on continuous wave Doppler (right panel), confirming the presence of severe prosthetic valve stenosis. Both patients underwent a valve-in-valve implantation.

PROSTHETIC VALVE STENOSIS

For valve stenosis, peak velocity and mean gradient (flow-dependent parameters) and the effective orifice area (EOA) (flow-independent parameter) should be evaluated. For the calculation of the EOA, it is important to measure the LVOT diameter and flow velocity immediately proximal of the prosthesis stent to prevent EOA overestimation caused by flow acceleration within the stent. The Valve Academic Research Consortium-2 (VARC-2) has proposed the use of one flow-independent (e.g., EOA) and one flow-dependent (e.g., mean transvalvular gradient) parameter for the assessment of prosthetic aortic valve stenosis [54]. Recent recommendations by the Valve in Valve Interventional Data (VIVID group) propose to define severe prosthetic valve stenosis by an increase in mean gradient >20 mmHg compared to the baseline post-procedural gradient accompanied by a decrease in EOA [56]. Alternatively, European recommendations suggest to define severe hemodynamic SVD as a mean gradient ≥40 mmHg and/or ≥20 mmHg change from baseline and/or severe new or worsening intraprosthetic aortic regurgitation [57].

Table 1: Parameters used for the assessment of severity of paravalvular regurgitation on echocardiography and cardiac magnetic resonance imaging.

Parameter	Severity of paravalvular regurgitation			Main limitation
	Mild	Moderate	Severe	
Echocardiography				
Qualitative or semi-quantitive parameters				
Jet length and width + number of jets and jet origins*	Non extensive, multiple jets possible	Extensive, multiple jets often present	Extensive, multiple jets often present	Jets may not be visible due to acoustic shadowing of stent and native valve or LVOT calcifications; jet length and width only weakly correlated with severity of regurgitation
Circumferential extent jet (color Doppler)*	<10%	10-29%	≥30%	Less reliable in the presence of multiple or eccentric jets, plane position dependent, poor correlation with cardiac magnetic resonance imaging
Ratio jet width at origin/LVOT diameter (color Doppler)*	5-30% (narrow/intermediate)	30-60% (intermediate)	>60% (large)	May be difficult to visualize (assessed visually)
Vena contracta width (color Doppler)	<3 mm	3-6 mm	>6 mm	Often irregularly shaped, may be difficult to visualize (assessed visually) due to acoustic shadowing and in case of multiple jets
Signal intensity of jet (CW Doppler)	Faint/variable	Dense	Dense	
Pressure half-time (CW Doppler)	>500 ms (slow)	200-500 ms (variable)	<200 ms (steep)	Heart rate and rhythm dependent, strongly influenced by compliance of LV and aorta
Diastolic flow reversal in descending aorta (PW Doppler)	Absent/intermediate	Intermediate/holodiastolic (>20 cm/s)	Holodiastolic (>25 cm/s)	Strongly influenced by compliance of LV and aorta

CW, continuous wave; LVOT, left ventricular outflow tract; PW, pulsed wave; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography.
*Of particular importance for the assessment of paravalvular regurgitation severity.

Table 1: Parameters used for the assessment of severity of paravalvular regurgitation on echocardiography and cardiac magnetic resonance imaging (*continued*).

Parameter	Severity of paravalvular regurgitation			Main limitation
	Mild	Moderate	Severe	
Quantitative parameters				
Regurgitant volume	<30 ml/beat	30-59 ml/beat	≥60 ml/beat	Large inter- and intra-observer variability, cannot be assessed in the presence of >mild mitral or pulmonary regurgitation
Other				
Left ventricular dimensions	Normal	Normal/mildly dilated	Moderately/severely dilated	More useful in the setting of chronic paravalvular regurgitation
TAVR stent position	Normal/abnormal	Normal/abnormal	Usually abnormal	
Cardiac magnetic resonance imaging				
Regurgitant fraction (phase-contrast velocity mapping)	<20%	20-30%	>30%	Variable cut-offs reported (not yet validated), often overestimation compared to TTE

TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography.

PROSTHETIC VALVE REGURGITATION

Prosthetic valve regurgitation after TAVR is assessed using both qualitative and quantitative criteria similar to surgical prosthetic valve regurgitation (Table 1) [46, 56]. Although this is primarily assessed using TTE, TEE may be considered if image quality is suboptimal. Proper evaluation of the severity of paravalvular aortic regurgitation after TAVR can be challenging, as it is often characterized by the presence of multiple eccentric and irregularly shaped jets which limit proper assessment of the circumferential extent and diameter of the regurgitant jet. Acoustic shadowing by the prosthesis stent and native valve calcifications further complicate correct quantification, particularly when measuring the vena contracta width. Furthermore, LV and aortic compliance is often lacking in elderly patients undergoing TAVR, which might influence pressure half time and potentially cause holodiastolic flow reversal in the absence of significant aortic regurgitation. These limitations and difficulties in the evaluation of paravalvular aortic regurgitation after TAVR emphasize the importance of the use of the multi-parametric approach [46]. Using this approach, both mild and moderate/severe paravalvular regurgitation were independently associated with higher late all-cause mortality in the patients of the PARTNER I trial [58], although other studies have reported no significant prognostic effect of mild paravalvular regurgitation [59]. When the severity of the paravalvular regurgitation remains uncertain after TEE assessment or insufficiently corresponds with clinical assessment, cardiac magnetic resonance imaging may help to confirm the severity of the aortic regurgitation. Ribeiro et al. quantified aortic regurgitation after TAVR in 135 patients using regurgitant fraction measured by phase-contrast velocity mapping [60]. Higher regurgitant fraction was associated with increased mortality and a regurgitant fraction ≥30% best predicted poorer clinical outcomes [60]. However, cardiac magnetic resonance imaging has multiple limitations, such as the inability to differentiate paravalvular from transvalvular regurgitation, and further studies are needed as variable cut-off values of regurgitant fraction have been reported.

FURTHER CONSIDERATIONS

Varying rates of SVD in TAVR have been reported in mid-term and long-term follow-up studies, partly caused by differences in the definition of SVD. In both balloon-expandable and self-expandable TAVR prostheses, 3 to 5 year follow-up studies have reported low rates of SVD [57]. A recent meta-analysis including 13 studies reporting SVD rates in TAVR, based on VARC-2 definition (i.e., need for repeat procedure, increased mean gradient >20 mmHg, EOA <0.9-1.1 cm^2 and/or Doppler velocity index <0.35 m/s), showed a pooled estimate of a SVD incidence rate of 28 per 10000 patient years [61].

When signs of prosthetic valve stenosis are observed, prosthetic valve thrombosis should be considered. Although TEE is the reference standard for the evaluation of prosthetic valve thrombosis, the high spatial resolution of CT allows for better distinction between thrombosis and other causes of obstruction such as pannus (Figure 9) [62]. In two multicentre registries, Del Trigo et al. demonstrated that 4.5% of patients treated with TAVR presented with valve hemodynamic deterioration (VHD) defined as an absolute increase in mean transprosthetic gradient ≥10 mmHg between discharge and last follow-up [63, 64]. Absence of anticoagulation therapy was an independent predictor for VHD [63], and when comparing propensity-matched populations, VHD appeared

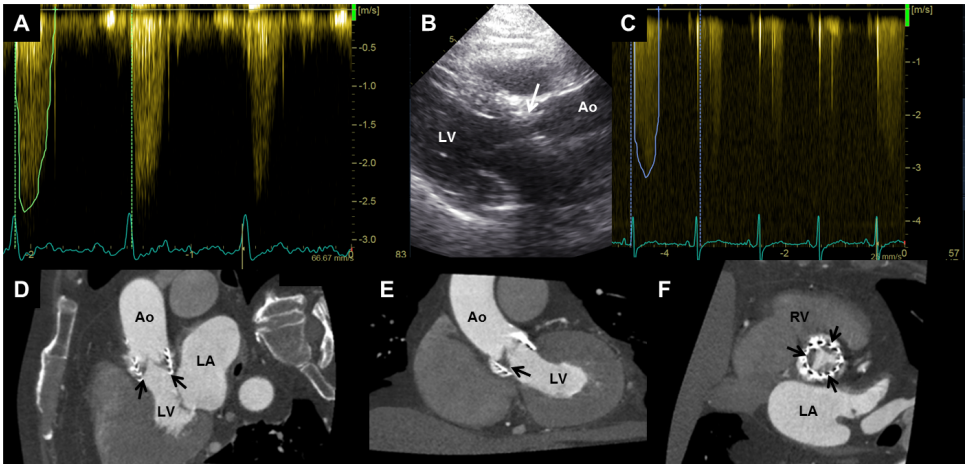


Figure 9: Prosthetic transcatheter aortic valve thrombosis in a patient presenting with heart failure symptoms 1 year after receiving a balloon-expandable valve. Directly after implantation, transoesophageal echocardiography showed low transprosthetic gradients (10 mmHg, *panel A*). After 1 year, follow-up transthoracic echocardiography demonstrated thickened prosthesis leaflets (white arrow, *panel B*) and increased transprosthetic gradients compared to baseline (25 mmHg, *panel C*) consistent with severe prosthetic valve stenosis. Four-dimensional computed tomography was performed showing hypoattenuated lesions and leaflet thickening (black arrows) with reduced leaflet mobility on the sagittal oblique (*panel D*), coronal oblique (*panel E*) and double oblique (*panel F*) reconstruction views, confirming the presence of prosthetic valve thrombosis. Ao, aortic root; LA, left atrium; LV, left ventricle; RV, right ventricle.

to be less prevalent in patients receiving anticoagulation treatment compared to patients without anticoagulation (0.6 vs. 3.9%. P<0.001) [64]. Although TEE or CT were not performed, the authors postulated that prosthetic valve thrombosis may be likely the main mechanism underlying VHD. Prior studies evaluating obstructive prosthetic valve thrombosis after TAVR, with patients often presenting with heart failure symptoms or increased transprosthetic gradients on follow-up echocardiography, have reported relatively low incidences ranging from 0.61 to 2.8% [65–67]. However, studies performing (4D) CT post-TAVR regardless of symptoms or transprosthetic gradients have detected the presence of hypoattenuated leaflet thickening with or without reduced leaflet motion suggestive of subclinical leaflet thrombosis in a significantly higher proportion of patients, with incidences ranging from 4 to 40% [68–74].

More interesting, the time course of hypoattenuated leaflet thickening was described by Sondergaard et al. [72] in 84 patients (61 patients treated with TAVR and 23 patients with SAVR). After a mean follow-up of 140 days, 38.1% of patients showed hypoattenuated leaflet thickening and 20.2% displayed hypoattentuation affecting motion (leaflet thickening with reduced leaflet motion). After a mean follow-up of 298 days, a second CT scan was performed showing that the abnormalities noted in the first CT scan progressed in 15.5% of patients, regressed in 10.7% and remained unchanged in 73.8%. Importantly, patients receiving oral antiocoagulation did not show progression of the abnormalities suggesting that this treatment prevents from further thickening and restriction of prosthesis leaflets. Future prospective studies will likely shed more light on the incidence,

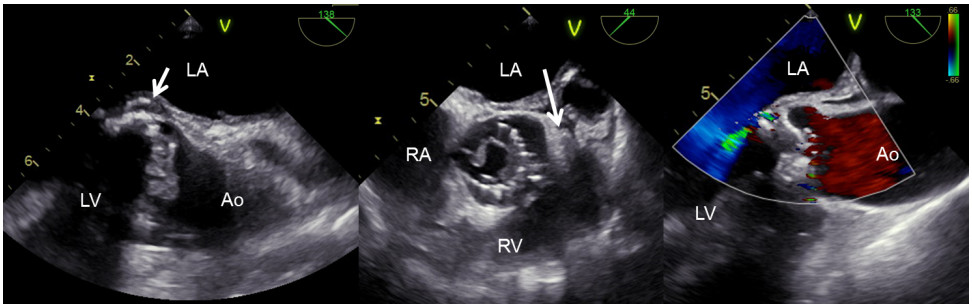


Figure 10: Prosthetic valve endocarditis 6 months after transcatheter aortic valve replacement assessed by two-dimensional transoesophageal echocardiography. The mid-oesophageal aortic valve long-axis (left panel) and short-axis (mid panel) views show signs of a paravalvular abcess (white arrows) and of vegetations located on the prosthetic valve leaflets. Color Doppler of the long-axis view (right panel) demonstrates mild paravalvular aortic regurgitation. Ao, aortic root; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

optimal antithrombotic/anticoagulant treatment regimen and effect on TAVR durability of subclinical prosthetic valve thrombosis.

Endocarditis is another complication that should be suspected based on the clinical presentation and when new periprosthetic valve regurgitation is detected. Echocardiography, in particular TEE, can be used for the detection of vegetations, abcesses or pseudoaneurysms (Figure 10), and to assess potential involvement of the mitral or tricuspid valve [75]. For improved prediction of embolic risk, real-time 3D TEE can be used for more precise estimation of vegetation morphology and size [76]. Recent multicentre registries have reported a 1.1% incidence of prosthetic valve endocarditis after TAVR, with the majority of patients presenting within 1 year after the procedure [77, 78]. Similarly to infective endocarditis after surgical valve replacement, the mortality rates are high (62% to 67%) [77, 78], emphasizing the importance of early detection and treatment. Unfortunately, the Duke criteria used for diagnosis of infective endocarditis have proven to be less sensitive if a prosthetic valve is involved and positive signs on TTE are often lacking in this setting [75]. A multimodality imaging approach adding ^{18}F-fluorodeoxyglucose positron emission (PET)/CT to the conventional modified Duke criteria has been recommended and has been shown to significantly increase diagnostic accuracy, especially in cases initially classified as “possible infective endocarditis” [75, 79, 80].

CONCLUSIONS AND FUTURE PERSPECTIVES: WILL THERE BE ROOM FOR ECHOCARDIOGRAPHY?

FOR symptomatic severe AS patients who are inoperable or have a high risk for surgery, TAVR has proven to be a feasible alternative to surgical valve replacement with good mid-term valve durability. Recently, TAVR has been increasingly performed in intermediate-risk patients and it is currently extending even to low-risk and asymptomatic patients. Proper patient and prosthesis selection, procedural surveillance and follow-up are para-mount for TAVR success. Echocardiography is an important imaging modality in all these steps of TAVR. However, emerging multimodality imaging techniques en-

able a more tailored approach based on patient-specific characteristics and often provide additional information in particular settings, emphasizing the importance of a multimodality imaging approach combining echocardiography with other modalities (Table 2). Numerous studies have established that 3D techniques such as CT and 3D TEE provide more accurate measurements of the aortic annulus and root, resulting in improved prosthesis selection and consequently higher procedural success rates. Additionally, growing operator experience and technical improvements in both prostheses and delivery systems have led to the increased use of conscious sedation with procedural guidance by fluoroscopy and TTE only instead of general anaesthesia guided by TEE, reducing invasiveness and procedural risks. At follow-up, echocardiography (particularly TTE) remains the main imaging modality for the assessment of prosthetic valve durability and detection of valve deterioration or late complications. However, for the detection of prosthetic valve thrombosis and endocarditis, alternative imaging modalities such as CT and PET/CT have demonstrated superior diagnostic accuracy and the implementation of these techniques in future studies will shed more light on the incidence, optimal patient management and effect on prosthetic valve durability of these complications.

Table 2: Role of multimodality imaging techniques in the different stages of the transcatheter aortic valve replacement procedure.

	Transcatheter aortic valve replacement procedure		
Imaging technique	**Preprocedural**	**Periprocedural**	**Follow-up**
Echocardiography			
TTE	Aortic valve morphology and degree of calcium deposition Aortic valve morphology and degree of calcium deposition Severity AS (+/- dobutamine stress echocardiography) Aortic root and ascending aorta dimensions Left ventricular function and dimensions Pulmonary arterial pressure Assessment of aortic regurgitation Concomitant valvular disease (mitral or tricuspid regurgitation)	Correct positioning and deployment of valve prosthesis Valve hemodynamics Assessment of aortic regurgitation Detection of other complications (pericardial effusion, mitral regurgitation, myocardial ischemia, aortic annular rupture, etc.)	Correct positioning and deployment of valve prosthesis Valve hemodynamics Assessment of aortic regurgitation Left ventricular function and dimensions Concomitant valvular disease (mitral or tricuspid regurgitation)
TEE (2D or 3D)	Aortic valve morphology and degree of calcium deposition Aortic annulus and root dimensions (3D)	Correct positioning of wires and catheters Guidance of balloon positioning Visualization of calcium displacement Correct positioning and deployment of valve prosthesis Valve hemodynamics Assessment of aortic regurgitation and distinguishing paravalvular and transvalvular regurgitation Detection of other complications (pericardial effusion, mitral regurgitation, myocardial ischemia, aortic annular rupture, etc.)	Correct positioning and deployment of valve prosthesis Valve hemodynamics Assessment of aortic regurgitation Left ventricular function and dimensions Concomitant valvular disease (mitral or tricuspid regurgitation) Detection prosthetic valve thrombosis and infective endocarditis

2D, two-dimensional; 3D, three-dimensional; AS, aortic stenosis; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 2: Role of multimodality imaging techniques in the different stages of the transcatheter aortic valve replacement procedure (*continued*).

	Transcatheter aortic valve replacement procedure		
Imaging technique	**Preprocedural**	**Periprocedural**	**Follow-up**
Computed tomography	Aortic valve morphology Severity AS (by quantification aortic valve calcification) Aortic annulus and root dimensions Thoracic aorta (+ degree of calcification) Peripheral artery accessibility Left ventricular function Projections C-arm for fluoroscopy		Correct positioning and deployment of valve prosthesis Detection (subclinical) prosthetic valve thrombosis, infective endocarditis and/or pannus
Fluoroscopy	Aortic annulus dimensions Peripheral artery accessibility	Correct positioning of wires and catheters Correct positioning and deployment of valve prosthesis Assessment of paravalvular regurgitation Detection of other complications (occlusion coronary ostia, rupture aortic annulus or ascending aorta, etc.)	
Cardiac magnetic resonance imaging	Aortic valve morphology and degree of calcium deposition Aortic root and ascending aorta dimensions Thoracic aorta dimensions Peripheral artery accessibility Left ventricular function		Correct positioning and deployment of valve prosthesis Assessment of aortic regurgitation Left ventricular function and dimensions
Nuclear imaging			^{18}F-FDG PET/CT: detection of prosthetic valve infective endocarditis

AS, aortic stenosis; CT, computed tomography; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

REFERENCES

[1] Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2477-84.

[2] Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, et al. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. Eur Heart J. 2017;38(36):2729-38.

[3] Douglas PS, Leon MB, Mack MJ, Svensson LG, Webb JG, Hahn RT, et al. Longitudinal hemodynamics of transcatheter and surgical aortic valves in the PARTNER Trial. JAMA Cardiology. 2017;2(11):1197-206.

[4] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[5] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. J Am Coll Cardiol. 2017;70(2):252-89.

[6] Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20.

[7] Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017;376(14):1321-31.

[8] Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the allcomers NOTION Randomized Clinical Trial. J Am Coll Cardiol. 2015;65(20):2184-94.

[9] Tarantini G, Nai Fovino L, Gersh BJ. Transcatheter aortic valve implantation in lower-risk patients: what is the perspective? Eur Heart J. 2018;39(8):658-66.

[10] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[11] Tanaka R, Yoshioka K, Niinuma H, Ohsawa S, Okabayashi H, Ehara S. Diagnostic value of cardiac CT in the evaluation of bicuspid aortic stenosis: comparison with echocardiography and operative findings. Am J Roentgenol. 2010;195(4):895-9.

[12] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg. 2007;133(5):1226-33.

[13] Mylotte D, Lefevre T, Søndergaard L, Watanabe Y, Modine T, Dvir D, et al. Transcatheter aortic valve replacement in bicuspid aortic valve disease. J Am Coll Cardiol. 2014;64(22):2330-9.

[14] Bauer T, Linke A, Sievert H, Kahlert P, Hambrecht R, Nickenig G, et al. Comparison of the effectiveness of transcatheter aortic valve implantation in patients with stenotic bicuspid versus tricuspid aortic valves (from the German TAVI Registry). Am J Cardiol. 2014;113(3):518-21.

[15] Perlman GY, Blanke P, Dvir D, Pache G, Modine T, Barbanti M, et al. Bicuspid Aortic Valve Stenosis: Favorable Early Outcomes with a Next-Generation Transcatheter Heart Valve in a Multicenter Study. J Am Coll Cardiol Intv. 2016;9(8):817-24.

[16] Yoon SH, Lefèvre T, Ahn JM, Perlman GY, Dvir D, Latib A, et al. Transcatheter Aortic Valve Replacement With Early- and New-Generation Devices in Bicuspid Aortic Valve Stenosis. J Am Coll Cardiol. 2016;68(11):1195-205.

[17] Yoon SH, Bleiziffer S, De Backer O, Delgado V, Arai T, Ziegelmueller J, et al. Outcomes in Transcatheter Aortic Valve Replacement for Bicuspid Versus Tricuspid Aortic Valve Stenosis. J Am Coll Cardiol. 2017;69(21):2579-89.

[18] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

[19] Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. Eur Heart J. 2016;37(34):2645-57.

[20] Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart. 2011;97(9):721-6.

[21] Chahal NS, Drakopoulou M, Gonzalez-Gonzalez AM, Manivarmane R, Khattar R, Senior R. Resting aortic valve area at normal transaortic flow rate reflects true valve area in suspected low-gradient severe aortic stenosis. J Am Coll Cardiol Img. 2015;8(10):1133-9.

[22] Vamvakidou A, Chahal N, Senior R. Lack of Stroke Volume Determined Flow Reserve Does Not Always Preclude Assessment of Severity of Aortic Stenosis in Low-Flow Low-Gradient State During Dobutamine Echocardiography. J Am Coll Cardiol Img. 2017;10(4):491-3.

[23] Vamvakidou A, Jin W, Danylenko O, Chahal N, Khattar R, Senior R. Low Transvalvular Flow Rate Predicts Mortality in Patients With Low-Gradient Aortic Stenosis Following Aortic Valve Intervention. J Am Coll Cardiol Img. 2019;12(9):1715-24.

[24] Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007;115(22):2856-64.

[25] Clavel MA, Ennezat PVl, Maréchaux S, Dumesnil JG, Capoulade R, Hachicha Z, et al. Stress echocardiography to assess stenosis severity and predict outcome in patients with paradoxical low-flow, low-gradient aortic stenosis and preserved LVEF. J Am Coll Cardiol Img. 2013;6(2):175-83.

[26] Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol. 2013;62(24):2329-38.

[27] Kamperidis V, Van Rosendael PJ, Katsanos S, Van Der Kley F, Regeer M, Al Amri I, et al. Low gradient severe aortic stenosis with preserved ejection fraction: reclassification of severity by fusion of Doppler and computed tomographic data. Eur Heart J. 2015;36(31):2087-96.

[28] Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a placement of aortic transcatheter valves (PARTNER) trial analysis. Circulation. 2013;127(23):2316-26.

[29] Delgado V, Ng ACT, Van De Veire NR, Van Der Kley F, Schuijf JD, Tops LF, et al. Transcatheter aortic valve implantation: role of multi-detector row computed tomography to evaluate prosthesis positioning and deployment in relation to valve function. Eur Heart J. 2010;31(9):1114-23.

[30] Altiok E, Koos R, Schröder J, Brehmer K, Hamada S, Becker M, et al. Comparison of two-dimensional and three-dimensional imaging techniques for measurement of aortic annulus diameters before transcatheter aortic valve implantation. Heart. 2011;97(19):1578-84.

[31] Jilaihawi H, Kashif M, Fontana G, Furugen A, Shiota T, Friede G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. J Am Coll Cardiol. 2012;59(14):1275-86.

[32] Otto CM, Kumbhani DJ, Alexander KP, Calhoon JH, Desai MY, Kaul S, et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2017;69(10):1313-46.

[33] Mohananey D, Griffin BP, Svensson LG, Popovic ZB, Tuzcu EM, Rodriguez LL, et al. Comparative Outcomes of Patients With Advanced Renal Dysfunction Undergoing Transcatheter Aortic Valve Replacement in the United States From 2011 to 2014. Circ Cardiovasc Interv. 2017;10(10):e005477.

[34] Ng ACT, Delgado V, Van Der Kley F, Shanks M, Van De Veire NRL, Bertini M, et al. Comparison of aortic root dimensions and geometries before and after transcatheter aortic valve implantation by 2-and 3-dimensional transesophageal echocardiography and multislice computed tomography. Circ Cardiovasc Imaging. 2010;3(1):94-102.

[35] Jilaihawi H, Doctor N, Kashif M, Chakravarty T, Rafique A, Makar M, et al. Aortic annular sizing for transcatheter aortic valve replacement using cross-sectional 3-dimensional transesophageal echocardiography. J Am Coll Cardiol. 2013;61(9):908-16.

[36] Vaquerizo B, Spaziano M, Alali J, Mylote D, Theriault-Lauzier P, Alfagih R, et al. Three-dimensional echocardiography vs. computed tomography for transcatheter aortic valve replacement sizing. Eur Heart J Cardiovasc Imaging. 2016;17(1):15-23.

[37] Khalique OK, Kodali SK, Paradis JM, Nazif TM, Williams MR, Einstein AJ, et al. Aortic annular sizing using a novel 3-dimensional echocardiographic method use and comparison with cardiac computed tomography. Circ Cardiovasc Imaging. 2014;7(1):155-63.

[38] Khalique OK, Hamid NB, White JM, Bae DJ, Kodali SK, Nazif TM, et al. Impact of Methodologic Differences in Three-Dimensional Echocardiographic Measurements of the Aortic Annulus Compared with Computed Tomographic Angiography Before Transcatheter Aortic Valve Replacement. J Am Soc Echocardiogr. 2017;30(4):414-21.

[39] García-Martín A, Lázaro-Rivera C, Fernández-Golfín C, Salido-Tahoces L, Moya-Mur JL, Jiménez-Nacher JJ, et al. Accuracy and reproducibility of novel echocardiographic three-dimensional automated software for the assessment of the aortic root in candidates for transcatheter aortic valve replacement. Eur Heart J Cardiovasc Imaging. 2016;17(7):772-8.

[40] Prihadi EA, van Rosendael PJ, Vollema EM, Bax JJ, Delgado V, Ajmone Marsan N. Feasibility, Accuracy, and Reproducibility of Aortic Annular and Root Sizing for Transcatheter Aortic Valve Replacement Using Novel Automated Three-Dimensional Echocardiographic Software: Comparison with Multi–Detector Row Computed Tomography. J Am Soc Echocardiogr. 2018 apr;31(4):505-14.e3.

[41] Stella S, Italia L, Geremia G, Rosa I, Ancona F, Marini C, et al. Accuracy and reproducibility of aortic annular measurements obtained from echocardiographic 3D manual and semi-automated software analyses in patients referred for transcatheter aortic valve implantation: implication for prosthesis size selection. Eur Heart J Cardiovasc Imaging. 2019;20(1):45-55.

[42] Podlesnikar T, Prihadi EA, van Rosendael PJ, Vollema EM, van der Kley F, de Weger A, et al. Influence of the Quantity of Aortic Valve Calcium on the Agreement Between Automated 3-Dimensional Transesophageal Echocardiography and Multidetector Row Computed Tomography for Aortic Annulus Sizing. Am J Cardiol. 2018;121(1):86-93.

[43] Zamorano JL, Badano LP, Bruce C, Chan Kl, Gonçalves A, Hahn RT, et al. EAE/ASE Recommendations for the Use of Echocardiography in New Transcatheter Interventions for Valvular Heart Disease. J Am Soc Echocardiogr. 2011;24(9):937-65.

[44] Bagur R, Rodés-Cabau J, Doyle D, De Larochellière R, Villeneuve J, Lemieux J, et al. Usefulness of TEE as the primary imaging technique to guide transcatheter transapical aortic valve implantation. J Am Coll Cardiol Img. 2011;4(2):115-24.

[45] Hahn RT, Little SH, Monaghan MJ, Kodali SK, Williams M, Leon MB, et al. Recommendations for comprehensive intraprocedural echocardiographic imaging during TAVR. J Am Coll Cardiol Img. 2015;8(3):261-87.

[46] Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves. Eur Heart J Cardiovasc Imaging. 2016;17(6):589-90.

[47] Hahn RT, Pibarot P, Weissman NJ, Rodriguez L, Jaber WA. Assessment of paravalvular aortic regurgitation after transcatheter aortic valve replacement: intra-core laboratory variability. J Am Soc Echocardiogr. 2015;28(4):415-22.

[48] Auffret V, Lefevre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, et al. Temporal Trends in Transcatheter Aortic Valve Replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol. 2017;70(1):42-55.

[49] Hyman MC, Vemulapalli S, Szeto WY, Stebbins A, Patel PA, Matsouaka RA, et al. Conscious sedation versus general anesthesia for transcatheter aortic valve replacement: insights from the National Cardiovascular Data Registry Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2017;136(22):2132-40.

[50] Babaliaros V, Devireddy C, Lerakis S, Leonardi R, Iturra SA, Mavromatis K, et al. Comparison of transfemoral transcatheter aortic valve replacement performed in the catheterization laboratory (minimalist approach) versus hybrid operating room (standard approach): outcomes and cost analysis. J Am Coll Cardiol Intv. 2014;7(8):898-904.

[51] Kamioka N, Wells J, Keegan P, Lerakis S, Binongo J, Corrigan F, et al. Predictors and Clinical Outcomes of Next-Day Discharge After Minimalist Transfemoral Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv. 2018;11(2):107-15.

[52] Husser O, Fujita B, Hengstenberg C, Frerker C, Beckmann A, Möllmann H, et al. Conscious Sedation Versus General Anesthesia in Transcatheter Aortic Valve Replacement: the German Aortic Valve Registry. J Am Coll Cardiol Intv. 2018;11(6):567-78.

[53] Bartel T, Edris A, Velik-Salchner C, Muller S. Intracardiac echocardiography for guidance of transcatheter aortic valve implantation under monitored sedation: a solution to a dilemma? Eur Heart J Cardiovasc Imaging. 2016;17(1):1-8.

[54] Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012 oct;60(15):1438-54.

[55] Pislaru SV, Nkomo VT, Sandhu GS. Assessment of Prosthetic Valve Function After TAVR. J Am Coll Cardiol Img. 2016;9(2):193-206.

[56] Dvir D, Bourguignon T, Otto CM, Hahn RT, Rosenhek R, Webb JG, et al. Standardized Definition of Structural Valve Degeneration for Surgical and Transcatheter Bioprosthetic Aortic Valves. Circulation. 2018;137(4):388-99.

[57] Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and sur- gical aortic bioprosthetic valves: a consensus statement from the Euro- pean Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017;38(45):3382-90.

[58] Kodali S, Pibarot P, Douglas PS, Williams M, Xu K, Thourani V, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J. 2015;36(7):449-56.

[59] Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013;61(15):1585-95.

[60] Ribeiro HB, Orwat S, Hayek SS, Larose É, Babaliaros V, Dahou A, et al. Cardiovascular Magnetic Resonance to Evaluate Aortic Regurgitation After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;68(6):577-85.

[61] Foroutan F, Guyatt GH, Otto CM, Siemieniuk RA, Schandelmaier S, Agoritsas T, et al. Structural valve deterioration after transcatheter aortic valve implantation. Heart. 2017;103(23):1899-905.

[62] Bonnichsen CR, Pellikka PA. Prosthetic Valve Thrombus Versus Pannus. Circ Cardiovasc Imaging. 2015;8(12).

[63] Del Trigo M, Muñoz-Garcia AJ, Wijeysundera HC, Nombela-Franco L, Cheema AN, Gutierrez E, et al. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. J Am Coll Cardiol. 2016;67(6):644-55.

[64] Del Trigo M, Muñoz-García AJ, Latib A, Auffret V, Wijeysundera HC, Nombela-Franco L, et al. Impact of anticoagulation therapy on valve haemodynamic deterioration following transcatheter aortic valve replacement. Heart. 2018;104(10):814-20.

[65] Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, et al. Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis. Circ Cardiovasc Interv. 2015;8(4).

[66] Franzone A, Pilgrim T, Haynes AG, Lanz J, Asami M, Praz F, et al. Transcatheter aortic valve thrombosis: incidence, clinical presentation and long-term outcomes. Eur Heart J Cardiovasc Imaging. 2018;19(4):398-404.

[67] Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. J Am Coll Cardiol Intv. 2017;10(7):686-97.

[68] Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. Circ Cardiovasc Interv. 2015;8(4):1-9.

[69] Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2016;37(28):2263-71.

[70] Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, et al. Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications. J Am Coll Cardiol. 2016;68(19):2059-69.

[71] Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, et al. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. N Engl J Med. 2015;373(21):2015-24.

[72] Sondergaard L, De Backer O, Kofoed KF, Jilaihawi H, Fuchs A, Chakravarty T, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. Eur Heart J. 2017;38(28):2201-7.

[73] Chakravarty T, Søndergaard L, Friedman J, De Backer O, Berman D, Kofoed KF, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017;389(10087):2383-92.

[74] Vollema EM, Kong WKF, Katsanos S, Kamperidis V, Van Rosendael PJ, Van Der Kley F, et al. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. Eur Heart J. 2017;38(16):1207-17.

[75] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J. 2015;36(44):3075-128.

[76] Berdejo J, Shibayama K, Harada K, Tanaka J, Mihara H, Gurudevan SV, et al. Evaluation of vegetation size and its relationship with embolism in infective endocarditis: a real-time 3-dimensional transesophageal echocardiography study. Circ Cardiovasc Imaging. 2014;7(1):149-54.

[77] Latib A, Naim C, De Bonis M, Sinning JM, Maisano F, Barbanti M, et al. TAVR-associated prosthetic valve infective endocarditis: results of a large, multicenter registry. J Am Coll Cardiol. 2014;64(20):2176-8.

[78] Regueiro A, Linke A, Latib A, Ihlemann N, Urena M, Walther T, et al. Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital death. JAMA. 2016;316(10):1083-92.

[79] Pizzi MN, Roque A, Fernandez-Hidalgo N, Cuellar-Calabria H, Ferreira-Gonzalez I, Gonzalez-Alujas MT, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18F-fluordeoxyglucose positron emission tomography. Circulation. 2015;132(12):1113-26.

[80] Salaun E, Sportouch L, Barral PA, Hubert S, Lavoute C, Casalta AC, et al. Diagnosis of Infective Endocarditis After TAVR: Value of a Multimodality Imaging Approach. J Am Coll Cardiol Img. 2018;11(1):143-6.

8

TRANSCATHETER AORTIC VALVE THROMBOSIS: THE RELATION BETWEEN HYPO-ATTENUATED LEAFLET THICKENING, ABNORMAL VALVE HEMODYNAMICS, AND STROKE

E. Mara Vollema*, William K.F. Kong*, Spyridon Katsanos, Vasileios Kamperidis, Philippe J. van Rosendael, Frank van der Kley, Arend de Weger, Nina Ajmone Marsan, Victoria Delgado, Jeroen J. Bax

*Drs. Vollema and drs. Kong contributed equally to this manuscript.

Published in Eur Heart J. 2017; 38(16):1207-1217

ABSTRACT

AIMS

The presence of hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion on multi- detector row computed tomography (MDCT) has been proposed as a possible marker for early transcatheter aortic valve thrombosis. However, its association with abnormal valve hemodynamics on echocardiography (another potential marker of thrombosis) and clinical outcomes (stroke) remains unclear. The present study evaluated the prevalence of HALT on MDCT and abnormal valve hemodynamics on echocardiography. In addition, the occurrence of ischemic stroke and/or transient ischemic attack (TIA) was assessed.

METHODS AND RESULTS

A total of 434 patients (mean age 80±7 years, 51% male) who underwent transcatheter aortic valve replacement (TAVR) were evaluated. Transcatheter valve hemodynamics were assessed on echocardiography at discharge, 6 months, and thereafter yearly (up to 3 years post-TAVR). The presence of HALT and/or reduced leaflet motion was assessed on MDCT performed 35 days [interquartile range 19-210] after TAVR in 128 of these 434 patients. Possible TAVR valve thrombosis was defined by mean transvalvular gradient ≥20 mmHg and aortic valve area (AVA) ≤1.1 cm^2 on echocardiography or by the presence of HALT or reduced leaflet motion on MDCT. The occurrence of ischemic stroke/TIA at follow-up was recorded. HALT and/or reduced leaflet motion was present in 12.5% of 128 patients undergoing MDCT, and was associated with a slightly higher mean transvalvular gradient (12.4±8.0 mmHg vs. 9.4±4.3mmHg; *P*=0.026) and smaller AVA (1.49±0.39 cm^2 vs. 1.78±0.45 cm^2, *P*=0.017). Only one patient with HALT on MDCT revealed abnormal valve hemodynamics on echocardiography. At 3-year follow-up, abnormal valve hemodynamics on echocardiography were observed in 3% of patients. HALT on MDCT and abnormal valve hemodynamics on echocardiography were not associated with increased risk of ischemic stroke/TIA.

CONCLUSION

On MDCT, 12.5% of patients showed HALT or reduced leaflet motion, whereas only one of these patients had abnormal valve hemodynamics on echocardiography. Neither HALT nor increased transvalvular gradient were associated with stroke/TIA.

Introduction

Over the last decade, transcatheter aortic valve replacement (TAVR) has emerged as an effective alternative to surgical replacement for patients with symptomatic severe aortic stenosis who are at high risk for surgery or are considered inoperable [1, 2]. The promising results of early randomized trials [1–3] have led to the use of this technology in intermediate- to low-risk patients [4–6], with the first large randomized controlled trial showing non-inferiority of TAVR compared with surgical replacement [7]. Since these patients are often younger, valve durability has become an important concern. Recent studies have reported good durability of TAVR prostheses, for both balloon- and self-expandable valves, up to 5 years follow-up using transthoracic echocardiography [8–12]. However, sophisticated 3- and 4-dimensional computed tomography (CT) have described hypo-attenuated leaflet thickening (HALT) with reduced leaflet motion of TAVR prostheses, which could be an early marker of prosthetic valve thrombosis [13–15]. The effects of this leaflet thickening and restrictive motion on valve hemodynamics (assessed with echocardiography) and clinical outcome (transient ischemic attack or stroke) remain unclear and has led to ongoing debate on how to follow-up patients with TAVR valves and which antiplatelet/anticoagulation regime would be more appropriate. The present study aimed at evaluating the occurrence of abnormal valve hemodynamics (suggesting valve thrombosis) in both balloon- and self-expandable TAVR prostheses in a large patient cohort and compared these with the presence of HALT and/or reduced leaflet motion on dynamic multi-detector row CT (MDCT) data in a subpopulation. In addition, the clinical outcome (occurrence of ischemic stroke and/or transient ischemic attack [TIA]) was assessed.

Methods

Patient population and data collection

A total of 434 patients who underwent TAVR for severe aortic stenosis or degenerated biological aortic valve prosthesis between November 2007 and June 2015 at the Leiden University Medical Center were analyzed. Severe aortic stenosis was defined according to current recommendations: an aortic valve area <1.0 cm^2 or indexed aortic valve area <0.6 cm^2/m^2 and/or mean transvalvular pressure gradient >40mmHg [16]. The decision of TAVR was based on heart team discussions.

Patients were followed-up clinically at the outpatient clinic at 1–3, 6, and 12 months and thereafter yearly. A subgroup of 128 patients underwent post-procedural MDCT (median 35 days [interquartile range 19–210] after TAVR) in the period of 2008–2013 as per institutional protocol (if there were no contraindications) and at the discretion of the treating cardiologist (see Supplementary Figure 4).

Demographic and clinical data were collected using electronic records (EPD Vision, version 11.4.29.0, EPD Vision, Leiden, The Netherlands). TAVR success and complications were registered as defined by the Valve Academic Research Consortium-2 (VARC-2) [17]. After the procedure, all patients received aspirin life long, whereas clopidogrel was prescribed for 3 months between 2007 and 2011 and thereafter for 1 month. If concomitant oral anticoagulants were used, aspirin was not prescribed.

The institutional review board approved this retrospective analysis of clinically ac-

quired data and waived the need for patient written informed consent.

TRANSCATHETER AORTIC VALVE REPLACEMENT PROCEDURE

TAVR was performed via transfemoral access, if adequate iliofemoral arterial anatomy was present as assessed with pre-procedural MDCT, or via transapical access otherwise. Transcatheter valve size was selected based on MDCT measurements of the aortic annulus, as previously described [18]. Contemporary balloon- and self-expandable valve prostheses were used: Edwards SAPIEN, SAPIEN XT, SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA), and the Medtronic CoreValve system (Medtronic, MN, Minnesota). Implantation procedures were performed under general anaesthesia with fluoroscopy and transesophageal echocardiography guidance. The hemodynamics of the implanted transcatheter valve were assessed immediately. If significant paravalvular or, less frequently, transvalvular regurgitation were noted, reballooning of the prosthesis or valve-in-valve implantation were performed, respectively.

ECHOCARDIOGRAPHIC FOLLOW-UP

Transthoracic echocardiography was performed at discharge, 6 and 12 months and yearly thereafter (up to 3 years) to assess the transcatheter valve hemodynamics over time. Commercially available ultrasound systems equipped with 3.5MHz or M5S transducers (Vivid-7 or E9 systems, General Electric Vingmed, Horten, Norway) were used and 2-dimensional, colour, continuous, and pulsed wave Doppler data were acquired from parasternal and apical views with the patient in the left lateral decubitus position. Images were stored digitally on hard disks for offline analysis (EchoPac version BT13; GE Medical Systems). Left ventricular ejection fraction was measured from the apical 2- and 4-chamber views using Simpson's method [19]. Aortic valve peak jet velocity was estimated from the continuous wave Doppler recordings obtained on the 3- or 5-chamber apical views and, if needed, on the right parasternal view using the Pedoff probe [16]. The peak and mean transaortic pressure gradients were calculated according to the Bernoulli equation. The aortic valve area was calculated using the continuity equation.

According to current recommendations, abnormal transcatheter aortic valve hemodynamics indicating valve stenosis caused probably by thrombosis was based on a mean transvalvular gradient ≥20mmHg and an aortic valve area ≤1.1 cm^2 [20]. The presence of paravalvular leakage at follow-up was graded using a multiparametric approach that integrates valve structure and motion, regurgitant flow characteristics including the circumferential extent of the paravalvular leak and left ventricular dimensions, as recommended by the VARC-2 criteria [17].

MULTI-DETECTOR ROW COMPUTED TOMOGRAPHY FOLLOW-UP

Using a 64-row (Aquilion 64; Toshiba Medical Systems, Tochigi-ken, Japan) or a 320-row (AquilionOne; Toshiba Medical Systems, Tochigiken, Japan) CT scanners, electrocardiographic-gated and contrastenhanced data acquisition of the aortic root was performed using previously described protocols [21, 22]. MDCT data were reconstructed at each 10% of RR-interval of the cardiac cycle. All data sets were analysed using dedicated post-processing software (Vitrea FX 6.5; Vital Images, Minnetonka, MN).

The structure and motion of the transcatheter valve leaflets were assessed. Struc-

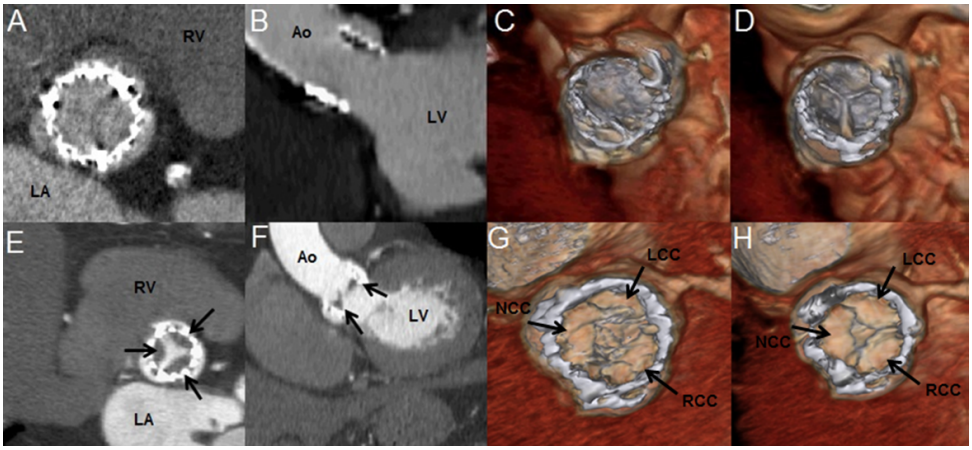


Figure 1: Multi-detector row computed tomography (MDCT) reconstructions after transcatheter aortic valve replacement with examples of normal structure of TAVR prosthesis (*panels A-D*) and transcatheter prosthesis with hypo-attenuated leaflet thickening and reduced leaflet motion (*panels E-H*). The double oblique reconstruction (*panel A*) on diastole of the transcatheter valve shows the stent frame and the leaflets without thickening and the coronal view of the transcatheter valve in systole (*panel B*) where the leaflets opened. The 3D volume renderings in systole (*panel C*) and diastole (*panel D*) show normal opening and closing of the prosthesis leaflets. In *panel E*, thickening of the prosthesis leaflets with hypo-attenuated lesions can be observed on the double oblique reconstruction. During systole, the leaflets remain immobile (*panel F*). *Panels G* and *H* show the 3D volume renderings in systole and diastole, respectively, with thickened leaflets that remain immobile (arrows). Ao, aorta; LA, left atrium; LCC, left coronary cusp of aortic valve; LV, left ventricle; NCC, non-coronary cusp of aortic valve; RCC, right coronary cusp of aortic valve; RV, right ventricle.

tural assessment focused on the presence of HALT, frame eccentricity and expansion, and transcatheter implantation depth. HALT was defined as hypo-attenuated thickening with or without reduced motion of one or more transcatheter valve leaflets and was assessed by 2-dimensional multiplanar reformation planes, and 3- and 4-dimensional volume rendered movies throughout the entire cardiac cycle (Figure 1) [15]. Stent eccentricity and expansion were evaluated at 3 levels (at inflow, mid-portion, and outflow) by using planimetered outer stent area and minimal and maximal diameters as described earlier [13, 15]. An expansion ratio of ≤90% of nominal stent dimensions at all three levels was defined as underexpansion. Non-circularity of the transcatheter frame was defined as an eccentricity index >0.1 at all three levels, with eccentricity index calculated as 1-(minimal diameter/maximal diameter) [13, 15]. In addition, implant depth was measured and defined as the distance between the aortic annular plane and lower transcatheter valve prosthesis rim.

Clinical end-points at follow-up

Patients were followed-up prospectively at the outpatient clinic of the Leiden University Medical Centre at 1–3, 6, and 12 months follow-up after TAVR, and yearly thereafter (at the referral centre). Patients with suspected neurologic events were evaluated by a neurologist. For this specific analysis, the occurrence of ischemic stroke (including TIA and ischemic stroke) was recorded.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±standard deviation or as median and interquartile range as appropriate. Categorical variables are expressed as frequencies and percentages. Differences between groups were analyzed using the unpaired Student *t*-test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed variables. Categorical variables were compared with the χ^2 test. General linear mixed models were used to analyze changes in transcatheter valve hemodynamics over time for the overall population and compared between patients with vs. without HALT and/or reduced leaflet motion on MDCT and between patients with vs. without stroke or TIA. Bonferroni's post-hoc analysis was used to compare the differences between groups over time. Statistical analyses were performed with SPSS software (version 23.0; IBM, Armonk, NY), all analyses were two-sided with *P* values <0.05 considered statistically significant.

RESULTS

PATIENT POPULATION

Baseline clinical, echocardiographic, and procedural characteristics for the overall population (mean age 80±7 years, 51% male) are shown in Table 1. Anticoagulant medication (vitamin K antagonists) was used in 37% of the patients, while 52% used aspirin and 33% clopidogrel. Baseline transthoracic echocardiography showed severe aortic stenosis (mean transvalvular gradient 42.3±18.1 mmHg, aortic valve area 0.78±0.28 cm^2) and mean LVEF 53.9±16.1%. The majority of the patients had tricuspid anatomy of the aortic valve, 21 (5%) had a bicuspid aortic valve and 13 (3%) patients underwent valve-in-valve procedure. TAVR access was transfemoral in 52% of the patients and the remaining 48% underwent transapical TAVR. The most frequently implanted prosthesis size was 26 mm (54%). The majority of the patients received a balloon-expandable transcatheter valve (91%), whereas 40 patients received a self-expandable prosthesis. At discharge, moderate and severe paravalvular regurgitation was observed in 7% of the patients. The post-procedural outcomes according to the VARC-2 criteria are summarized in the Supplementary Table 7.

ABNORMAL VALVE HEMODYNAMICS ON ECHOCARDIOGRAPHY AT FOLLOW-UP

During the follow-up period, transthoracic echocardiography was performed in 431 patients at hospital discharge, in 350 patients at 6 months follow-up, in 229 patients at 1-year follow-up and in 116 and 61 patients at 2 and 3 years follow-up, respectively. After TAVR, a significant decrease in transvalvular gradients (peak gradient: from 65.5±26.5 mmHg to 17.1±8.1 mmHg, *P*<0.001; mean gradient: from 42.3±18.1 mmHg to 9.3±4.7 mmHg, *P*<0.001) and an increase in aortic valve area (from 0.78±0.28 cm^2 to 1.99±0.56 cm^2, *P*<0.001) were observed. Table 2 and Figure 2 present the hemodynamic changes of TAVR prostheses over time for the overall population. The peak and mean transvalvular gradients remained unchanged. However, the aortic valve area showed a statistically significant decrease after hospital discharge until 1 year follow-up, with a maximum decrease to 1.61±0.51 cm^2. In addition, a significant increase in LVEF was noted (from

Table 1: Baseline demographic, procedural and echocardiographic characteristics of the entire patient population undergoing transcatheter aortic valve replacement (TAVR).

Variables	Total population (N = 434)
Clinical characteristics	
Female gender, *N* (%)	212 (49)
Age (years)	80±7
BSA (m^2)	1.85±0.2
Logistic EuroSCORE (%)	21±14
Creatinin level (µmol/ml)	93 [73;115]
Coronary artery disease, *N* (%)	271(62)
NYHA classification, *N* (%)	
I-II	192 (44)
III-IV	242 (56)
Prior myocardial infarction, *N* (%)	100(23)
Diabetes, *N* (%)	125 (29)
Hypertension, *N* (%)	345 (80)
Hyperlipidaemia, *N* (%)	319 (74)
Peripheral vascular disease, *N* (%)	147(34)
History of smoking, *N* (%)	134 (31)
Atrial fibrillation, *N* (%)	94 (22)
Medication, *N* (%)	
ACE-inhibitors/ARB	239 (55)
Calcium antagonist	116 (27)
Beta-blocker	26 7(62)
Diuretics	275 (63)
Spironolactone	68 (16)
Statins	277 (64)
Vitamin K antagonists	162 (37)
Aspirin	224 (52)
Clopidogrel	141 (33)
Baseline echocardiography	
Valve anatomy, *N* (%)	
Tricuspid	400 (92)
Bicuspid	21 (5)
Biological valve prosthesis, *N* (%)	13 (3)
Peak transvalvular gradient (mmHg)	65.5±26.5
Mean transvalvular gradient (mmHg)	42.3±18.1
Aortic valve area (cm^2)	0.78±0.28
Left ventricular ejection fraction (%)	53.9±16.1
Procedural variables	
TAVR access route, *N* (%)	
Transfemoral	224 (52)
Transapical	210 (48)
Valve type, *N* (%)	
Edwards SAPIEN	117 (27)
Edwards SAPIEN XT	162 (37)
Edwards SAPIEN 3	115 (27)
Medtronic CoreValve	40 (9)
Prosthesis size, *N* (%)	
23 mm	121 (28)
26 mm	236 (55)
29 mm	77 (18)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BSA, body surface area; NYHA, New York Heart Association functional classification; TAVR, transcatheter aortic valve replacement.

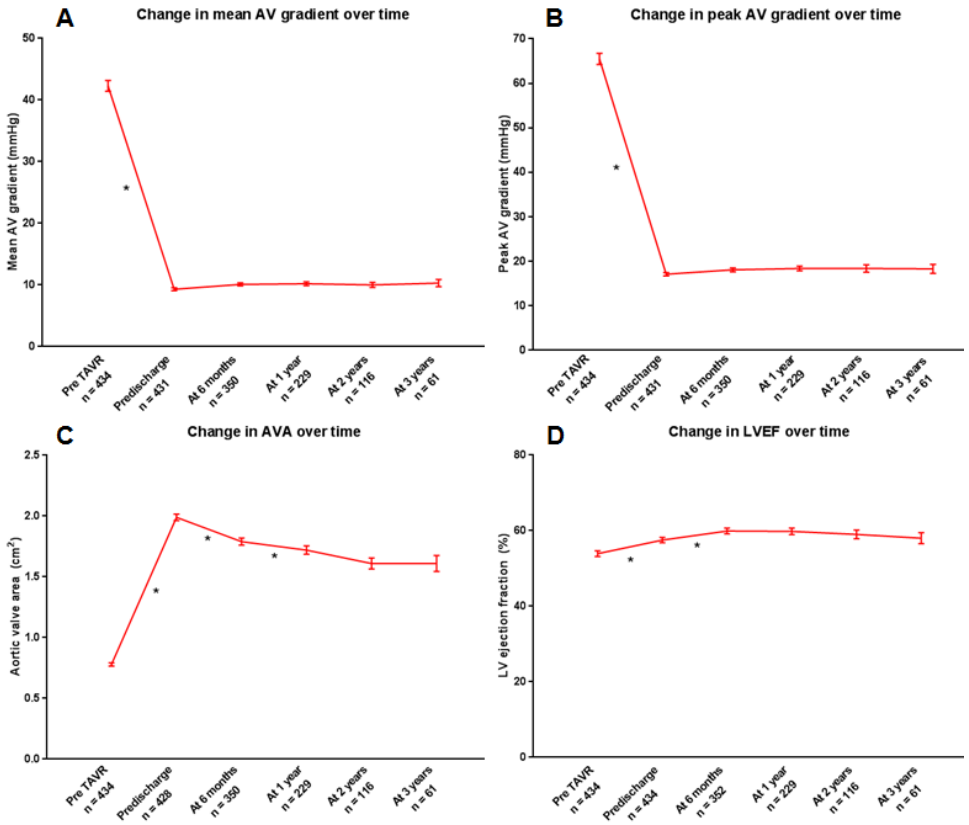


Figure 2: Echocardiographic follow-up for the overall population. Changes in mean and peak aortic valve gradients, aortic valve area and LVEF were analysed with linear mixed models. The means and standard error of the mean are presented. AV, aortic valve; AVA, aortic valve area; LV, left ventricular; LVEF, left ventricular ejection fraction. *Significant changes between time points (P<0.05).

Table 2: Echocardiographic characteristics of the entire patient population undergoing transcatheter aortic valve replacement (TAVR) over time.

Variables	Pre-TAVR (N = 434)	Pre-discharge (N = 431)	6 months (N = 350)	1 year (N = 229)
LVOT diameter (cm)	2.1±0.2	2.0±0.2	2.0±0.2	2.0±0.2
Stroke volume (ml)	71.4±22.0	72.5±21.8	76.4±22.4	75.2±22.5
Stroke volume index (ml/m^2)	38.9±11.9	39.4±11.3	41.6±12.1	40.5±11.3
Mean gradient (mmHg)	42.3±18.1	9.3±4.7	10.1±4.9	10.2±4.9
Peak gradient (mmHg)	65.5±26.5	17.1±8.1	18.1±8.2	18.4±8.3
Aortic valve area (cm^2)	0.78±0.28	1.99±0.56	1.79±0.54	1.73±0.52
LV ejection fraction (%)	53.9±16.1	57.5±14.7	59.9±13.9	59.8±12.9

LVOT, left ventricular outflow tract; LV, left ventricular; TAVR, transcatheter aortic valve replacement.

53.9±16.1% to 57.5±14.7%, P<0.001) (Figure 2).

According to current recommendations, abnormal valve hemodynamics (mean trans-valvular gradient ≥20mmHg and aortic valve area ≤1.1 cm^2) indicating possible transcatheter valve thrombosis were observed in 1 (0.2%) patient before discharge, 6 (2%) patients at 6 months, 4 (2%) at 1 year, 0 (0%) patients at 2 years, and 2 (3%) at 3 years follow-up. Worsening of paravalvular or transvalvular regurgitation to moderate regurgitation was observed in 17 (4%) patients at follow-up.

HALT OR REDUCED LEAFLET MOTION ON MDCT AT FOLLOW-UP

In a subgroup of 128 patients with analysable post-TAVR MDCT data, the presence of HALT and/or reduced leaflet motion was evaluated. The MDCT data were acquired at a median interval of 35 [interquartile range 19–210] days after TAVR (see Supplementary Figure 4). The presence of HALT and/or reduced leaflet motion was noted in 16 (12.5%) patients. Baseline clinical, echocardiographic, and procedural characteristics between patients showing HALT and/or reduced leaflet motion and patients without are presented in Tables 3 and 4. There were no statistically significant differences between both groups with the exception of diabetes mellitus which was more prevalent among patients without HALT compared to patients with HALT and/or reduced leaflet motion (32% vs. 6%, respectively; P=0.033). Importantly, there were no differences in anticoagulation use prior to MDCT (38 [30%] in the overall group, 35 [31%] in patients without HALT and 3 [19%] patients with HALT and/or reduced leaflet motion, P=0.603). Table 5 shows the post-TAVR MDCT characteristics in patients with and without HALT. Both groups were comparable in terms of stent expansion, eccentricity index at the inflow and outflow levels of the stent and valve implantation depth. Patients with HALT and/or reduced leaflet motion showed slightly more circular stent deployment at the mid-portion level as compared with patients without HALT (0.01 [0.01;0.01] vs. 0.01 [0.01;0.02], respectively; P=0.041).

CORRELATION BETWEEN ABNORMAL VALVE HEMODYNAMICS AND HALT

Concomitant presence of HALT and/or reduced leaflet motion and abnormal valve hemodynamics (defined by mean transvalvular gradient ≥20mmHg and aortic valve area ≤1.1 cm^2) suggesting valve thrombosis was observed in only one patient (Figure 1). Figure 3 presents the changes in echocardiographic parameters of transcatheter valve function at follow-up in patients with HALT on MDCT and patients without. Patients showing HALT and/or reduced leaflet motion on post-TAVR MDCT had higher peak and mean transvalvular gradients and smaller aortic valve area at follow-up as compared with patients without, but the difference was statistically significant only for the mean transvalvular gradient at 6 months follow-up (12.4±8.0 mmHg vs. 9.4±4.3 mmHg, respectively; P=0.026) and for the aortic valve area at the echocardiogram performed at the time of MDCT (1.49±0.39 cm^2 vs. 1.78±0.45 cm^2, respectively; P=0.017) and at 6 months (1.32±0.35 cm^2 vs. 1.76±0.49 cm^2, respectively; P<0.001). LVEF was comparable in both groups without significant differences over time. Similarly, both groups were comparable in terms of paravalvular regurgitation grade over time.

CORRELATION BETWEEN STROKE AND ECHOCARDIOGRAPHIC/MDCT FINDINGS

A total of 14 (3.2%) patients were diagnosed with stroke (N = 9)/TIA (N = 5) after TAVR. Possible transcatheter aortic valve thrombosis on echocardiography (mean transvalvular gradient ≥20 mmHg and aortic valve area ≤1.1 cm^2) was not present in any of the patients diagnosed with stroke/TIA. Similarly, HALT and/or reduced leaflet motion was not observed on MDCT in any of the patients presenting with stroke/TIA. Table 6 shows the mean and peak transvalvular gradients, aortic valve area, and LVEF over time for patients with vs. without stroke/TIA. There were no differences in valve hemodynamics between patients with and without stroke/TIA (Table 6).

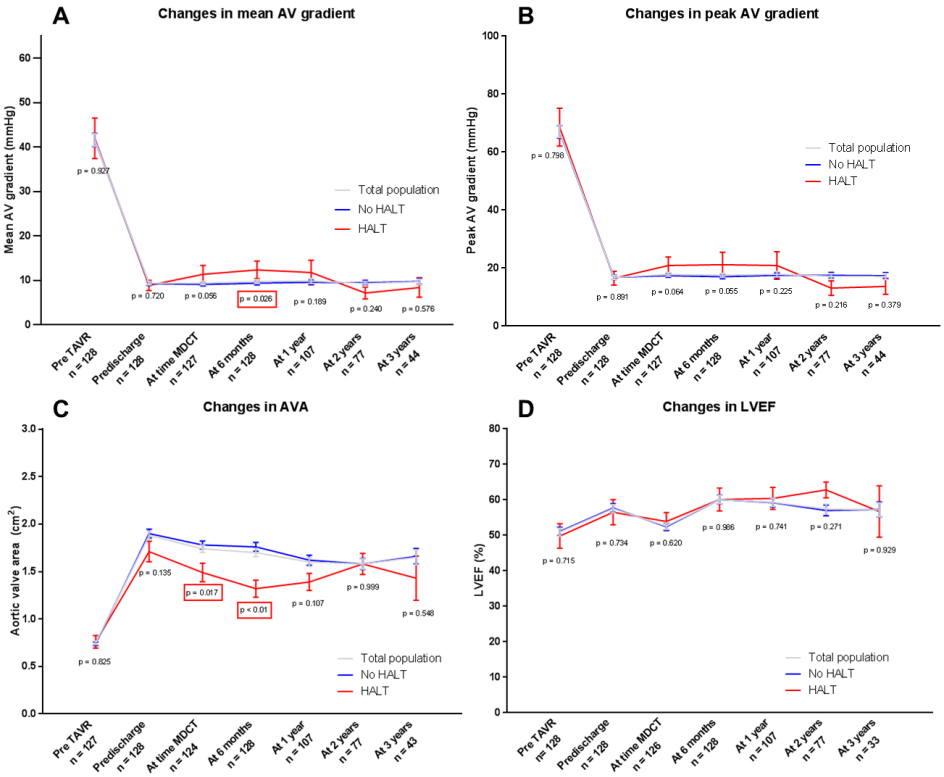


Figure 3: Echocardiographic follow-up of patients with and without evidence of hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion on MDCT. Changes in mean and peak aortic valve gradients, aortic valve area and LVEF were analysed with linear mixed models. The means and standard error of the mean are presented. AV, aortic valve; AVA, aortic valve area; HALT, hypo-attenuated leaflet thickening; LVEF, left ventricular ejection fraction; MDCT: multi-detector row computed tomography. *P* values indicate differences between groups (HALT vs. no HALT).

Table 3: Baseline clinical characteristics of patients with and without hypo-attenuated leaflet thickening (HALT) and/or restrictive leaflet motion.

Variables	Patients with post-TAVR MDCT (N = 128)	No HALT (N = 112)	HALT (N = 16)	*P* value
Female gender, *N* (%)	62 (48)	54 (48)	8 (50)	0.894
Age (years)	81±7	81±7	81±8	0.968
BSA (m^2)	1.75±0.3	1.77±0.3	1.62±0.3	0.084
Logistic EuroSCORE (%)	23±13	23±13	23±13	0.939
Creatinin level (µmol/ml)	86 [72;103]	88 [73;103]	77 [67; 103]	0.303
Coronary artery disease, *N* (%)	86 (67)	74 (66)	12 (75)	0.477
NYHA classification, *N* (%)				0.211
I-II	51 (40)	43 (38)	8 (50)	
III-IV	77 (60)	69 (62)	8 (50)	
Prior MI, *N* (%)	27 (21)	24 (21)	3 (19)	0.806
PCI within 30 days, *N* (%)	29 (23)	25 (22)	4 (25)	0.811
Prior thromboembolism, *N* (%)	4 (3)	4 (4)	0 (0)	0.442
History of cancer, *N* (%)	30 (24)	26 (23)	4 (25)	0.890
Diabetes, *N* (%)	37 (29)	36 (32)	1 (6)	0.033
Hypertension, *N* (%)	98 (77)	87 (78)	11 (69)	0.430
Hyperlipidemia, *N* (%)	76 (59)	68 (61)	8 (50)	0.414
History of smoking, *N* (%)	58 (45)	54 (48)	4 (25)	0.081
Previous stroke or TIA, *N* (%)	27 (21)	21 (19)	6 (38)	0.086
Atrial fibrillation, *N* (%)	37 (29)	33 (30)	4 (25)	0.713
Only anticoagulation therapy, *N* (%)	29 (23)	26 (23)	3 (19)	0.603
Anticoagulation + antiplatelet therapy, *N* (%)	9 (7)	9 (8)	0(0)	

BSA, body surface area; HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; MI, myocardial infarction; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

Table 4: Baseline echocardiographic and procedural characteristics of patients with and without hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion.

Variables	**Patients with post-TAVR MDCT (N = 128)**	**No HALT (N = 112)**	**HALT (N = 16)**	***P* value**
Baseline echocardiography				
Valve anatomy, *N* (%)				0.589
Tricuspid	121 (94)	105 (94)	16 (100)	
Bicuspid	6 (5)	6 (5)	0 (0)	
Biological valve prosthesis	1 (1)	1 (1)	0 (0)	
Peak TV gradient (mmHg)	67.2±24.0	67.0±23.8	68.6±26.2	0.798
Mean TV gradient (mmHg)	41.6±16.1	41.6±15.9	42.0±18.2	0.927
Aortic valve area (cm^2)	0.75±0.22	0.74±0.21	0.76±0.26	0.825
LV ejection fraction (%)	50.9±12.7	51.1±12.6	49.8±13.9	0.715
Stroke volume (ml)	71.6±20.0	72.2±19.3	67.1±24.2	0.361
Procedural variables				
TAVR access route, *N* (%)				0.399
Transfemoral	44 (34)	37 (33)	7 (44)	
Transapical	84 (66)	75 (67)	9 (56)	
Valve type, *N* (%)				0.414
Edwards SAPIEN	76 (59)	68 (61)	8 (50)	
Edwards SAPIEN XT	52 (41)	44 (39)	8 (50)	
Edwards SAPIEN3	0 (0)	0 (0)	0 (0)	
Medtronic CoreValve	0 (0)	0 (0)	0 (0)	
Prosthesis size, *N* (%)				0.689
23 mm	38 (30)	33 (30)	5 (31)	
26 mm	85 (66)	74 (66)	11 (69)	
29 mm	5 (4)	5 (4)	0 (0)	
Post-dilatation performed, *N* (%)	20 (16)	17 (15)	3 (19)	0.713

HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; TAVR, transcatheter aortic valve replacement; TV, transvalvular.

Table 5: MDCT characteristics of patients with and without hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion.

Variables	Patients with post-TAVR MDCT (N = 128)	No HALT (N = 112)	HALT (N = 16)	*P* value
Stent expansion (%)				
Inflow	102±7	102±7	98±6	0.060
Mid-portion	106±8	106±9	106±6	0.796
Outflow	109±9	109±9	110±8	0.590
Underexpansion, *N* (%)	3 (2.3)	3 (2.7)	0 (0)	0.508
Stent eccentricity index				
Inflow	0.01 [0.01;0.02]	0.01[0.01;0.02]	0.01[0.01;0.01]	0.126
Mid-portion	0.01 [0.01;0.02]	0.01[0.01;0.02]	0.01[0.01;0.01]	0.041
Outflow	0.01 [0.01;0.02]	0.01[0.01;0.02]	0.01[0.01;0.01]	0.360
Eccentric, *N* (%)	1 (0.8)	1 (0.9)	0(0)	0.704
Valve implant depth (mm)	5.1±1.8	5.1±1.8	5.1±2.0	0.947

HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography; TAVR, transcatheter aortic valve replacement.

Discussion

The present study showed stable, normal hemodynamics and morphological features of transcatheter aortic valves during mid-term follow- up in a large cohort of patients treated with TAVR indicating good mid-term durability of these prosthetic valves. Only a mild, clinically irrelevant, decrease in aortic valve area was observed during the first year post-TAVR, while average transvalvular gradients remained within the normal range. Possible transcatheter valve thrombosis based on abnormal valve hemodynamics on echocardiography was rare (3% of patients at 3 years follow-up). Post-TAVR MDCT showed HALT and/or reduced leaflet motion in 12.5% of patients. In patients with HALT and/or reduced leaflet motion, echocardiographic transvalvular gradients were slightly higher and the aortic valve area was significantly smaller compared with patients without HALT. However, possible TAVR valve thrombosis by MDCT (presence of HALT and/or reduced leaflet motion) was only accompanied by abnormal valve hemodynamics on echocardiography (mean gradient ≥20mmHg and aortic valve area ≤1.1 cm^2) in one patient. These abnormal findings were not associated with an increased risk of ischemic stroke/TIA.

Echocardiographic valve hemodynamics after TAVR

Since TAVR is increasingly used as an alternative for surgical aortic valve replacement in intermediate- and low-risk patients, valvular prosthesis durability and structural integrity are important issues. Thrombosis of biological surgical aortic valves is a rare complication with a reported incidence ranging between 0.8% and 4% [23, 24]. In transcatheter aortic valve prostheses, the reported incidence of valve dysfunction and specifically thrombosis is low. Five-year follow-up data from the Placement of Aortic Transcatheter Valves (PARTNER) trial have shown stable valve hemodynamics in 348 high-risk patients

Table 6: Valve hemodynamics over time for patients with versus without stroke/TIA.

Variable	Stroke/TIA	Pre-TAVR (N = 434)	Pre-discharge (N = 431)	6 months (N = 350)	1 year (N = 229)	2 years (N = 116)	3 years (N = 61)
Mean gradient (mmHg)	Non stroke	42.4±18.2	9.3±4.7	10.1±4.9	10.2±5.0	10.0±4.7	10.3±4.6
	Stroke/TIA	40.3±17.0	9.1±3.4	11.0±4.5	9.0±3.1	9.6±4.8	11.2±5.2
Peak gradient (mmHg)	Non stroke	65.5±26.5	17.1±8.2	18.0±8.2	18.5±8.4	18.5±8.9	18.3±7.7
	Stroke/TIA	63.6±25.9	16.8±6.4	18.7±8.7	15.9±4.4	17.3±8.7	17.7±8.5
Aortic valve area (cm^2)	Non stroke	0.79±0.28	1.99±0.56	1.79±0.54	1.73±0.52	1.60±0.50	1.61±0.50
	Stroke/TIA	0.72±0.23	2.00±0.60	1.70±0.50	1.73±0.54	1.71±0.63	1.60±0.72
LV ejection fraction (%)	Non stroke	53.9±16.1	57.4±14.6	59.8±13.9	59.8±12.9	59.0±12.3	58.7±11.2
	Stroke/TIA	53.2±17.3	58.5±16.4	62.3±14.2	57.4±15.2	58.9±16.6	48.3±13.7

LV, left ventricular; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

(mean transvalvular gradient was 10.7 mmHg and aortic valve area was 1.6 cm^2) without occurrence of structural valve deterioration requiring surgical valve replacement [10, 11]. Similarly, Barbanti et al. [8] showed only a slight increase of mean transvalvular gradient (12.8±10.9 mmHg) 5 years after self-expanding transcatheter valve implantation in 353 high-risk patients. Late prosthesis failure occurred in 1.4% and was defined as symptomatic prosthesis stenosis, endocarditis, and severe transvalvular or paravalvular regurgitation. Mild prosthesis stenosis, defined by a mean gradient between 20 and 40 mmHg, was observed in 2.8% of patients [8]. Data from a multicentre study including 1521 patients treated with self-expandable (49.7%) and balloon-expandable prostheses (48.5%) reported an incidence of structural valve degeneration of 4.5% at 2 years of follow-up [25]. The relatively high incidence of valve degeneration in that registry compared with previous studies can be explained by the definition itself: absolute increase in mean transvalvular gradient ≥10 mmHg. An increase in mean transvalvular gradient ≥10 mmHg during follow-up can be caused by changes in loading conditions, stroke volume, or increase in body mass index leading to increased prosthesis–patient mismatch and not necessarily because of valve thrombosis or stenosis. Current recommendations define transcatheter aortic valve stenosis potentially caused by valve thrombosis when the mean transvalvular gradient is ≥20 mmHg and the aortic valve area is ≤1.1 cm^2 on echocardiography [20]. In the present study, aortic valve area and transvalvular aortic gradients remained stable during 3 years follow-up and 3% of the population showed abnormal valve hemodynamics at 3 years follow-up, consistent with previous studies. Therefore, based on echocardiographic criteria, transcatheter aortic valves appear to have good durability.

HALT AND/OR ABNORMAL LEAFLET MOTION ON MDCT, AND RELATION WITH ECHOCARDIOGRAPHIC VALVE HEMODYNAMICS

The high-spatial resolution of MDCT data has shown that abnormal leaflet motion with apposition of hypo-attenuated masses (HALT) in surgical and transcatheter valves may be more frequent than expected. Leetmaa et al. [13] observed low-attenuation masses attached to prosthetic valve leaflets on post-TAVR MDCT in 4% of patients (5/140). Pache et al. [15] reported a 10.3% (16/156 patients) prevalence of HALT after TAVR. Makkar et al. [14] evaluated the presence of leaflet motion and HALT using 4-dimensional MDCT in a clinical trial including 55 patients undergoing TAVR and two registries with 132 patients undergoing either TAVR or surgical aortic valve replacement. HALT was noted in 40% (22/55) of patients in the clinical trial, while it was only present in 13% (17/132) of patients included in the registries [14]. The factors associated with higher risk of developing HALT are still unclear. Reduced LVEF has been associated with higher prevalence of HALT [13], whereas use of anticoagulation has been associated with lower prevalence of HALT [14]. Importantly, adding anticoagulants to antiplatelet therapy resolved HALT and reduced leaflet motion rapidly [15]. Other procedural factors such as prosthesis frame deployment were not associated with HALT [14, 15]. Nevertheless, the relation between HALT and valve hemodynamics at short- and long-term follow-up remains unclear. The majority of the patients showing HALT did not have increased mean transvalvular gradients ≥20 mmHg or decreased aortic valve area ≤1.1 cm^2 (the echocardiographic definitions of possible prosthetic valve thrombosis) [13–15, 26]. In the present

study, the incidence of HALT on MDCT was 12.5%, comparable with previous studies [13, 15, 26]. The patients with HALT had a slightly more circular deployment of the transcatheter valve frame compared with those without HALT. The present study provides additional information by reporting transcatheter aortic valve hemodynamics at mid-term follow-up. Although there was a mild change in valve hemodynamics with an increase in both mean and peak transvalvular gradients and a significant decrease in aortic valve area in patients with HALT and/or reduced leaflet motion shortly after TAVR compared with their counterparts, concomitant mean transvalvular gradient ≥20 mmHg and aortic valve area ≤1.1 cm^2 was anecdotally observed during the 3 years of follow-up (1 patient). Therefore, the HALT and/or reduced leaflet motion on MDCT was not accompanied by functional echocardiographic criteria of thrombosis.

CLINICAL IMPLICATIONS OF HALT

While surgical prosthetic aortic valve thrombosis is associated with an increased risk of stroke [23, 24], this association is not consistently observed with the presence of HALT on transcatheter aortic valve prostheses [13–15]. The reported rates of stroke and TIA in the Cohort A PARTNER trial ranged from 5.5% to 8.3% at 30 days and 1-year follow-up, respectively, and to 15.9% at 5 years follow-up [3, 11]. In the NOTION (Nordic Aortic Valve Intervention) trial, randomizing low surgical risk patients to TAVR or surgical aortic valve replacement, the rates of stroke and TIA were, respectively, 2.9% and 2.1% at 1-year follow-up [6]. In these trials, no structural valve degeneration was observed and valve hemodynamics remained stable over time. Therefore, these results suggest that the source of stroke/TIA may not primarily be related to the transcatheter valve or that the echocardiographic findings may not be sensitive enough to detect early structural changes of the valve before they present with increased gradients and that can cause embolic events. The use of MDCT showing the presence of HALT and reduced leaflet motion of transcatheter valves has questioned these assumptions. Similar to previous studies, patients in the present study who showed HALT and/or reduced leaflet motion on MDCT did not develop stroke/TIA at follow-up. However, the use of anticoagulation has been shown to restore the normal leaflet aspect and motion in patients who presented with HALT [14, 15] and it could be considered to perform MDCT in these patients for early detection of these structural changes. However, it remains unknown when and in whom the MDCT should be performed and if it should be systematically included in the surveillance of TAVR patients. The important associated risks of MDCT such as renal deterioration associated with the use of contrast and cumulative radiation should be weighed against the risk of stroke/TIA in elderly patients with associated comorbidities and, in the future, in younger patients. Current guidelines recommend transthoracic echocardiography within 6 weeks–3 months after implantation of bioprostheses, when there are changes in the clinical symptoms or signs of valve dysfunction and yearly after 5–10 years of bioprosthesis implantation even if there are no changes in the patient's clinical condition [27, 28]. Specific recommendations for follow-up in patients treated with TAVR have not been defined yet. The cumulative evidence provided by registries and ongoing randomized clinical trials will have an impact on current recommendations [27, 28].

Study limitations

Several limitations should be acknowledged. This was a retrospective, single-centre study. MDCT after TAVR was performed in a relatively small subgroup of patients. This may have introduced a selection bias. In addition, the findings observed on the MDCT scans relate to previous generations of transcatheter valves and may not be generalizable to newer aortic valve prostheses (Edwards SAPIEN 3 and Medtronic CoreValve Evolut R). Furthermore, the vast majority of patients received a balloon-expandable prosthesis. Patients who deceased during follow-up may have died due to transcatheter valve thrombosis which may underestimate the true incidence of this complication. Assessment of reduced leaflet motion with MDCT may be challenging due to the low temporal resolution of the technique.

Conclusion

Transcatheter aortic valves showed good mid-term durability with low rates of abnormal valve hemodynamics at 3 years follow-up. The rate of possible valve thrombosis based on echocardiographic criteria was low (3% at 3 years follow-up). MDCT detected HALT and/or reduced leaflet motion in 12.5% of patients. Only one patient with HALT presented with abnormal valve hemodynamics (the echocardiographic criterium of valve thrombosis). Importantly, both HALT and abnormal valve hemodynamics were not associated with increased risk of ischemic stroke/TIA in the current population.

REFERENCES

[1] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med. 2010;363(17):1597-607.

[2] Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, et al. Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery. J Am Coll Cardiol. 2014;63(19):1972-81.

[3] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. N Engl J Med. 2011;364(23):2187-98.

[4] Hamm CW, Möllmann H, Holzhey D, Beckmann A, Veit C, Figulla HR, et al. The German Aortic Valve Registry (GARY): in-hospital outcome. Eur Heart J. 2014;35(24):1588-98.

[5] Tamburino C, Barbanti M, D'Errigo P, Ranucci M, Onorati F, Covello RD, et al. 1-year outcomes after transfemoral transcatheter or surgical aortic valve replacement: results from the Italian OBSERVANT study. J Am Coll Cardiol. 2015;66(7):804-12.

[6] Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the allcomers NOTION Randomized Clinical Trial. J Am Coll Cardiol. 2015;65(20):2184-94.

[7] Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20.

[8] Barbanti M, Petronio AS, Ettori F, Latib A, Bedogni F, De Marco F, et al. 5-Year Outcomes after Transcatheter Aortic Valve Implantation with CoreValve Prosthesis. J Am Coll Cardiol Intv. 2015;8(8):1084-91.

[9] Bouleti C, Himbert D, Iung B, Alos B, Kerneis C, Ghodbane W, et al. Long-term outcome after transcatheter aortic valve implantation. Heart. 2015;101(12):936-42.

[10] Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2485-91.

[11] Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2477-84.

[12] Sawaya F, Kappetein AP, Wisser W, Nataf P, Thomas M, Schächinger V, et al. Five-year haemodynamic outcomes of the first-generation SAPIEN balloon-expandable transcatheter heart valve. EuroIntervention. 2016;12(6):775-82.

[13] Leetmaa T, Hansson NC, Leipsic J, Jensen K, Poulsen SH, Andersen HR, et al. Early aortic transcatheter heart valve thrombosis: diagnostic value of contrast-enhanced multidetector computed tomography. Circ Cardiovasc Interv. 2015;8(4):1-9.

[14] Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, et al. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. N Engl J Med. 2015;373(21):2015-24.

[15] Pache G, Schoechlin S, Blanke P, Dorfs S, Jander N, Arepalli CD, et al. Early hypo-attenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2016;37(28):2263-71.

[16] Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr. 2009;10(1):1-25.

[17] Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012;33(19):2403-18.

[18] Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). J Cardiovasc Comput Tomogr. 2012;6(6):366-80.

[19] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[20] Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves. Eur Heart J Cardiovasc Imaging. 2016;17(6):589-90.

[21] Delgado V, Ng ACT, Van De Veire NR, Van Der Kley F, Schuijf JD, Tops LF, et al. Transcatheter aortic valve implantation: role of multi-detector row computed tomography to evaluate prosthesis positioning and deployment in relation to valve function. Eur Heart J. 2010;31(9):1114-23.

[22] van Rosendael PJ, Kamperidis V, van der Kley F, Katsanos S, Al Amri I, Regeer MV, et al. Atherosclerosis burden of the aortic valve and aorta and risk of acute kidney injury after transcatheter aortic valve implantation. J Cardiovasc Comput Tomogr. 2015;9(2):129-38.

[23] Jander N, Sommer H, Pingpoh C, Kienzle RP, Martin G, Zeh W, et al. The porcine valve type predicts obstructive thrombosis beyond the first three postoperative months in bioprostheses in the aortic position. Int J Cardiol. 2015;199:90-5.

[24] Puvimanasinghe JPA, Steyerberg EW, Takkenberg JJM, Eijkemans MJC, Van Herwerden LA, Bogers AJJC, et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. Circulation. 2001;103(11):1535-41.

[25] Del Trigo M, Muñoz-Garcia AJ, Wijeysundera HC, Nombela-Franco L, Cheema AN, Gutierrez E, et al. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. J Am Coll Cardiol. 2016;67(6):644-55.

[26] Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, et al. Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications. J Am Coll Cardiol. 2016;68(19):2059-69.

[27] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451-96.

[28] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

SUPPLEMENTARY MATERIAL

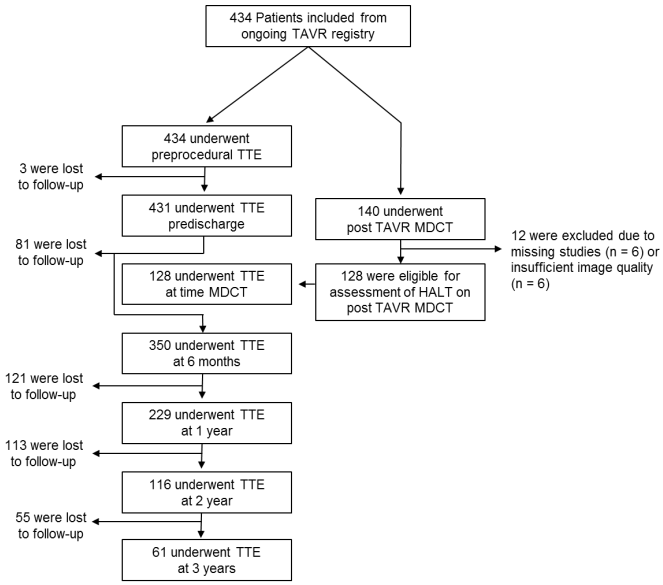


Figure 4: Patient flow chart. HALT, hypo-attenuated leaflet thickening; MDCT, multi-detector row computed tomography, TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiogram.

Table 7: Post-procedural outcomes of entire patient population undergoing transcatheter aortic valve replacement (TAVR).

Postprocedural outcomes	**Total population (N = 434)**
Mortality (within 30 days), *N* (%)	24(6)
Vascular injury, *N* (%)	
Minor	34 (8)
Major	20 (5)
Bleeding, *N* (%)	
Minor	35 (8)
Major	22 (5)
Stroke and TIA, *N* (%)	
Stroke	9 (2)
TIA	5 (1)
Acute kidney injury (stage 1-3), *N* (%)	22 (5)
Conduction disturbances and arrhythmias, *N* (%)	
New high-grade atrioventricular block needing pacemaker implantation	37 (9)
Cardiac tamponade, *N* (%)	10 (2)
Myocardial infarction (<72 h after the procedure), *N* (%)	1 (0.2)
Valve migration, *N* (%)	2 (0.4)
Prosthetic dysfunction, *N* (%)	
Severe AR needing valve-in-valve procedure	3 (0.7)

AR, aortic regurgitation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

9

TIME COURSE OF LEFT VENTRICULAR REMODELLING AND MECHANICS AFTER AORTIC VALVE SURGERY: AORTIC STENOSIS VERSUS AORTIC REGURGITATION

E. Mara Vollema, Gurpreet K. Singh, Edgard A. Prihadi, Madelien V. Regeer, See H. Ewe, Arnold C.T. Ng, Bart J.A. Mertens, Robert J.M. Klautz, Nina Ajmone Marsan, Jeroen J. Bax, Victoria Delgado

Published in Eur Heart J Cardiovasc Imaging. 2019: 0; 1-7

ABSTRACT

AIMS

Pressure overload in aortic stenosis (AS) and both pressure and volume overload in aortic regurgitation (AR) induce concentric and eccentric hypertrophy, respectively. These structural changes influence left ventricular (LV) mechanics, but little is known about the time course of LV remodelling and mechanics after aortic valve surgery (AVR) and its differences in AS versus AR. The present study aimed to characterize the time course of LV mass index (LVMI) and LV mechanics (by LV global longitudinal strain [LV GLS]) after AVR in AS vs. AR.

METHODS AND RESULTS

Two hundred and eleven (61±14 years, 61% male) patients with severe AS (63%) or AR (37%) undergoing surgical AVR with routine echocardiographic follow-up at 1, 2 and/or 5 years were evaluated. Before AVR, LVMI was larger in AR patients compared to AS. Both groups showed moderately impaired LV GLS, but preserved LV ejection fraction. After surgery, both groups showed LV mass regression, although a more pronounced decline was seen in AR patients. Improvement in LV GLS was observed in both groups, but characterized by an initial decline in AR patients while LV GLS in AS patients remained initially stable.

CONCLUSIONS

In severe AS and AR patients undergoing AVR, LV mass regression and changes in LV GLS are similar despite different LV remodelling before AVR. In AR, relief of volume overload led to reduction in LVMI and an initial decline in LV GLS. In contrast, relief of pressure overload in AS was characterized by a stable LV GLS and more sustained LV mass regression.

Introduction

In severe aortic stenosis (AS) and severe chronic aortic regurgitation (AR), aortic valve replacement (AVR) is indicated when patients have symptoms or show signs of left ventricular (LV) dysfunction [1, 2]. The pathophysiology of these two valvular heart diseases and the time course of LV remodelling and development of symptoms are different. While AS induces a pressure overload on the left ventricle, AR imposes both a pressure and a volume overload. These abnormal hemodynamic conditions induce different remodelling responses of the LV: concentric hypertrophy due to increased muscle fibre diameter and parallel addition of new myofibrils occurs in AS, whereas in AR the growth of cardiomyocytes and the addition of new sarcomeres in series induces eccentric remodelling and LV dilation [3]. In both situations, there is increased formation of interstitial fibrosis that may not regress when the volume and/or pressure overload are relieved after AVR [3–6]. These structural changes influence LV mechanics and, although LV ejection fraction (LVEF) may be preserved for long time, measures of LV deformation such as LV global longitudinal strain (GLS) assessed by speckle tracking imaging have shown that the LV systolic function may be impaired at earlier stages [7–10]. Impaired LV GLS prior to AVR has been correlated with adverse outcomes after AVR in both AS and AR [11, 12]. However, little is known about the time course of LV remodelling and LV mechanics after AVR and how they differ in patients with AS vs. patients with AR. Therefore, the present study characterizes and compares the time course of LV remodelling and changes in LV mechanics as assessed with 2-dimensional speckle tracking LV GLS after AVR in AS vs. AR.

Methods

Study population and data collection

From an ongoing registry of patients with aortic valve disease, patients with severe AS or AR who underwent surgical aortic valve replacement or repair (AVR) at the Leiden University Medical Center were selected based on echocardiographic data available at baseline (prior to surgery) and at least one or more echocardiograms at specific follow-up times: within 1 year after surgery and/or at approximately 2- and/or 5-year follow-up. Patients with concomitant coronary artery bypass grafting (CABG) and elective aortic surgery were not excluded. If reoperation of the aortic valve and/or aortic root was performed during follow-up, the last transthoracic echocardiogram before reoperation was used for the analysis. Reasons for patient exclusion were: non-severe AS or AR, previous mitral valve replacement or AVR, active endocarditis, type A aortic dissection or non-feasible LV GLS analysis due to insufficient data.

Demographic and clinical data were collected using electronic records (EPD Vision, version 11.4.29.0, EPD Vision, Leiden, The Netherlands). Echocardiographic data was digitalized and stored in the departmental server (Imagevault, GE Healthcare, Norway). The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

TWO-DIMENSIONAL TRANSTHORACIC ECHOCARDIOGRAPHY

All patients underwent transthoracic echocardiography prior to surgery. Images were acquired with patients at rest in the left decubitus position using commercially available ultrasound systems (System 5, Vivid 7 and E9, GE Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Two-dimensional, color, pulsed- and continuous-wave Doppler data were obtained in parasternal and apical views. Data were stored digitally and analysed offline retrospectively on a dedicated workstation (EchoPac version BT13; GE Medical Systems). Apical 2- and 4-chamber views were used for quantification of LV end-diastolic and end-systolic volumes and LVEF was calculated using the Simpson's biplane method [13]. LV dimensions and wall thicknesses were measured on M-mode recordings of the parasternal long-axis view. LV mass was calculated according to the formula of Devereux et al. and was indexed (LVMI) to body surface area [13]. Two-dimensional speckle tracking longitudinal strain analysis was performed on the apical 2-, 3- and 4-chamber views to calculate LV GLS [13]. Aortic valve mean and peak gradients were evaluated using continuous-wave Doppler on the 3- or 5-chamber LV apical views with the simplified Bernoulli equation. Pulsed-wave Doppler recordings of the LV outflow tract were obtained on the same apical views and the aortic valve area was calculated using the continuity equation [14]. Severe AS was defined based on an aortic valve area <1.0 cm^2 or indexed aortic valve area <0.6 cm^2/m^2 and/or mean transvalvular pressure gradient ≥40 mmHg and/or peak aortic jet velocity ≥4 m/s [14]. AR grade was assessed using a multi-parametric approach that included the measurement of the vena contracta on the parasternal long-axis view or the apical 3- or 5-chamber views, the ratio between the regurgitant jet width and the LV outflow tract diameter on color M-mode recordings on the parasternal long-axis views and the diastolic flow reversal velocity on the suprasternal view of the aortic arch [15]. In addition, the pressure half time was measured from continuous-wave Doppler recordings of the regurgitant jet on the apical 3- or 5-chamber views [15].

FOLLOW-UP

Patients were evaluated after AVR at the outpatient clinic of the Leiden University Medical Center. Transthoracic echocardiography was performed at the discretion of the treating physician. Left ventricular dimensions and function, including LV GLS, were measured. Echocardiograms performed within 1 year (0-12 months), at 2 years and/or at 5 years after AVR were analysed. If more than one echocardiogram was performed within one time period, the latest one was analysed.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean±standard deviation or median and interquartile range if not normally distributed. Comparison of continuous variables between the AS and AR groups at baseline (prior to AVR) were performed using the Student's independent t test or Mann-Whitney U test (for normally or non-normally distributed variables, respectively) and categorical variables using χ^2 test or Fisher's exact test, as appropriate. Linear mixed model analyses were used to assess changes in LV GLS, LVMI and LVEF between sequential time points. Correction for age, gender, LV end-diastolic diameter (LVEDD) at base-

line and time between echocardiograms was applied by incorporating these parameters in the models as fixed variables (for gender) or covariates (for age, LVEDD and time to follow-up). Analyses were performed per separate time interval (between baseline and 1-year follow-up, 1- and 2-year follow-up and between 2- and 5-year follow-up, respectively) using a stepwise approach: first, interaction between the AS and AR groups and time (*P* for interaction) was assessed and then excluded from the model if not statistically significant and secondly, time as factor (*P* for time) was assessed and then excluded from the model if not statistically significant. All statistical analyses were two-sided and *P* values <0.05 were considered statistically significant. The SPSS software (version 23.0; IBM, Armonk, New York) was used to perform the analyses.

Table 1: Baseline clinical characteristics of patients with aortic stenosis (AS) and aortic regurgitation (AR) undergoing AVR.

Variables	Total population (N = 211)	Patients with AS (N = 132)	Patients with AR (N = 79)	*P* value
Female gender, *N* (%)	83 (39)	55 (42)	28 (35)	0.370
Age (years)	61.3±13.5	64.6±11.5	55.9±14.7	**<0.001**
BSA (m^2)	1.90±0.19	1.90±0.19	1.91±0.18	0.598
Logistic EuroSCORE (%)	4.7 [2.3-8.1]	4.6 [2.7-8.0]	5.3 [2.2-9.7]	0.548
Creatinine level (μmol/ml)	85 [74-99]	87 [74-101]	84 [74-99]	0.576
Cardiovascular risk factors, *N* (%)				
Hypertension	122 (58)	73 (55)	49 (62)	0.339
Hyperlipidaemia	81 (38)	55 (42)	26 (33)	0.206
Diabetes mellitus	22 (10)	17 (13)	5 (6)	0.132
Current smoking	50 (24)	24 (19)	26 (33)	**0.018**
Coronary artery disease, *N* (%)	85 (40)	70 (53)	15 (19)	**<0.001**
Prior MI, *N* (%)	25 (11)	20 (15)	5 (6)	0.055
Systolic blood pressure (mmHg)	140.3±22.7	141.8±23.2	138.0±21.7	0.241
Diastolic blood pressure (mmHg)	76.4±11.9	79.1±11.1	71.8±12.0	**<0.001**
Medications, *N* (%)				
Beta blocker	108 (52)	66 (51)	42 (54)	0.708
ACE-inhibitor/ARB	121 (59)	62 (48)	59 (76)	**<0.001**
Diuretics	65 (31)	39 (30)	26 (33)	0.641
Spironolactone	9 (4)	2 (2)	7 (9)	**0.011**
Statins	100 (48)	74 (57)	26 (33)	**0.001**
Aspirin	81 (39)	58 (45)	23 (30)	**0.027**
Anticoagulation	40 (19)	19 (15)	21 (27)	**0.029**
Symptomatic status, *N* (%)	163 (78)	97 (74)	66 (85)	0.074
NYHA-classification, *N* (%)				0.909
I-II	159 (76)	100 (76)	59 (76)	
III-IV	50 (24)	31 (24)	19 (24)	

ACE, angiotensin-converting enzyme; AR, aortic regurgitation; ARB, angiotensin II receptor blocker; AS, aortic stenosis; AVR, aortic valve replacement or repair; BSA, body surface area; MI, myocardial infarction; NYHA, New York Heart Association functional classification.

RESULTS

CLINICAL CHARACTERISTICS

A total of 211 patients (mean age 61.3±13.5 years, 61% male) with echocardiographic follow-up were evaluated: severe AS was present in 132 (63%) patients and severe AR in 79 (37%) patients. The clinical characteristics of the overall population and both subgroups are shown in Table 1. Patients with AS were older and more often had coronary artery disease and prior myocardial infarction as compared to patients with AR. Cardiovascular risk factors were equally distributed with the exception of current smoking, which was more prevalent in AR patients. Patients with AR were more frequently treated with angiotensin-converting enzyme-inhibitors, spironolactone and anticoagulants, whereas patients with AS received aspirin and statins more frequently. Both patient groups had comparable logistic EuroSCORE and New York Heart Association heart failure symptoms.

ECHOCARDIOGRAPHIC AND PROCEDURAL CHARACTERISTICS AT BASELINE

Baseline echocardiographic and procedural characteristics of the total population and both AS and AR patient subgroups are displayed in Table 2. The majority of patients had tricuspid anatomy of the aortic valve (77%) whereas bicuspid valve anatomy was present in 23%. AR patients more frequently showed bicuspid aortic valve anatomy (33% vs. 17%, P=0.010). Patients with AR had larger LVEDD (59.8±7.4 vs. 50.2±8.3 mm, P<0.001) as compared to AS patients. Both groups showed a preserved LVEF. During AVR, both AS and AR patients received biological prostheses more often than mechanical prostheses. Larger valves were implanted in patients with AR. Concomitant CABG was more frequently performed in AS patients (42% vs. 24%, P=0.009).

TIME COURSE OF LV REMODELLING AND LV MECHANICS

The total median echocardiographic follow-up duration was 57 [51 – 65] months, with the first post-operative echocardiogram performed at 3 [0 – 7] months and subsequent controls at 21 [17 – 25] months and 58 [53 – 66] months of follow-up after AVR.

Table 3 shows LVMI, LV GLS, LVEF and stroke volumes at baseline and follow-up. At baseline, due to eccentric remodelling, LVMI was larger in patients with AR (154.9±40.0 vs. 127.1±36.0 g/m^2, P<0.001; respectively) and stroke volume was larger (115.4±45.6 vs. 80.9±22.4 ml, P<0.001; respectively) compared to patients with AS. Both patients with AR and AS showed preserved LVEF (53.5±9.1 vs. 55.9±11.4%, P=0.117; respectively) and moderately impaired LV GLS (-15.3±4.1 vs. -15.1±4.3%, P=0.685; respectively). Examples of a patient with AR and a patient with AS before and after AVR are displayed in Figure 1.

Figure 2 presents the changes in LVMI (*panel A*) and LV GLS (*panel B*) between sequential time points after AVR for both groups. Despite differences in LV remodelling at baseline, both AS and AR patients showed LV mass regression and improvement in LV GLS after AVR. Both patient groups showed significant LVMI regression within 1 year after AVR (P for time <0.001), although this decline was more pronounced in patients with AR (P for interaction=0.001), leading to comparable LVMI after AVR in both groups (AR: 126.1±30.5 vs. AS: 113.4±31.6 g/m^2; P=0.512). LVMI continued to regress in both AS and AR patients from 1- to 2-year follow-up (P for time<0.001) and from 2- to 5-year follow-

up (*P* for time=0.041) with a slightly steeper decline for the AR patient group during the second year (*P* for interaction=0.08). At 2- and 5-year follow-up, no differences in LVMI were observed between the groups (*P*=0.217 and *P*=0.485, respectively).

At 1-year follow-up after AVR, the AR group showed a further decline in LV GLS (*P* for time=0.810) resulting in a significantly more impaired LV GLS compared to the AS group (-14.0±3.9 vs. -15.0±4.0%, respectively; *P*=0.014). Thereafter, LV GLS significantly improved over time during the second year (*P* for time <0.001) in similar magnitude for both AS and AR patients (*P* for interaction=0.152) and remained stable in the period between 2- and 5-year follow-up.

Table 2: Baseline echocardiographic and procedural characteristics of patients with aortic stenosis (AS) and aortic regurgitation (AR) undergoing AVR.

Variables	Total population (N = 211)	Patients with AS (N = 132)	Patients with AR (N = 79)	*P* value
Baseline echocardiography				**0.010**
Valve anatomy, *N* (%)				
Bicuspid	49 (23)	23 (17)	26 (33)	
Tricuspid	162 (77)	109 (83)	53 (67)	
LV end-diastolic diameter (mm)	53.8±9.2	50.2±8.3	59.8±7.4	**<0.001**
LV end-diastolic volume (ml)	142.9±62.7	115.2±42.0	188.6±64.6	**<0.001**
LV end-systolic volume (ml)	66.8±39.2	53.5±33.4	88.7±38.3	**<0.001**
LV ejection fraction (%)	55.0±10.6	55.9±11.4	53.5±9.1	0.117
Aortic valve area (cm^2)	1.42±1.1	0.82±0.2	2.72±1.0	**<0.001**
AV peak gradient (mmHg)	53.3±32.3	71.5±24.6	21.9±15.0	**<0.001**
AV mean gradient (mmHg)	32.7±21.5	44.4±17.5	12.5±9.2	**<0.001**
Procedural variables				
Concomitant CABG, *N* (%)	74 (35)	55 (42)	19 (24)	**0.009**
Valve type, *N* (%)				0.293
Biological	135 (64)	95 (72)	40 (51)	
Mechanical	59 (28)	37 (28)	22 (28)	
Aortic valve repair	18 (9)	-	18 (23)	
Implanted valve size, *N* (%)				**< 0.001**
21 mm	24 (12)	19 (14)	5 (6)	
23 mm	53 (25)	47 (36)	6 (8)	
25 mm	62 (29)	42 (32)	19 (24)	
27 mm	34 (16)	19 (14)	15 (19)	
29 mm	22 (10)	5 (4)	17 (22)	
CPB duration (min)	149 [116-189]	140 [113-183]	170 [120-217]	0.053
Aorta clamp time (min)	116 [80-143]	109 [78-139]	122 [83-154]	0.109

AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVR, aortic valve replacement or repair; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; LV, left ventricular.

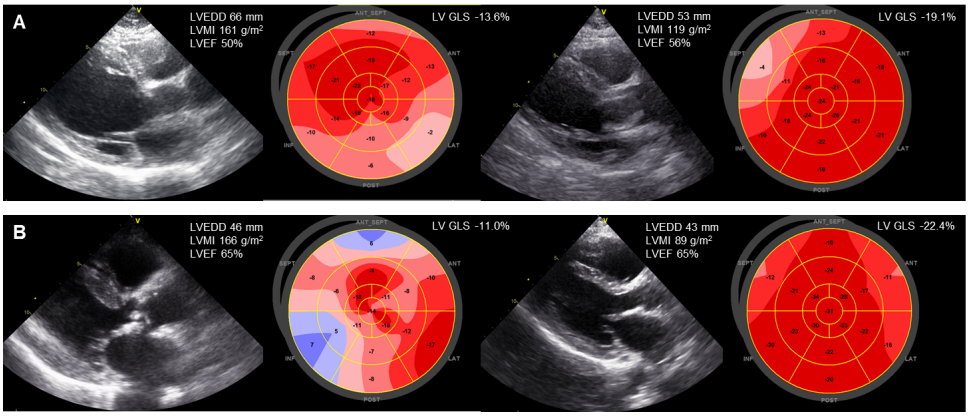


Figure 1: Examples of two patients with preserved LV ejection fraction before (left) and two years after AVR (right). (*Panel A*) Patient with aortic regurgitation (AR) with eccentric LV hypertrophy due to increased LV end-diastolic diameter (LVEDD). (*Panel B*) Patient with aortic stenosis (AS) with concentric LV hypertrophy due to thickening of inter-ventricular septum and posterior wall. Despite differences in LV remodelling, both patients show LV mass regression and improvement of LV GLS after AVR. AVR, aortic valve replacement or repair; GLS, global longitudinal strain; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

Table 3: Course of LVMI, LV GLS, LV ejection fraction, and stroke volume in AS and AR after AVR.

	Patients with AS	**Patients with AR**	***P* value**
At baseline	N = 132	N = 79	
LVMI (g/m^2)	127.1±36.0	154.9±40.0	**<0.001***
LV GLS (%)	-15.1±4.3	-15.3±4.1	0.685*
LVEF (%)	55.9±11.4	53.5±9.1	0.117*
Stroke volume (ml)	80.9±22.4	115.4±45.6	**<0.001***
At 1-year follow-up	N = 119	N = 72	
LVMI (g/m^2)	113.4±31.6	126.1±30.5	0.512**
LV GLS (%)	-15.0±4.0	-14.0±3.9	**0.014****
LVEF (%)	55.1±9.3	50.4±9.7	0.310**
Stroke volume (ml)	82.5±22.4	82.9±26.0	**<0.001****
At 2-year follow-up	N = 102	N = 62	
LVMI (g/m^2)	103.6±26.6	110.3±31.2	0.217**
LV GLS (%)	-16.8±4.0	-16.3±4.1	0.133**
LVEF (%)	56.4±8.8	55.1±8.6	0.158**
Stroke volume (ml)	86.2±20.1	89.2±25.0	0.913**
At 5-year follow-up	N = 129	N = 53	
LVMI (g/m^2)	100.7±28.8	104.7±28.9	0.485**
LV GLS (%)	-17.2±4.1	-17.1±3.6	0.301**
LVEF (%)	56.8±8.9	54.8±8.1	0.255**
Stroke volume (ml)	85.9±23.5	85.9±27.3	0.328**

AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement or repair; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index. *Calculated using the Student's independent *t*-test. **Calculated using linear mixed models correcting for gender, age, LV end-diastolic diameter at baseline, and time between echocardiographic follow-up points.

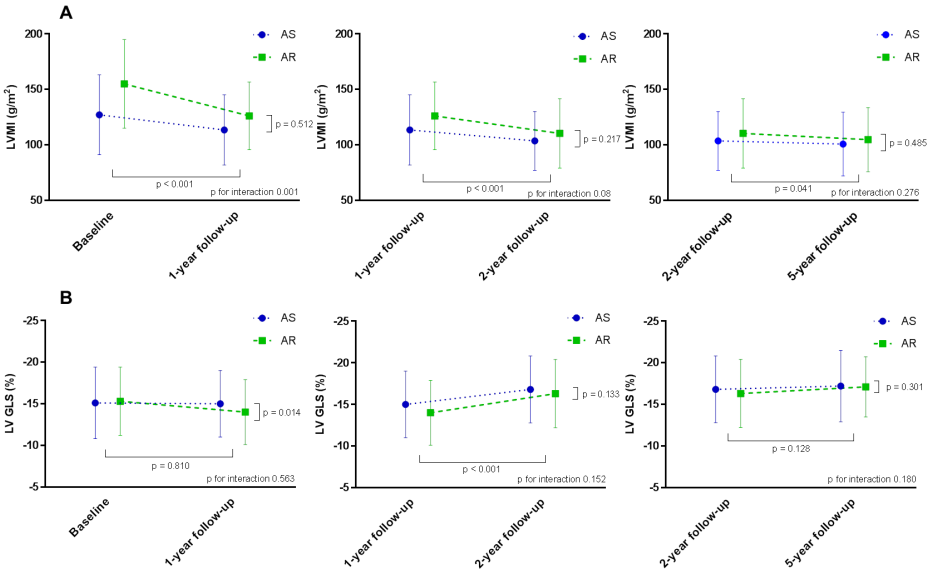


Figure 2: Changes in LV mass index (*panel A*) and LV mechanics (*panel B*) over time after AVR for patients with AS and AR after correction for age, gender, baseline LV end-diastolic diameter and time between echocardiographic follow-up points. AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement or repair; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

Discussion

The present study demonstrates that in severe AS and severe AR patients undergoing AVR, LV mass regression and changes in LV GLS are similar despite showing different LV remodelling before AVR. However, in patients with AR, the reduction in LVMI was more pronounced during the first year of follow-up as compared to AS patients. In addition, LV GLS showed an initial impairment in AR patients during the first year after AVR. The reduction (within 1 year) in LV end-diastolic dimensions as a response to the relief of volume overload led to a reduction in LVMI and, according to the Frank-Starling law, an impairment in LV GLS in AR patients. In contrast, relief of pressure overload in patients with AS was characterized by a stable LV GLS and a more sustained regression of LVMI during follow-up.

Pre- and postoperative LV remodelling in AS and AR

Hemodynamic overload conditions imposed onto the left ventricle, characterized by pressure overload in AS and both volume and pressure overload in AR, result in remodelling of the LV to normalize wall stress and to maintain the systolic function. AS is characterized by LV concentric hypertrophy, whereas in AR eccentric hypertrophy with LV dilatation is observed. These structural changes are accompanied by myocardial oxygen demand mismatch and progressive myocardial fibrosis that may lead to LV systolic dys-

function in both AS and AR, even before symptoms develop [3, 16]. At this time, AVR is strongly recommended [1, 2]. Following surgery, the immediate reduction in afterload has been shown to improve LV systolic function and to result in prompt LV mass reduction in both AS and AR patients [16, 17]. In AS, multiple studies have demonstrated that excessive LV hypertrophy is independently associated with increased mortality after AVR [18–20]. Similarly, larger LV mass in severe AR patients is associated with mortality and impaired LV systolic function after intervention [21, 22]. LV mass regression after AVR seems critical for clinical improvement and long-term survival [23]. Several studies have described the time course of LV mass regression in severe AS patients within 12 months after intervention [24, 25]. In a more recent longitudinal assessment of the cohort A in the Placement of AoRTic TraNscathetER Valve Trial (PARTNER) I trial, Daubert et al. [26] showed sustained LV mass regression up to 5 years after surgical AVR. In contrast, the postoperative LV mass regression process in patients with AR is less extensively studied. Studies performing sequential measurements of LV dimensions showed a steep decline of indexed LV diameters in the early postoperative period and at 1- to 2-year follow-up with stabilization of this reduction thereafter [22, 27].

How the time course of LV mass regression after aortic valve intervention in severe AS compares to patients with severe AR has not been extensively studied. Monrad et al. [17] demonstrated that the greatest fall in LVMI occurred 1 to 2 years after surgery for both AS and AR and that LV mass regression continued until late postoperative follow-up (mean 8.1±2.9 years). More recently, and using the presently recommended formula for the calculation of LVMI [13], Une et al. [28] showed a steep decline in LVMI in both AS and AR during the first 24 months after surgery without further significant reduction at longer term follow-up in both patient groups. Of note, patients with AR showed a larger LV mass regression as compared to AS patients [28]. However, the reduction in LVMI among AR patients occurred at a slower pace than in patients with AS. The present study provides further insight in the time course of LV mass regression in AS and AR patients by demonstrating, using sequential echocardiographic measurements, a marked decline of LVMI in both patient groups within 1 and 2 years after surgery which continued up to 5 years after AVR. Interestingly, patients with AR showed a more pronounced and faster regression in LV mass during the early post-operative phase as compared to AS patients.

PRE- AND POSTOPERATIVE LV MECHANICS IN AS AND AR

Timing for AVR in both AS and AR is largely guided by the presence of symptoms or LV systolic dysfunction, conventionally expressed as a LVEF <50% [1, 2]. However, multiple studies have demonstrated that even in an early stage, when patients are still asymptomatic, subclinical myocardial dysfunction can occur [7, 11, 12]. Impaired LV GLS has been shown in patients with severe AS or AR with preserved LVEF and has been associated with poor prognosis, even after AVR [10, 11, 29–31]. Studies evaluating the time course of LV GLS after surgery in AS and AR are limited. In severe AR patients treated with AVR, Smedsrud et al. [32] and Regeer et al. [33] demonstrated a significant improvement of LV GLS normalized for LV end-diastolic volume at 229±159 days and 26 [16-64] months, respectively. For severe AS, LV GLS has been described to improve as early as several days after AVR [34, 35]. The present study is first to describe an impaired LV GLS in AR patients in the early period (within 1 year) after AVR compared to AS patients,

reflecting the different responses in LV mechanics to a relief of volume vs. pressure overload. According to the Frank-Starling law, volume overload by AR results in an increase in preload which stimulates force of contraction by stretching of the myocytes to maintain LV systolic function in the progressively dilated LV. After AVR, this preload will dramatically fall and chamber dimensions will decrease, resulting in a decrease of activation of the Frank-Starling mechanism. As a consequence, myocardial contraction force will drop and most likely, longitudinal shortening of myocardial fibres will also decrease, manifesting as a more impaired LV GLS as seen in the present study.

Limitations

Several limitations should be acknowledged. The present study was retrospective in design and performed in a single tertiary centre. Referral for AVR was left at the discretion of the treating cardiologist. Therefore, referral and selection bias could have been introduced. In this study, LVMI was calculated on 2-dimensional transthoracic echocardiography using the Devereux formula [13]. Especially in the presence of eccentric hypertrophy, a prevalent finding in AR, this approach may be inaccurate due to reliance on the LV end-diastolic diameter of this formula. However, our analyses were corrected for LV end-diastolic diameter at baseline, resulting in a fair comparison between AS and AR despite differences in remodelling at baseline. Future studies using 3-dimensional imaging methods (e.g., cardiac magnetic resonance imaging) are needed to optimize accurate assessment of LV mass.

Conclusions

After AVR, LV remodelling and improvement of LV mechanics occur both in AS and AR. However, postoperative LV mass regression in AR patients was characterized by a steep decline within 1 year after surgery and associated with a less preserved LV GLS compared to patients with AS, who showed a more gradual and sustained LV mass regression and improvement of LV mechanics. These findings provide further insight in the differences in myocardial response to the relief of pressure overload in AS and a combination of pressure and volume overload in AR, as displayed by the distinct patterns in LV remodelling and mechanics.

REFERENCES

[1] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

[2] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-86.

[3] Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. Circulation. 1989;79(4):744-55.

[4] Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol. 2010;56(4):278-87.

[5] Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, et al. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. J Am Coll Cardiol Img. 2017;10(11):1320-33.

[6] Weidemann F, Herrmann S, Störk S, Niemann M, Frantz S, Lange V, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation. 2009;120(7):577-84.

[7] Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart. 2010;96(17):1364-71.

[8] Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. Circ Cardiovasc Imaging. 2012;5(6):719-25.

[9] Ng ACT, Delgado V, Bertini M, Antoni ML, Van Bommel RJ, Van Rijnsoever EPM, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J. 2011;32(12):1542-50.

[10] Ewe SH, Haeck MLA, Ng ACT, Witkowski TG, Auger D, Leong DP, et al. Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis. Eur Heart J Cardiovasc Imaging. 2015;16:992-9.

[11] Alashi A, Mentias A, Abdallah A, Feng K, Gillinov AM, Rodriguez LL, et al. Incremental Prognostic Utility of Left Ventricular Global Longitudinal Strain in Asymptomatic Patients With Significant Chronic Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction. J Am Coll Cardiol Img. 2018;11(5):673-82.

[12] Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2012;13(10):827-33.

[13] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[14] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):254-75.

[15] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013;14(7):611-44.

[16] Carabello BA. Aortic regurgitation: a lesion with similarities to both aortic stenosis and mitral regurgitation. Circulation. 1990;82(3):1051-3.

[17] Monrad ES, Hess OM, Nonogi H, Corin WJ, Krayenbuehl HP. Time course of regression of left ventricular hypertrophy after aortic valve replacement. Circulation. 1988;77(6):1345-55.

[18] Orsinelli DA, Aurigemma GP, Battista S, Krendel S, Gaasch WH. Left ventricular hypertrophy and mortality after aortic valve replacement for aortic stenosis. J Am Coll Cardiol. 1993;22(6):1679-83.

[19] Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart. 2011;97(4):301-7.

[20] Capoulade R, Clavel MA, Le Ven F, Dahou A, Thébault C, Tastet L, et al. Impact of left ventricular remodelling patterns on outcomes in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2017;18(12):1378-87.

[21] Brown ML, Schaff HV, Suri RM, Zhuo L, Sundt TM, Dearani JA, et al. Indexed Left Ventricular Dimensions Best Predict Survival After Aortic Valve Replacement in Patients With Aortic Valve Regurgitation. Ann Thorac Surg. 2009;87(4):1170-6.

[22] Murashita T, Schaff HV, Suri RM, Daly RC, Li Z, Dearani JA, et al. Impact of Left Ventricular Systolic Function on Outcome of Correction of Chronic Severe Aortic Valve Regurgitation: Implications for Timing of Surgical Intervention. Ann Thorac Surg. 2017;103(4):1222-8.

[23] Ali A, Patel A, Ali Z, Abu-Omar Y, Saeed A, Athanasiou T, et al. Enhanced left ventricular mass regression after aortic valve replacement in patients with aortic stenosis is associated with improved long-term survival. J Thorac Cardiovasc Surg. 2011;142(2):285-91.

[24] Kim SJ, Samad Z, Bloomfield GS, Douglas PS. A critical review of hemodynamic changes and left ventricular remodeling after surgical aortic valve replacement and percutaneous aortic valve replacement. Am Heart J. 2014;168(2):150-9.e7.

[25] Ngo A, Hassager C, Thyregod HGH, Søndergaard L, Olsen PS, Steinbrüchel D, et al. Differences in left ventricular remodelling in patients with aortic stenosis treated with transcatheter aortic valve replacement with corevalve prostheses compared to surgery with porcine or bovine biological prostheses. Eur Heart J Cardiovasc Imaging. 2018;19(1):39-46.

[26] Daubert MA, Weissman NJ, Hahn RT, Pibarot P, Parvataneni R, Mack MJ, et al. Long-Term Valve Performance of TAVR and SAVR: A Report From the PARTNER I Trial. J Am Coll Cardiol Img. 2017;10(1):15-25.

[27] Saisho H, Arinaga K, Kikusaki S. Long Term Results and Predictors of Left Ventricular Function Recovery after Aortic Valve Replacement for Chronic Aortic Regurgitation. Ann Thorac Cardiovasc Surg. 2015;21(4):388-95.

[28] Une D, Mesana L, Chan V, Maklin M, Chan R, Masters RG, et al. Clinical impact of changes in left ventricular function after aortic valve replacement: analysis from 3112 patients. Circulation. 2015;132(8):741-7.

[29] Dahl JS, Videbæk L, Poulsen MK, Rudbæk TR, Pellikka PA, Møller JE. Global Strain in Severe Aortic Valve Stenosis: Relation to Clinical Outcome After Aortic Valve Replacement Jordi. Circ Cardiovasc Imaging. 2012 sep;5(5):613-20.

[30] Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circ Cardiovasc Imaging. 2014;7(6):938-45.

[31] Kusunose K, Agarwal S, Marwick TH, Griffin BP, Popovic ZB. Decision making in asymptomatic aortic regurgitation in the era of guidelines: incremental values of resting and exercise cardiac dysfunction. Circ Cardiovasc Imaging. 2014;7(2):352-62.

[32] Smedsrud MK, Pettersen E, Gjesdal O, Svennevig JL, Andersen K, Ihlen H, et al. Detection of left ventricular dysfunction by global longitudinal systolic strain in patients with chronic aortic regurgitation. J Am Soc Echocardiogr. 2011;24(11):1253-9.

[33] Regeer MV, Versteegh MIM, Ajmone Marsan N, Schalij MJ, Klautz RJM, Bax JJ, et al. Left ventricular reverse remodeling after aortic valve surgery for acute versus chronic aortic regurgitation. Echocardiography. 2016;33(10):1458-64.

[34] Dinh W, Nickl W, Smettan J, Kramer F, Krahn T, Scheffold T, et al. Reduced global longitudinal strain in association to increased left ventricular mass in patients with aortic valve stenosis and normal ejection fraction: a hybrid study combining echocardiography and magnetic resonance imaging. Cardiovasc Ultrasound. 2010;8(1):29.

[35] Carasso S, Cohen O, Mutlak D, Adler Z, Lessick J, Aronson D, et al. Relation of myocardial mechanics in severe aortic stenosis to left ventricular ejection fraction and response to aortic valve replacement. Am J Cardiol. 2011;107(7):1052-7.

Part III

SUMMARY & APPENDICES

10

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY

THE general introduction of this thesis (Chapter 1) outlines the epidemiology of aortic valve disease in the developed countries and describes the differences in pathophysiology between aortic stenosis (AS) and aortic regurgitation (AR). In both valvular diseases, aortic valve intervention is indicated when patients are symptomatic or show signs of left ventricular (LV) dysfunction (defined as a LV ejection fraction [EF] <50%). Conventional two-dimensional and Doppler transthoracic echocardiography is the imaging modality of first choice for the correct assessment of severity of aortic stenosis or regurgitation, LV function and preprocedural risk stratification and is also the main imaging technique for the evaluation of therapy results. The additional value of multidetector row computed tomography (MDCT) in the evaluation of AS severity and subclinical leaflet thrombosis after transcatheter aortic valve implantation (TAVI) is introduced. The role of speckle tracking echocardiography for the assessment of LV global longitudinal strain (GLS), particularly in patients with aortic valve disease with preserved LVEF, is described. The current thesis aims at evaluating the role of multimodality imaging, in particular two-dimensional (speckle tracking) echocardiography and MDCT, in the risk stratification and evaluation of therapy in patients with aortic valve disease.

PART I: RISK STRATIFICATION AND TIMING OF INTERVENTION

In the first part of this thesis, the role of conventional and speckle tracking echocardiography in risk stratification and timing of aortic valve intervention in severe AS patients is explored. Also, the role of MDCT for the assessment of aortic valve calcium load is introduced.

In severe AS patients, signs of extra-aortic valvular injury are often observed and can be classified according to a newly proposed staging classification. In Chapter 2, the prevalence of the different stages of extra-aortic valvular cardiac damage as assessed by echocardiography and its impact on prognosis are evaluated in a large real-world multicenter cohort of symptomatic severe AS patients. Patients were classified as Stage 0 (no cardiac damage), Stage 1 (LV damage), Stage 2 (mitral valve or left atrial damage), Stage 3 (tricuspid valve or pulmonary artery vasculature damage), or Stage 4 (right ventricular (RV) damage). On the basis of the proposed classification, 8% of patients were classified as Stage 0, 24% as Stage 1, 49% as Stage 2, 7% as Stage 3, and 12% as Stage 4. After correcting for clinically relevant variables (e.g., aortic valve replacement), cardiac damage was independently associated with all-cause mortality and the combined outcome (i.e., all-cause mortality, stroke, and cardiac-related hospitalization). However, this seemed to be predominantly driven by tricuspid valve or pulmonary artery vasculature damage (Stage 3) and RV dysfunction (Stage 4).

Cardiac damage as classified by a recently proposed staging classification has been shown to be strongly associated with prognosis in severe AS patients. LV GLS has also been demonstrated to be independently associated with outcome in severe AS patients with both preserved and impaired LVEF. In Chapter 3, the prognostic implications of the incorporation of LV GLS into this staging system are evaluated and the incremental prognostic value of LV GLS over the staging classification algorithm is investigated for a large population of symptomatic patients with severe AS. Patients were classified into five independent stages of cardiac damage and LV GLS was divided by quintiles and assigned

to these different stages of cardiac damage. According to the original staging classification, 9% of patients had no signs of cardiac damage (Stage 0), 27% had LV damage (Stage 1), 45% had left atrial or mitral valve damage (Stage 2), 6% had pulmonary vasculature or tricuspid valve damage (Stage 3) and 13% had RV damage (Stage 4). Patients were reclassified by taking into account LV GLS: 4% of patients were categorized as Stage 0, 15% as Stage 1, 37% as Stage 2, 19% as Stage 3 and 25% as Stage 4. LV GLS was associated with all-cause mortality independent of stage of cardiac damage. After incorporation of LV GLS by quintiles into the staging classification, Stages 2 to 4 were independently associated with outcome. LV GLS showed incremental prognostic value over clinical characteristics and the originally proposed staging classification. Incorporation of LV GLS into a novel proposed staging classification resulted in refinement of risk stratification by identifying patients with more advanced cardiac damage.

In asymptomatic severe AS patients, aortic valve intervention is indicated if LV dysfunction (i.e., LVEF <50%) is present. In asymptomatic AS patients with preserved LVEF, the optimal timing to operate remains controversial. LV GLS has been proposed as a marker for subclinical myocardial dysfunction and may help to identify patients who might benefit from undergoing earlier aortic valve replacement. In Chapter 4, the prevalence of impaired LV GLS (defined as LV GLS >-18.2% based on the median value of the population), its natural course and the association of impaired LV GLS with symptom development and need for aortic valve intervention are assessed in a multicenter cohort of asymptomatic patients with severe AS with preserved LVEF. Despite comparable LVEF, LV GLS was significantly impaired in patients with asymptomatic severe AS compared with age- and sex-matched controls without AS. During follow-up, LV GLS significantly deteriorated while LVEF remained unchanged. Patients with impaired LV GLS at baseline (>-18.2%) showed a higher risk for developing symptoms and needing aortic valve intervention at follow-up compared with patients with more preserved LV GLS (≤-18.2%).

Renal dysfunction is a prevalent comorbidity in severe AS patients and has a negative influence on prognosis. However, the influence of renal dysfunction on the prognosis of patients with various grades of AS has not been extensively described. In Chapter 5, a large population of patients with aortic sclerosis and mild to severe AS is divided according to renal function by estimated glomerular filtration rate (eGFR) and the prognostic impact of renal dysfunction (i.e., eGFR <60 ml/min/1.73 m^2) is evaluated. In total, 28% of patients had aortic sclerosis, 7% had mild AS, 24% had moderate AS, and 41% had severe AS. Renal dysfunction was present in 37% of patients, and moderate to severe AS was observed more often in these patients compared to patients without renal dysfunction (70 vs. 62%, respectively). Severely impaired renal function (eGFR <30 ml/min/1.73 m^2) and aortic valve replacement (AVR) were independently associated with all-cause mortality after correcting for AS severity. Independent of renal function, AVR was associated with improved survival.

In the majority of patients with severe AS, a combination of high transvalvular gradients and a small aortic valve area is present. However, in up to 30% of patients with severe AS, a small aortic valve area is measured in the presence of low transvalvular gradients. In these low-gradient AS patients, discerning true severe AS (caused by degenerative calcification of the aortic valve) from pseudosevere AS (caused by a dysfunctional LV generating inadequate stroke volume) can be challenging. Assessment of the morphol-

ogy and calcification burden of the aortic valve can help to identify the patients with true severe AS who may benefit from intervention. In Chapter 6, the role of computed tomography for the assessment of aortic valve calcium scoring as evaluated by a recent study is discussed and questioned.

PART II: EVALUATION OF THERAPY

The second part of this thesis focusses on the role of conventional and advanced echocardiography and MDCT in the evaluation of therapy in aortic valve disease, in particular follow-up after surgical aortic valve replacement or TAVI.

Echocardiography plays a crucial role in all steps of the TAVI procedure: proper selection of both patient and prosthesis, procedural guidance and follow-up of prosthesis performance. In Chapter 7, an overview of the clinical applications and current role of echocardiographic techniques in patient selection, prosthesis sizing, periprocedural guidance and post-procedural follow-up in TAVI is provided.

The presence of hypo-attenuated leaflet thickening (HALT) and/or reduced leaflet motion by MDCT has been proposed as a possible marker for early transcatheter aortic valve thrombosis. However, its association with abnormal valve hemodynamics on echocardiography (another potential marker of thrombosis) and clinical outcomes (i.e., stroke/transient ischemic attack [TIA]) remains unclear. In Chapter 8, the presence of HALT and/or reduced leaflet motion is assessed using MDCT and transcatheter valve hemodynamics are assessed by echocardiography in severe AS patients undergoing TAVI. On MDCT, 12.5% of patients showed HALT and/or reduced leaflet motion, whereas only one of these patients had abnormal valve hemodynamics on echocardiography. Neither HALT nor increased transvalvular gradient were associated with stroke or TIA.

Pressure overload in AS and both pressure and volume overload in AR induce concentric and eccentric LV hypertrophy, respectively. These structural changes influence LV mechanics, but little is known about the time course of LV remodelling and mechanics after aortic valve surgery and its differences in AS vs. AR. In Chapter 9, the time course of LV mass regression and changes in LV mechanics (by LV GLS) in patients with severe AS (63%) or severe AR (37%) undergoing aortic valve intervention are characterized and compared. LV mass regression and changes in LV GLS were similar despite different LV remodelling before aortic valve intervention. In AR, relief of volume overload led to reduction in LV mass and an initial decline in LV GLS. In contrast, relief of pressure overload in AS was characterized by a stable LV GLS and more sustained LV mass regression.

10 CONCLUSIONS AND FUTURE PERSPECTIVES

WITH the rising global health burden of aortic valve disease, growing awareness of the consequences of severe AS (mainly on LV myocardium and outcomes) and the need of intervention with current available interventions (surgical or transcatheter aortic valve replacement) at an earlier stage of the disease, the number of patients who will be referred for aortic valve replacement is expected to increase. The evidence of the efficacy of TAVI in lower risk and potentially even asymptomatic patients is currently being evaluated and multimodality imaging remains of paramount importance for proper patient selection for intervention, determining optimal timing of intervention and in the

evaluation of therapy results.

For risk stratification and defining optimal timing of intervention, conventional and advanced echocardiography and computed tomography are crucial. Conventional echocardiography can be used to assess extra-aortic valvular cardiac damage in patients with severe AS. Especially the presence of tricuspid regurgitation or pulmonary hypertension and RV dysfunction showed a significant impact on prognosis. These components of advanced cardiac injury are generally not included in current risk prediction models, and therefore, prospective studies will need to evaluate whether incorporation of these aspects in future risk models will result in improved risk stratification. On top of conventional echocardiography, advanced echocardiography can provide additional insights. Left ventricular GLS by speckle tracking echocardiography has been suggested as a more sensitive marker of LV systolic dysfunction. In patients with asymptomatic severe AS and preserved LVEF, LV GLS declined over time while LVEF remained unchanged. Furthermore, impaired LV GLS was associated with symptom development and need for intervention. Therefore, LV GLS may be of help to define more optimal timing of intervention in asymptomatic patients with severe AS, before irreversible myocardial damage occurs. However, prospective studies are needed to determine the exact role of LV GLS in timing of intervention and to define potential cut-off values. In symptomatic severe AS patients, LV GLS had an incremental value on top of conventional echocardiographic parameters for the assessment of cardiac injury. Incorporation of LV GLS into a recently proposed staging classification for cardiac damage resulted in the identification of patients with more advanced cardiac damage compared to the original classification. Therefore, implementation of LV GLS in current risk prediction algorithms may provide better preprocedural risk assessment, although this needs to be confirmed in future studies. Computed tomography can be used for the quantification of aortic valve calcification (CT-AVC) in patients with low-gradient severe AS, identifying patients with true severe AS who might benefit from aortic valve intervention. Current and future randomized controlled trials will determine if CT-AVC may aid in decision making of these patients.

For the evaluation of prothesis function and durability after aortic valve implantation and detection of possible (late) complications, echocardiography is the mainstay imaging modality. Also, both conventional and advanced echocardiography can provide additional information on the effects of therapy on LV function and remodelling. Due to its high spatial resolution, computed tomography has emerged as a valuable modality to detect subclinical valve thrombosis after TAVI. HALT and/or reduced leaflet motion after TAVI was seen in 12.5% of patients. These patients showed slightly higher echocardiographic transvalvular gradients compared to patients without HALT, but this was not associated with stroke or TIA. However, the use of anticoagulation has been shown to restore the normal leaflet aspect and motion in patients who presented with HALT and it could be considered to perform computed tomography in these patients for early detection of these structural changes. Therefore, future clinical trials are needed to define specific recommendations for the use of computed tomography in post-TAVI follow-up and to determine optimal anticoagulation management in patients treated with TAVI.

11

SAMENVATTING, CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

SAMENVATTING

De algemene introductie van dit proefschrift (Hoofdstuk 1) geeft een overzicht van de epidemiologie van aortaklepaandoeningen in de ontwikkelde landen en beschrijft de pathofysiologische verschillen tussen aortaklepstenose (AS) en aortaklepinsufficiëntie (AI). In beide hartklepaandoeningen is een interventie aan de aortaklep geïndiceerd als patiënten symptomatisch zijn of als er aanwijzingen zijn voor linkerventrikel (LV)-disfunctie (gedefinieerd als een linkerventrikelejectiefractie [LVEF] <50%). Conventionele tweedimensionale en transthoracale Doppler-echocardiografie is de eerste keus beeldvormingsmodaliteit voor de correcte beoordeling van de ernst van AS of AI, LV-functie en voor preprocedurele risicostratificatie en is ook de voornaamste beeldvormingstechniek voor de evaluatie van de resultaten van behandeling. De toegevoegde waarde van multidetector computertomografie (MDCT) voor de evaluatie van de ernst van AS en de aanwezigheid van subklinische klepbladtrombose na transkatheter-aortaklepimplantatie (TAVI) wordt geïntroduceerd. De rol van speckle-tracking-echocardiografie voor de beoordeling van LV-globale longitudinale strain (LV GLS), vooral bij patiënten met aortaklepziekte met behouden ejectiefractie, wordt benoemd. Het huidige proefschrift is gericht op de evaluatie van de rol van multimodale beeldvorming, met name tweedimensionale (speckle-tracking) echocardiografie en MDCT, in de risicostratificatie en evaluatie van therapie bij patiënten met aortaklepaandoeningen.

DEEL 1: RISICOSTRATIFICATIE EN TIMING VAN INTERVENTIE

In het eerste deel van dit proefschrift wordt de rol van conventionele en speckle-tracking echocardiografie in de risicostratificatie en timing van aortaklepinterventie bij patiënten met ernstige AS onderzocht. Ook wordt de rol van MDCT voor de beoordeling van calcificaties van de aortaklep geïntroduceerd.

Bij patiënten met ernstige AS worden vaak aanwijzingen gezien voor cardiale schade buiten de aortaklep, dit kan worden geclassificeerd met behulp van een recent voorgesteld stadiëringssysteem. Hoofdstuk 2 evalueert de prevalentie van cardiale schade buiten de aortaklep, onderzocht door middel van echocardiografie, en de impact hiervan op prognose in een groot cohort van symptomatische patiënten met ernstige AS uit meerdere centra. Patiënten werden geclassificeerd als Stadium 0 (geen cardiale schade), Stadium 1 (LV-schade), Stadium 2 (mitraalklep- of linkeratriumschade), Stadium 3 (tricuspidaalklepschade of schade aan het arterieel pulmonaal vaatbed) of Stadium 4 (rechterventrikel [RV]-schade). Conform de voorgestelde classificatie werden 8% van de patiënten geclassificeerd als Stadium 0, 24% als Stadium 1, 49% als Stadium 2, 7% als Stadium 3 en 12% als Stadium 4. Na correctie voor klinisch relevante variabelen (zoals aortaklepvervanging) bleek cardiale schade onafhankelijk geassocieerd te zijn met mortaliteit en de gecombineerde uitkomstmaat (namelijk mortaliteit, herseninfarct en cardiaal-gerelateerde hospitalisatie). Dit bleek echter voornamelijk gedreven te worden door tricuspidaalklepschade of schade aan het arterieel pulmonaal vaatbed (Stadium 3) en RV-schade (Stadium 4).

Bij patiënten met ernstige AS is aangetoond dat cardiale schade zoals geclassificeerd volgens een recent voorgesteld stadiëringssysteem sterk geassocieerd is met prognose. Van LV GLS is ook aangetoond dat het onafhankelijk geassocieerd is met uitkomst bij patiënten met ernstige AS met zowel behouden als verminderde LVEF. In Hoofdstuk 3 wor-

den de prognostische implicaties van de incorporatie van LV GLS in dit stadiëringssysteem geëvalueerd en wordt de toegevoegde prognostische waarde van LV GLS boven het algoritme van de stadiëringsclassificatie bestudeerd bij een grote populatie van symptomatische patiënten met ernstige AS. Patiënten werden geclassificeerd in vijf onafhankelijke stadia van cardiale schade. Linkerventrikel GLS werd verdeeld in kwintielen en toegekend aan deze verschillende stadia van cardiale schade. Volgens het originele stadiëringssysteem toonde 9% van de patiënten geen tekenen van cardiale schade (Stadium 0), 27% toonde LV-schade (Stadium 1), 45% toonde linkeratrium- of mitraalklepschade (Stadium 2), 6% toonde schade aan de pulmonale vasculatuur of tricuspidaalklep (Stadium 3) en 13% toonde RV-schade (Stadium 4). Patiënten werden gereclassificeerd na incorporatie van LV GLS: 4% van de patiënten werd gecategoriseerd als Stadium 0, 15% als Stadium 1, 37% als Stadium 2, 19% als Stadium 3 en 25% als Stadium 4. LV GLS was geassocieerd met mortaliteit, onafhankelijk van het stadium van cardiale schade. Na incorporatie van LV GLS in kwintielen in het stadiëringssysteem waren Stadia 2 tot 4 onafhankelijk geassocieerd met uitkomst. L inkerventrikel GLS toonde toegevoegde prognostische waarde boven klinische karakteristieken en het originele voorgestelde stadiëringssysteem. Incorporatie van LV GLS in het originele stadiëringssysteem resulteerde in verfijning van risicostratificatie door de identificatie van patiënten met meer vergevorderde cardiale schade.

Bij asymptomatische patiënten met ernstige AS is een interventie aan de aortaklep geïndiceerd wanneer er sprake is van LV-disfunctie (LVEF <50%). Echter, bij asymptomatische AS-patiënten met behouden LVEF is er tot op heden controverse over de optimale timing voor operatie. LV GLS is voorgesteld als een marker voor subklinische myocardiale disfunctie en zou behulpzaam kunnen zijn bij het identificeren van patiënten die mogelijk voordeel zouden kunnen hebben bij eerdere aortaklepvervanging. In Hoofdstuk 4 wordt de prevalentie van verminderde LV GLS (gedefinieerd als LV GLS >-18.2% gebaseerd op de mediane waarde van de populatie), het natuurlijke beloop van LV GLS en de associatie van verminderde LV GLS met het ontwikkelen van symptomen en noodzaak tot aortaklepinterventie beschreven in een cohort van asymptomatische patiënten met ernstige AS met behouden LVEF afkomstig uit meerdere centra. Ondanks vergelijkbare LVEF was LV GLS op significante wijze verminderd bij patiënten met asymptomatische ernstige AS ten opzichte van controles zonder AS gematcht voor leeftijd en geslacht. Gedurende follow-up trad er significante verslechtering van LV GLS op terwijl LVEF onveranderd bleef. Patiënten met verminderde LV GLS bij baseline (>-18.2%) toonden een hoger risico op het ontwikkelen van symptomen en noodzaak tot het ondergaan van een aortaklepinterventie bij follow-up vergeleken met patiënten met meer behouden LV GLS (≤-18.2%).

Renale disfunctie is een veelvoorkomende co-morbiditeit bij patiënten met ernstige AS en heeft een negatieve invloed op de prognose. Over de invloed van renale disfunctie op de prognose van patiënten met verschillende gradaties van AS is echter weinig beschreven. In Hoofdstuk 5 is een grote populatie van patiënten met aortaklepsclerose en milde tot ernstige AS verdeeld volgens nierfunctie (door middel van geschatte glomerulaire filtratiesnelheid [eGFR]) en werd de prognostische impact van renale disfunctie (gedefinieerd als eGFR <60 ml/min/1.73 m^2) geëvalueerd. In totaal had 28% van de patiënten aortaklepsclerose, 7% had milde AS, 24% had matige AS en 41% had ern-

stige AS. Renale disfunctie was aanwezig in 37% van de patiënten en matig tot ernstige AS werd vaker geobserveerd in deze patiënten, vergeleken met patiënten zonder renale disfunctie (70% vs. 62%, respectievelijk). Ernstig verminderde nierfunctie (eGFR <30 ml/min/1.73 m^2) en aortaklepvervanging (AVR) waren onafhankelijk geassocieerd met mortaliteit na correctie voor de ernst van AS. AVR was geassocieerd met betere overleving onafhankelijk van nierfunctie.

In de meerderheid van patiënten met ernstige AS wordt een combinatie van hoge transvalvulaire gradiënten en een vernauwde aortaklepopening gezien. Bij 30% van de patiënten met ernstige AS wordt echter een vernauwde aortaklepopening gemeten in de aanwezigheid van lage transvalvulaire gradiënten. Bij deze AS-patiënten met lage gradiënten kan het moeilijk zijn ware ernstige AS (veroorzaakt door degeneratieve calcificatie van de aortaklep) te onderscheiden van pseudo-ernstige AS (veroorzaakt door een disfunctionele LV die onvoldoende slagvolume genereert). Evaluatie van de morfologie en gradatie van de calcificatie van de aortaklep kan behulpzaam zijn bij het identificeren van patiënten met ware ernstig AS die voordeel kunnen hebben van interventie. In Hoofdstuk 6 wordt de rol van computertomografie voor de beoordeling van de calciumscore van de aortaklep zoals geëvalueerd door een recente studie besproken en beschouwd.

DEEL 2: EVALUATIE VAN THERAPIE

Het tweede deel van dit proefschrift richt zich op de rol van conventionele en geavanceerde echocardiografie en MDCT voor de evaluatie van therapie bij aortaklepaandoeningen, specifiek de follow-up na chirurgische aortaklepvervanging of TAVI.

Echocardiografie speelt een cruciale rol bij alle stappen van de TAVI-procedure: de juiste selectie van zowel patiënt als prothese, procedurele begeleiding en follow-up van het functioneren van de prothese. Hoofdstuk 7 geeft een overzicht van de klinische applicaties en huidige rol van echocardiografische technieken bij patiëntenselectie, selectie van de juiste grootte van de prothese, periprocedurele begeleiding en postprocedurele follow-up bij TAVI.

De aanwezigheid van hypo-geattenueerde klepbladverdikking (HALT) en/of verminderde klepbladmobiliteit op MDCT is voorgesteld als een mogelijke marker van vroege transkatheter aortakleptrombose. Echter, de associatie hiervan met abnormale hemodynamiek van de aortaklep op echocardiografie (een andere potentiële marker voor trombose) en klinische uitkomstmaten (namelijk herseninfarct of "transient ischemic attack" [TIA]) is tot op heden onduidelijk. In Hoofdstuk 8 wordt de aanwezigheid van HALT en/of verminderde klepbladmobiliteit bekeken door middel van MDCT en wordt transkatheterklephemodynamiek geëvalueerd door middel van echocardiografie bij patiënten met ernstige AS die TAVI ondergaan. Middels MDCT werd bij 12.5% van de patiënten de aanwezigheid van HALT en/of verminderde klepbladmobiliteit vastgesteld, terwijl slechts één van deze patiënten ook abnormale klepgradiënten bij echocardiografie vertoonde. Noch HALT, noch een toegenomen transvalvulaire gradiënt waren geassocieerd met herseninfarct of TIA.

Drukoverbelasting bij AS en zowel druk- als volumeoverbelasting bij AI induceren concentrische- en eccentrische-LV-hypertrofie, respectievelijk. Deze structurele veranderingen beïnvloeden de mechanica van de LV, maar er is slechts weinig bekend over

het tijdsbeloop van hoe de LV remodelleert en hoe de LV-mechanica verandert na aortaklepoperatie en hoe dit verschilt tussen AS en AI. In Hoofdstuk 9 wordt het tijdsbeloop van LV-massaregressie en veranderingen in LV-mechanica (door middel van LV GLS) bij patiënten met ernstige AS (63%) of ernstige AI (37%) die een aortaklepinterventie ondergaan gekarakteriseerd en vergeleken. LV-massaregressie en veranderingen in LV GLS bleken gelijk, ondanks verschillen in LV-remodelling voorafgaand aan de aortaklepinterventie. Bij AI leidde het opheffen van de druk- en volumeoverbelasting tot een reductie van LV-massa en een initiële vermindering van LV GLS. In tegenstelling tot bij AI werd het opheffen van drukoverbelasting bij AS gekarakteriseerd door een stabiele LV GLS en meer constante LV-massaregressie.

Conclusies en toekomstperspectieven

Met de stijgende globale belasting voor de gezondheidszorg door aortaklepaandoeningen, het groeiende bewustzijn van de gevolgen van ernstige AS (voornamelijk aan het LV-myocard en op uitkomsten) en de noodzaak tot interventie in een vroeger stadium van de ziekte met de huidige beschikbare interventies (chirurgische of transkatheter-aortaklepimplantatie), is de verwachting dat het aantal patiënten dat zal worden verwezen voor aortaklepvervanging zal toenemen. Het bewijs voor de werkzaamheid van TAVI bij laag-risico- en potentieel zelfs asymptomatische patiënten wordt op dit moment geëvalueerd en multimodaliteitbeeldvorming blijft van essentieel belang voor de correcte selectie van patiënten voor interventie, het bepalen van optimale timing voor interventie en voor de evaluatie van therapieresultaten.

Voor risicostratificatie en het bepalen van de optimale timing voor interventie zijn conventionele en geavanceerde echocardiografie en computertomografie cruciaal. Conventionele echocardiografie kan worden gebruikt om cardiale schade buiten de aortaklep te bekijken bij patiënten met ernstige AS. Vooral de aanwezigheid van tricuspidaalklepinsufficiëntie of pulmonale hypertensie en RV-disfunctie toonden een significant effect op prognose. Deze componenten van vergevorderde cardiale schade zijn over het algemeen niet geïncludeerd in de huidige risicomodellen en daarom zijn prospectieve studies nodig om te evalueren of de incorporatie van deze aspecten in toekomstige risicomodellen kan resulteren in de verbetering van risicostratificatie. Aanvullend aan conventionele echocardiografie kan geavanceerde echocardiografie additionele inzichten verschaffen. Linkerventrikel GLS gemeten door middel van speckle-tracking-echocardiografie is voorgesteld als een sensitievere marker voor LV-systolische disfunctie. Tevens was verminderde LV GLS geassocieerd met de ontwikkeling van symptomen en noodzaak tot interventie. Daarom zou LV GLS behulpzaam kunnen zijn voor het definiëren van optimalere timing voor interventie bij asymptomatische patiënten met ernstige AS voordat irreversibele myocardiale schade optreedt. Er zijn echter prospectieve studies nodig om de exacte rol van LV GLS in de timing voor interventie te onderzoeken en om potentiële afkapwaarden te bepalen. In symptomatische patiënten met ernstige AS bleek LV GLS van toegevoegde waarde te zijn aanvullend aan conventionele echocardiografische parameters voor de evaluatie van cardiale schade. Incorporatie van LV GLS in een recent voorgestelde stadiëringsclassificatie voor cardiale schade resulteerde in de identificatie van patiënten met meer vergevorderde cardiale schade in vergelijking tot de originele classificatie. Om deze reden zou implementatie van LV GLS in huidige

risicovoorspellingsalgoritmes kunnen leiden tot betere inschatting van preprocedurele risico's, al zal dit moeten worden bevestigd in toekomstige studies. Computertomografie kan worden gebruikt voor de kwantificatie van aortaklepcalcificatie (CT-AVC) in AS-patiënten met lage gradiënten, om zo patiënten te identificeren met ware ernstige AS die mogelijk profijt kunnen hebben van aortaklepinterventie. Huidige en toekomstige gerandomiseerde en gecontroleerde onderzoeken zullen uitwijzen of CT-AVC kan helpen in de besluitvorming bij deze patiëntengroep.

Echocardiografie is de voornaamste beeldvormingsmodaliteit voor de evaluatie van de functie en durabiliteit van de prothese na aortaklepimplantatie en voor de detectie van mogelijke (late) complicaties. Verder kan zowel conventionele als geavanceerde echocardiografie additionele informatie verschaffen over de effecten van therapie op LV-functie en remodelling. Door zijn hoge spatiële resolutie is computertomografie een waardevolle modaliteit gebleken voor de detectie van subklinische kleptrombose na TAVI. HALT en/of verminderde klepbladmobiliteit na TAVI werd gezien in 12.5% van de patiënten. Deze patiënten toonden iets hogere echocardiografische transvalvulaire gradiënten vergeleken met patiënten zonder HALT, maar dit was niet geassocieerd met een beroerte of TIA. Het is echter aangetoond dat het gebruik van antistolling weer tot herstel van het normale klepbladaspect en -mobiliteit kan leiden bij patiënten met HALT en het kan worden overwogen om computertomografie te verrichten bij deze patiënten voor vroegtijdige detectie van deze structurele veranderingen. Daarom zijn toekomstige studies nodig om specifieke aanbevelingen voor het gebruik van computertomografie bij de follow-up na TAVI te definiëren en om het optimale antistollingsbeleid te bepalen bij patiënten behandeld met TAVI.

LIST OF PUBLICATIONS

32. Kuneman J.H., Singh G.K., Hansson N.C., Fusini L., Poulsen S.H., Fortuni F., **Vollema E.M.**, Pedersen A.L.D., Annoni A.D., Nørgaard B.L., Pontone G., Ajmone Marsan N., Delgado V., Bax J.J., Knuuti J. Subclinical leaflet thrombosis after transcatheter aortic valve implantation: no association with left ventricular reverse remodeling at 1-year follow-up. Int J Cardiovasc Imaging. 2022; 38(3): 695-705.

31. Singh G.K., van der Bijl P., Goedemans L., **Vollema E.M.**, Abou R., Ajmone Marsan N., Bax J.J., Delgado V. Prevalence of aortic valve stenosis in patients with ST-segment elevation myocardial infarction and effect on long-term outcome. Am J Cardiol. 2021; 153: 30-35.

30. Jean G., Van Mieghem N.M., Gegeneva T., van Gils L., Bernard J., Geleijnse M.L., **Vollema E.M.**, El Azzouzi I., Spitzer E., Delgado V., Bax J.J., Pibarot P., Clavel M.A. Moderate aortic stenosis in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2021; 77(22): 2796-2803.

29. Hirasawa, K., van Rosendael P.J., Fortuni F., Singh G.K., Kuneman J.H., **Vollema E.M.**, Ajmone Marsan N., Knuuti J., Bax J.J., Delgado V. Prognostic implications of cardiac damage classification based on computed tomography in severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2021; jeab071.

28. Butcher S.C., Fortuni F., Kong W., **Vollema E.M.**, Prevedello F., Perry R., Ng A.C.T., Keong Poh K., Almeida A.G., Gonzalez-Gomez A., Shen M., Yeo T.C., Shanks M., Popescu B.A., Galian-Gay L., Fijalkowski M., Liang M., Tay E., Ajmone Marsan N., Selvanayagam J.B., Pinto F.J., Zamorano J., Pibarot P., Evangelista A., Bax J.J., Delgado V. Prognostic implications of left atrial dilation in aortic regurgitation due to bicuspid aortic valve. Heart. 2021; heartjnl-2020-318907.

27. El Faquir N., **Vollema E.M.**, Delgado V., Ren B., Spitzer E., Rasheed M., Rahhab Z., Geleijnse M.L., Budde R.P.J., de Jaegere P.P., Bax J.J., Van Mieghem N.M. Reclassification of aortic stenosis by fusion of echocardiography and computed tomography in low-gradient aortic stenosis. Neth Heart J., 2020.

26. **Vollema E.M.**, Amanullah M.R., Prihadi E.A., Ng A.C.T., van der Bijl P., Sin Y.K., Ajmone Marsan N., Ding Z.P., Généreux P., Leon M.B., Ewe S.H., Delgado V., Bax J.J. Incremental value of left ventricular global longitudinal strain in a newly proposed staging classification based on cardiac damage in patients with severe aortic stenosis. Eur Heart J Cardiovasc Imaging. 2020; 21(11): 1248-1258.

25. **Vollema E.M.**, Prihadi E.A., Ng A.C.T., Gegeneva T., Ajmone Marsan N., Bax J.J., Delgado V. Prognostic implications of renal dysfunction in patients with aortic stenosis. Am J Cardiol. 2020; 125(7): 1108-1114.

24. Gegenava T., van der Bijl P., **Vollema E.M.**, van der Kley F., de Weger A., Hautemann D., Reiber J.H.C., Ajmone Marsan N., Bax J.J., Delgado V. Prognostic influence of feature tracking multidetector row computed tomography-derived left ventricular global longitudinal strain in patients with aortic stenosis treated with transcatheter aortic valve implantation. Am J Cardiol. 2020; 125(6): 948-955.

23. Gegenava T., van der Bijl P., Hirasawa K., **Vollema E.M.**, van Rosendael A., van der Kley F., de Weger A., Hautemann D.J., Reiber J.H.C., Ajmone Marsan N., Bax J.J., Delgado V. Feature tracking computed tomography-derived left ventricular global longitudinal strain in patients with aortic stenosis: a comparative analysis with echocardiographic measurements. J Cardiovasc Comput Tomogr. 2020; 14(3):240-245.

22. Kong W.K.F., **Vollema E.M.**, Prevedello F., Perry R., Ng A.C.T., Poh K.K., Almeida A.G., González A., Shen M., Yeo T.C., Shanks M., Popescu B.A., Galian Gay L., Fijałkowski M., Liang M., Chen R.W., Ajmone Marsan N., Selvanayagam J., Pinto F., Zamorano J.L., Pibarot P., Evangelista A., Delgado V., Bax J.J. Prognostic implications of left ventricular global longitudinal strain in patients with bicuspid aortic valve disease and preserved left ventricular ejection fraction. Eur Heart J Cardiovasc Imaging. 2020; 21(7): 759-767.

21. Rahhab Z., El Faquir N., Tchetche D., Delgado V., Kodali S., **Vollema E.M.**, Bax J.J., Leon M.B., Van Mieghem N.M. Expanding the indications for transcatheter aortic valve implantation. Nat Rev Cardiol. 2020; 17(2): 75-84.

20. Dolci G., **Vollema E.M.**, van der Kley F., de Weger A., Ajmone Marsan N., Delgado V., Bax J.J. One-year follow-up of conduction abnormalities after transcatheter aortic valve implantation with the SAPIEN 3 valve. Am J Cardiol. 2019; 124(8): 1239-1245.

19. **Vollema E.M.**, Amanullah M.R., Ng A.C.T., van der Bijl P., Prevedello F., Sin Y.K., Prihadi E.A., Ajmone Marsan N., Ding Z.P., Généreux P., Pibarot P., Leon M.B., Narula J., Ewe S.H., Delgado V., Bax J.J. Staging cardiac damage in patients with symptomatic aortic valve stenosis. J Am Coll Cardiol. 2019; 74(4): 538-549.

18. Tastet L., Tribouilloy C., Maréchaux S., **Vollema E.M.**, Delgado V., Salaun E., Shen M., Capoulade R., Clavel M.A., Arsenault M., Bédard É., Bernier M., Beaudoin J., Narula J., Lancellotti P., Bax J.J., Généreux P., Pibarot P. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. J Am Coll Cardiol. 2019; 74(4): 550-563.

17. Gegeneva T., **Vollema E.M.**, van Rosendael A.R., Abou R., Goedemans L., van der Kley F., de Weger A., Ajmone Marsan N., Bax J.J., Delgado V. Changes in left ventricular global longitudinal strain after transcatheter aortic valve implantation according to calcification burden of the thoracic aorta. J Am Soc Echocardiogr. 2019; 32(9):1058-1066.e2.

16. **Vollema E.M.**, Singh G.K., Prihadi E.A., Regeer M.V., Ewe S.H., Ng A.C.T., Mertens B.J.A., Klautz R.J.M., Ajmone Marsan N., Bax J.J., Delgado V. Time course of left ventricular remodelling and mechanics after aortic valve surgery: aortic stenosis vs. aortic regurgitation. Eur Heart J Cardiovasc Imaging. 2019; 20(10):1105-1111.

15. **Vollema E.M.**, Delgado V., Bax J.J. Echocardiography in transcatheter aortic valve replacement. Heart Lung Circ. 2019; 28(9):1384-1399.

14. Prihadi E.A., van der Bijl P., Dietz M., Abou R., **Vollema E.M.**, Ajmone Marsan N., Delgado V., Bax J.J. Prognostic implications of right ventricular free wall longitudinal strain in patients with significant functional tricuspid regurgitation. Circ Cardiovasc Imaging. 2019; 12(3):e008666.

13. Prihadi E.A., **Vollema E.M.**, Ng A.C.T., Ajmone Marsan N., Bax J.J., Delgado V. Determinants and prognostic implications of left ventricular mechanical dispersion in aortic stenosis. Eur Heart J Cardiovasc Imaging. 2019; 20(7): 740-748.

12. Gegeneva T., **Vollema E.M.**, Abou R., Goedemans L., van Rosendael A.R., van der Kley F., de Weger A., Ajmone Marsan N., Bax J.J., Delgado V. Prognostic value of thoracic aorta calcification burden in patients treated with TAVR. J Am Coll Cardiol Imaging. 2019; 12(1): 216-217.

11. Lancellotti P., Magne J., Dulgheru R., Clavel M.A., Donal E., Vannan M.A., Chambers J., Rosenhek R., Habib G., Lloyd G., Nistri S., Garbi M., Marchetta S., Fattouch K., Coisne A., Montaigne D., Modine T., Davin L., Gach O., Radermecker M., Liu S., Gillam L., Rossi A., Galli E., Ilardi F., Tastet L., Capoulade R., Zilberszac R., **Vollema E.M.**, Delgado V., Cosyns B., Lafitte S., Bernard A., Pierard L.A., Bax J.J., Pibarot P., Oury C. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. JAMA Cardiol. 2018; 3(11): 1060-1068.

10. Prihadi E.A., van der Bijl P., Gursoy E, Abou R., **Vollema E.M.**, Hahn R.T., Stone G.W., Leon M.B., Ajmone Marsan N., Delgado V., Bax J.J. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. Eur Heart J. 2018; 39(39): 3574-3581.

9. **Vollema E.M.**, Sugimoto T., Shen M., Tastet L., Ng A.C.T., Abou R., Ajmone Marsan N., Mertens B.J.A., Dulgheru R., Lancellotti P., Clavel M.A., Pibarot P., Généreux P., Leon M.B., Delgado V., Bax J.J. Association of left ventricular global longitudinal strain with asymptomatic severe aortic stenosis: natural course and prognostic value. JAMA Cardiol. 2018; 3(9): 839-847.

8. **Vollema E.M.**, Delgado V., Bax J.J. Aortic valve calcium load: diagnostic and prognostic implications in aortic stenosis. Circ Cardiovasc Imaging. 2018; 11(3): e007643.

7. Yoon S.H., Schmidt T., Bleiziffer S., Schofer N., Fiorina C., Munoz-Garcia A.J., Yzeiraj E., Amat-Santos I.J., Tchetche D., Jung C., Fujita B., Mangieri A., Deutsch M.A., Ubben T., Deuschl F., Kuwata S., De Biase C., Williams T., Dhoble A., Kim W.K., Ferrari E., Barbanti M., **Vollema E.M.**, Miceli A., Giannini C., Attizzani G.F., Kong W.K.F., Gutierrez-Ibanes E., Jimenez Diaz V.A., Wijeysundera H.C., Kaneko H., Chakravarty T., Makar M., Sievert H, Hengstenberg C., Prendergast B.D., Vincent F., Abdel-Wahab M., Nombela-Franco L., Silaschi M., Tarantini G., Butter C., Ensminger S.M., Hildick-Smith D., Petronio A.S., Yin W.H., De Marco F., Testa L., Van Mieghem N.M., Whisenant B.K., Kuck K.H., Colombo A., Kar S., Moris C., Delgado V., Maisano F., Nietlispach F., Mack M.J., Schofer J., Schaefer U., Bax J.J., Frerker C., Latib A., Makkar R.R. Transcatheter aortic valve replacement in pure native aortic valve regurgitation. J Am Coll Cardiol. 2017; 70(22): 2752-2763.

6. Prihadi E.A., van Rosendael P.J., **Vollema E.M.**, Bax J.J., Delgado V., Ajmone Marsan N. Feasibility, accuracy and reproducibility of aortic annular and root sizing for transcatheter aortic valve replacement using novel automated three-dimensional echocardiographic software: comparison with multi-detector row computed tomography. J Am Soc Echocardiogr. 2018; 31(4): 505-514.

5. Podlesnikar T., Prihadi E.A., van Rosendael P.J., **Vollema E.M.**, van der Kley F., de Weger A., Ajmone Marsan N., Naji F., Fras Z., Bax J.J., Delgado V. Influence of the quantity of aortic valve calcium on the agreement between automated 3-dimensional transesophageal echocardiography and multidetector row computed tomography for aortic annulus sizing. Am J Cardiol. 2017; 121(1): 86-93.

4. Prihadi E.A., Leung M., **Vollema E.M.**, Ng A.C.T., Ajmone Marsan N., Bax J.J., Delgado V. Prevalence and prognostic relevance of ventricular conduction disturbances in patients with aortic stenosis. Am J Cardiol. 2017; 120(12): 2226-2232.

3. van Gils L., Clavel M.A., **Vollema E.M.**, Hahn R.T., Spitzer E., Delgado V., Nazif T., De Jaegere P.P., Geleijnse M.L., Ben-Yehuda O., Bax J.J., Leon M.B., Pibarot P., Van Mieghem N.M. Prognostic implications of moderate aortic stenosis in patients With left ventricular systolic dysfunction. J Am Coll Cardiol. 2017; 69(19): 2383-2392.

2. **Vollema E.M**., Kong W.K.F., Katsanos S., Kamperidis V., van Rosendael P.J., van der Kley F., de Weger A., Ajmone Marsan N., Delgado V., Bax J.J. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. Eur Heart J. 2017; 38(16): 1207-1217.

1. Westerhof G.A., **Vollema E.M.**, Weersink E.J., Reinartz S.M., de Nijs S.B., Bel E.H. Predictors for the development of progressive severity in new-onset adult asthma. J Allergy Clin Immunol. 2014; 134(5): 1051-1056.

DANKWOORD

De artikelen die in dit proefschrift zijn beschreven zijn tot stand gekomen op de afdeling cardiologie van het Leids Universitair Medisch Centrum, mede dankzij de kennis en inspanningen van vele collega's. Ik wil graag iedereen bedanken met wie ik de afgelopen jaren heb mogen samenwerken. De volgende personen wil ik graag in het bijzonder bedanken:

Beste prof. dr. Bax, beste Jeroen. Jouw enthousiasme voor de wetenschap is stimulerend, bedankt voor de mogelijkheid om te promoveren bij imaging.

Dear Victoria, to you I want to convey my deepest gratitude. As my daily supervisor, you have shown the greatest amount of patience and support in my scientific pursuits and without you, this thesis would not have been possible.

Dear Nina, thank you for all your input in journal clubs and with manuscripts, I've greatly appreciated your kindness and feedback.

Mijn collega's van de imaging: Philippe, Mand, Rachid, Liselotte, Yasmine, Suzanne, Mai, Aniek, Gurpreet, Alexander, Jeff en Mo en natuurlijk Farnaz, Marlieke en Laurien. Jullie collegialiteit en support bij de dagelijkse strubbelingen met statistiek, meten en schrijven en natuurlijk bij onze vele journal clubs en congressen heb ik als bijzonder waardevol ervaren.

My international imaging colleagues: Melissa, William, Tea, Guilia, Francesca and in particular Tomaz, Edgard and Pieter. I've learned a great deal of you all in the past years and have greatly enjoyed our conversations (both scientific and non-scientific) and especially our excursions during congresses abroad. After Universal Studios in LA, theme park excursions will never be the same again!

Laurien Z., Claire K., Jarieke en overige "tuin"collega's, bedankt voor alle gezelligheid tijdens de koffie- en lunchpauzes in de tuin en voor de onvergetelijke tijd bij NVVC- en ESC-congressen!

Beste Laurien, ik bewonder je vindingrijkheid en doorzettingsvermogen. Je staat altijd klaar met een luisterend oor en goede raad, daar ben ik je erg dankbaar voor. Bedankt dat je mij wilt bijstaan tijdens mijn verdediging als paranimf.

Ook ben ik ook veel dank verschuldigd aan alle vrienden buiten het LUMC.

Vrienden van Sempre Crescendo, bijpraten tijdens borrels en concerten en zelfs bij huwelijken en promoties was een welkome afleiding van promotiebezigheden.

Laura, samen hebben wij een zeer leerzame maar ook pittige ANIOS-tijd doorstaan en hebben het nu allebei geschopt tot cardioloog in opleiding. Jouw nuchtere blik op alles heeft me dikwijls geholpen!

Leden van de Wedding en tegenwoordig Baby Jitters, onze gastronomische onderonsjes boden welkome afleiding. Franka, al vanaf onze tijd in Aruba (alweer 25 jaar geleden!) zijn wij goede vriendinnen! Dorothée, jouw eeuwige enthousiasme en optimisme geven mij altijd een boost, enorm veel dank hiervoor. Guus, Constanteyn, Gerrit en Charlotte, ik kan altijd op jullie rekenen voor een goed gesprek!

Zonder mijn (schoon)familie had ik dit avontuur niet aan kunnen gaan en voltooien.

Lieve opa Frits en oma Marie-Anne en lieve oma Carin, jullie wijze lessen (onder het genot van een kop thee of borrel) hebben mij door menig dip geholpen!

Lieve Anton en Fenneken, Helianne, Eveline en Leander, wat heb ik het getroffen met jullie als schoonfamilie. Heli, Eef en Leander, mijn extra broertje en zusjes, ik heb jullie steun, goede gesprekken en natuurlijk alle gezelligheid ontzettend gewaardeerd.

Anton en Fenneken, ik heb bijzonder veel respect voor jullie probleemoplossend vermogen en nuchterheid, bedankt dat ik hier zo vaak van heb mogen profiteren!

Lieve mam en pap, zonder jullie zou ik niet zijn wie ik ben en zou ik nooit zijn gekomen waar ik nu ben. Jullie hebben me altijd gemotiveerd het beste uit mezelf te halen, altijd mezelf te zijn/blijven en uitdagingen aan te gaan. Onze tijd in Aruba was zo'n uitdaging en dit heeft de band tussen ons als gezin enorm sterk gemaakt. De kaft van dit proefschrift, met een prachtige troepiaal, is een ode hieraan. Met jullie onvoorwaardelijke steun, liefde en vertrouwen, weet ik zeker dat ik elke uitdaging aankan!

Lieve Victor, mijn lieve broertje! Ons 3-jarig verblijf op Aruba was ons eerste echte avontuur samen, hoe toepasselijk dat we ook tegelijk het avontuur van promoveren doorlopen! We delen een wens naar perfectie en nieuwsgierigheid en natuurlijk eigenwijsheid. Bedankt dat jij mijn paranimf wilt zijn.

Mijn liefste Floris, al 29 jaar zijn we maatjes en inmiddels mag ik je al meer dan 6 jaar mijn echtgenoot noemen. Je bent op alle vlakken mijn wederhelft en in alles mijn steun en toeverlaat. Je hebt me geleerd tegenslagen te accepteren en altijd de moed gegeven om door te zetten. Zonder jou was mijn promotie en dit prachtige proefschrift niet mogelijk geweest, daarom wil ik deze graag aan je opdragen.

Lieve Marianne en Isabella, mijn prachtige dochters, wat zijn jullie een verrijking van mijn leven. Ik kan niet wachten op onze toekomstige uitdagingen en avonturen samen.

CURRICULUM VITÆ

Elise Mara Vollema werd geboren op 18 april 1989 in Den Haag. Van 2005 tot 2007 nam zij deel aan het Pre-University College-programma van de Universiteit Leiden, een programma voor getalenteerde en gemotiveerde vwo-leerlingen. In 2007 behaalde zij cum laude het gymnasiumdiploma aan het Vrijzinnig Christelijk Lyceum te Den Haag. Van 2007 tot en met 2013 studeerde zij geneeskunde aan de Universiteit Leiden. In januari 2014 startte zij als arts niet in opleiding tot specialist bij de afdeling interne geneeskunde van het Bronovo Ziekenhuis in Den Haag onder begeleiding van dr. Y.W.J. Sijpkens en per juni 2015 als arts niet in opleiding tot specialist bij de afdeling cardiologie in het Leids Universitair Medisch Centrum. Van oktober 2015 tot en met november 2018 heeft zij promotieonderzoek verricht op de afdeling cardiologie van het Leids Universitair Medisch Centrum onder leiding van prof. dr. J.J. Bax en dr. V. Delgado. De resultaten van dit onderzoek staan beschreven in dit proefschrift. Zij presenteerde haar bevindingen op een groot aantal internationale congressen. Per 1 december 2018 is zij gestart met de opleiding tot cardioloog vanuit het Leids Universitair Medisch Centrum (opleiders prof. dr. M.J. Schalij en dr. S.A.I.P. Trines). Per maart 2021 heeft zij succesvol haar vooropleiding interne geneeskunde bij het Haaglanden Medisch Centrum in Den Haag afgerond (opleider dr. A.H. Bootsma). Momenteel is zij werkzaam als arts-assistent in opleiding op de afdeling cardiologie in het Haaglanden Medisch Centrum (opleider dr. A.P. van Alem).