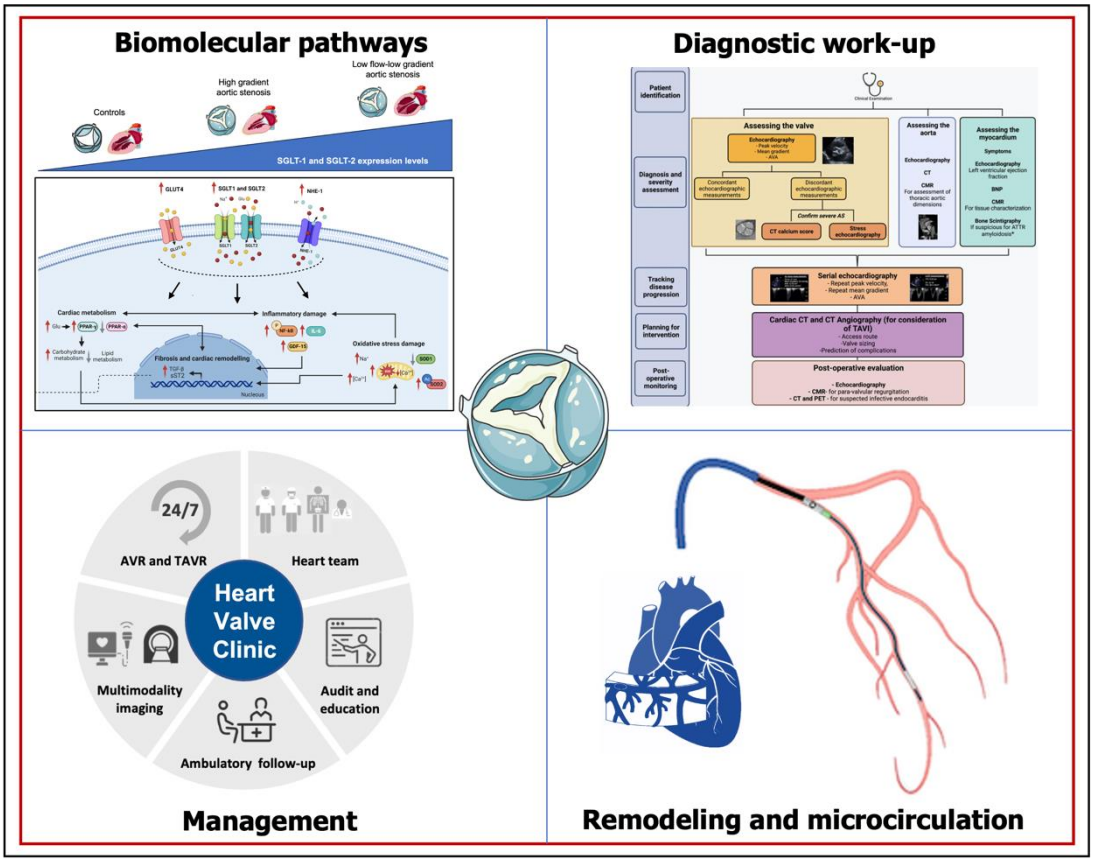
International PhD Programme in Cardiovascular Pathophysiology and Therapeutics - 36° cycle



Contemporary challenges in diagnosis, risk stratification, and management of patients with clinically significant aortic stenosis

Ph.D. Thesis

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To my family …

CONTENTS

CHAPTER 1

Introduction

Aortic stenosis (AS) accounts for substantial global morbidity and premature mortality, affecting 2-6% of the population older than 65 years and 12.4% of adults over the age of 75 years (1-4). According to the latest Valve Heart Disease II Survey, the frequency of AS among patients seeking for medical attention due to valvular heart disease (VHD) has increased from 34% in 2001 to 41% in 2017, with further projections of a two-fold increase in the next decades (4). Yet, the pathology of AS remains poorly understood, and there is no medical therapy effective in slowing disease progression and improving survival. This significantly raised the interest in exploring the natural history of AS over the last decade, with considerable advances in diagnostics and risk stratification of patients with AS.

In this thesis, we report the main findings of our research projects about the diagnosis, risk stratification, and management of patients with AS, with a particular focus on recent developments and future directions.

Starting from pathophysiology, recently, there has been a first clear shift from the paradigm of passive "wear and tear" to consider AS as a metabolically "active, highly regulated, and potentially modifiable" disease process, with both an initiation and progression phase, sharing several similarities with atherosclerosis. Biological markers enabling early detection of focal fibrosis or monitoring the natural history of AS are highly warranted to improve risk stratification, determine optimal timing for aortic valve replacement (AVR), and anticipate the potential futility of the treatment strategy adopted. Blood and tissue biomarkers have a differential pattern and expression level in patients with AS, which may retain a pathophysiological role in cardiac remodeling and metabolism (5,6). However, data available are limited and contradictory (7). The relationship between markers of cardiac remodeling, fibrosis, inflammation, oxidative stress, and cardiac metabolism remains unexplored.

The second paradigm shift concerns the conception of AS as a pathology of both the valve and myocardium rather than an isolated pathology of the aortic valvular apparatus. In this perspective, besides grading AS severity, the assessment of the extravalvular cardiac damage appears to be crucial for risk stratification and prognosis of patients with AS. In the diagnostic work-up of patients with AS, echocardiography remains the reference standard; however, other imaging modalities are now increasingly being used, providing complementary information to guide clinical decision-making (8). Indeed, the myocardial remodeling response to AS varies among individuals and has an important influence on the development of symptoms, heart failure (HF), and long-term prognosis. AS causes an increase in the afterload, triggering a hypertrophic remodeling response that restores wall stress and cardiac performance for many years in accordance with the law of Laplace. Importantly, the degree of left ventricular (LV) hypertrophy is not well predicted by AS severity alone, being influcenced by multiple other factors (i.e. arterial hypertension, sex, and genetic polymorphisms), driving the patients' transition to adverse clinical events (9). Other echocardiographic techniques are emerging to provide more sensitive assessments of LV function in AS. In particular, speckle-tracking echocardiography with global longitudinal strain is a more sensitive marker of systolic dysfunction than ejection fraction. Assessment of left atrial dilatation, pulmonary artery pressure, right ventricular dysfunction, and tricuspid regurgitation provides additional information on the stage of disease and may impact the prognosis of patients with AS (10). On this basis, a classification for staging the extent of “extravalvular” cardiac damage has recently been proposed, integrating progressive involvement of the chambers of the heart (11-14). The cardiac damage staging may also be useful in selecting the optimal type and timing of AVR, either surgical or transcatheter (SAVR/TAVR). Careful consideration should be given to whether the cardiac chamber remodeling is due to AS or other co-morbidities (e.g. pulmonary hypertension or right ventricular dysfunction) and, thus, whether improvement could be expected after AVR.

The third paradigm shift consists in the spread of III-level specialized centers for the management and treatment of patients with AS. Indeed, recently, an increasing number of patients with VHD is

being managed in Heart Valve Clinics (HVCs), which offer multidisciplinary services and fast and easy referral to other necessary disciplines, enhancing the quality of patient care (15). According to the ESC/AHA Guidelines, the HVCs include: i) availability of the entire spectrum of surgical and transcatheter valve procedures with 24/7 services, ii) weekly Heart Team meetings; iii) organization of a HVC for ambulatory management; iv) use of multimodality imaging including echocardiography, cardiac CT, cardiac magnetic resonance and nuclear medicine, v) yearly evaluation of patients outcomes with quality check and planning of educational programs (16,17). The HVC involves cardiologists with expertise in VHD, cardiac imaging specialists, cardio-anesthesiologists, cardiac surgeons, and dedicated nurses.

The last part of this thesis is dedicated to the role of coronary microvascular dysfunction in the natural history of AS. Severe AS is associated with variable impact on LV remodeling and coronary flow regulation (18). Development of left ventricular hypertrophy in patients with AS is an adaptive response aimed at increasing contractile forces and reducing wall stress in LV to eventually maintain a preserved stroke volume for many years despite an elevated LV afterload (19). In this setting, a series of unfavorable hemodynamic changes, including high LV cavity pressure, low coronary perfusion pressure, and increased extravascular compressive forces, lead to a flow shift from the endocardium to the epicardium, resulting in subendocardial ischemia, despite the absence of significant obstructive coronary artery disease (20). In addition, the progression of LV hypertrophy increases myocardial oxygen demand, resulting in a supply-demand mismatch, which requires an increase of the resting coronary flow due to the vasodilation of intramyocardial arterioles induced by the autoregulation phenomenon (20). On the clinical ground, as a result of the LV oxygen supply-demand mismatch, exercise/tachycardia-induced myocardial ischemia and exertional angina might occur in patients with severe AS. However, the interplay among coronary flow, microvascular regulation, severity of AS, LV hypertrophy, and hemodynamic overload remains complex, multifactorial, and poorly understood.

PART I

Aortic stenosis: a metabolically “active, highly regulated, and potentially modifiable” disease.

CHAPTER 2

MYOCARDIAL SGLT2 EXPRESSION AND CARDIAC REMODELING OF PATIENTS WITH SEVERE AORTIC STENOSIS: THE BIO-AS STUDY

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Introduction

Cardiac remodeling plays a major role in the prognosis of patients with AS and could impact the benefits of AVR. Based on transvalvular gradient and forward stroke volume, two distinct phenotypes of severe AS can be distinguished: high-gradient (HG) and low-flow low-gradient (LF-LG) AS (21). Compared to patients with HG AS, those with LF-LG AS have a markedly poorer prognosis with mortality rates of 30–50% at 2 years despite aortic valve replacement (AVR), being a challenging sub-group for both diagnosis and therapeutic management (22-24). The pathophysiology of LF-LG AS and mechanisms responsible for left ventricular (LV) dysfunction are poorly understood. Compared to HG AS, patients with LF-LG AS show more extensive myocardial fibrosis on cardiac magnetic resonance (CMR) (25-27). Focal fibrosis at CMR rapidly develops in up to 50% of asymptomatic AS patients (28) and remains irreversible even up to 1 year after AVR, predicting long-term mortality (29-31). Biological markers enabling early detection of focal fibrosis to monitor the natural history of AS are highly warranted to improve risk stratification, determine optimal timing for AVR, and anticipate the potential futility of the treatment strategy adopted.

Blood and tissue biomarkers have a differential pattern and expression level in patients with AS, which may retain a pathophysiological role in cardiac remodeling and metabolism (5,6). However, data available are limited and contradictory (7). So far, no study has examined the expression of SGLT2 gene and protein in patients with severe AS and its association with markers of cardiac remodeling and metabolism. Thus, we aimed to characterize the differential patterns of expression of blood and tissue biomarkers, including SGLT-2: i) in human cardiomyocytes in patients with severe AS (versus controls without AS); ii) in patients with severe AS stratified into HG and LF-LG.

Methods

In this multicenter study, consecutive patients older than 18 years with severe AS referred for AVR at Cardiovascular Center OLV, Aalst (Belgium) and University of Campania "Luigi Vanvitelli" Monaldi Hospital, Naples (Italy) were considered eligible. Patients with severe aortic and/or mitral regurgitation or mitral stenosis, previous cardiac surgery, rheumatic cardiac disease, bicuspid aortic valve, connective tissue disorders, pacemakers, unable to provide informed consent were excluded. Moreover, patients for whom biopsies were too small for laboratory analysis were also excluded. In addition, contemporary control patients from the same centers who underwent non-valvular cardiac surgery were included. The control group included patients with diseases unrelated to pressure or volume overload (ascending aortic aneurysm and atrial myxoma).

All patients in the study population underwent 12-lead electrocardiography, complete echocardiographic evaluation, pre-operative invasive coronary angiography and/or cardiac CT, intra-operative blood sampling, and myocardial biopsy. Gene expression and protein levels of main biomarkers of cardiac fibrosis (Galectin-3, sST2, Serpin4, Collagen, TGF-β), inflammation (GDF-15, IL-6, NF-kB), oxidative stress (SOD1, SOD2), and cardiac metabolism (NHE, PPAR-α, PPAR-γ, GLUT1, and GLUT4) were evaluated in blood samples and myocardial biopsies with Elisa assay, RNA extraction and Real-time-polymerase chain reaction (RT-PCR) and protein extraction and immunoblotting assay (**Figure 1**).

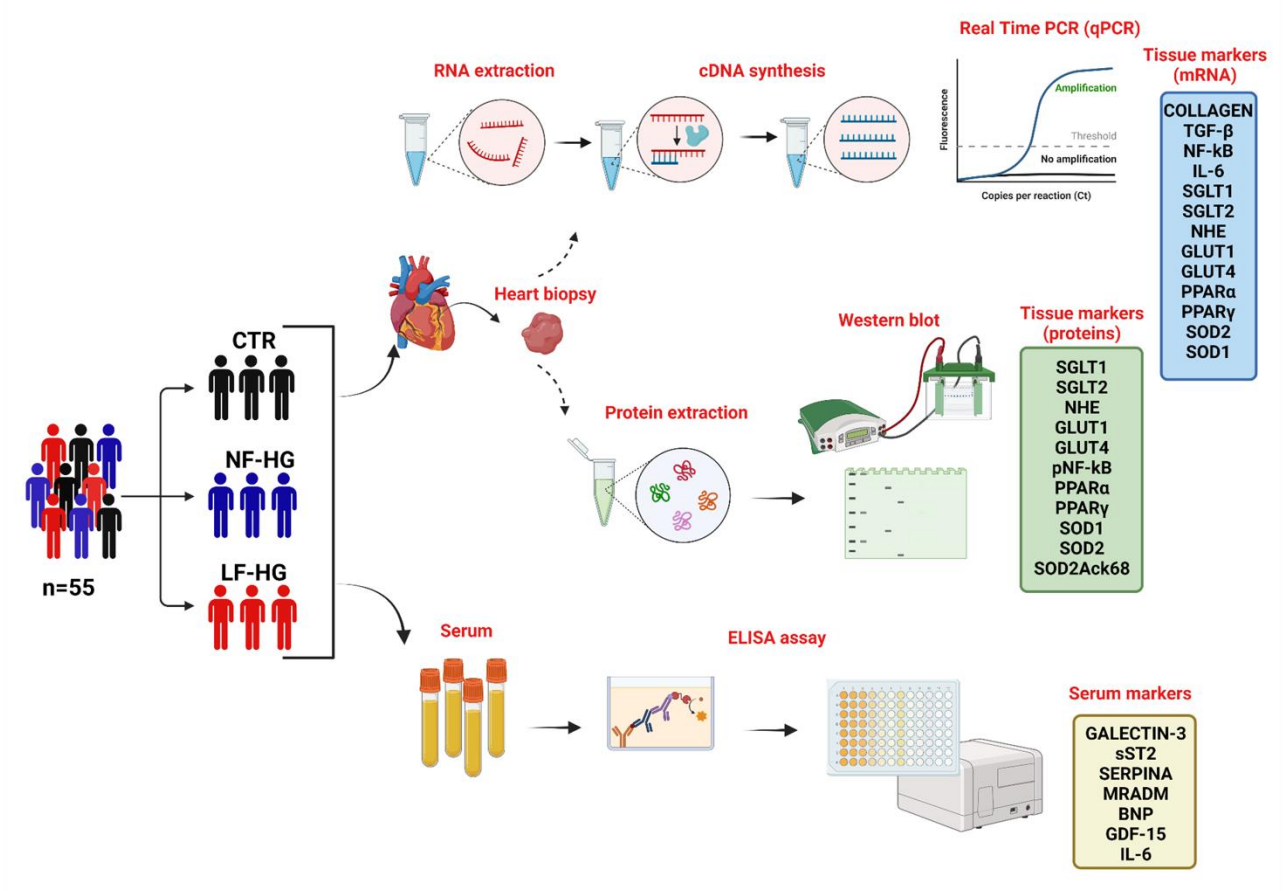


Figure 1. Study procedures.

Results

Study population

The study population consisted of 45 patients with severe AS classified in HG (n=34) and LF-LG (n=11), compared to 10 contemporary controls. Cardiovascular risk factors, co-morbidities, and clinical presentation were similar between the two cohorts (**Table 1**). There were no significant differences in the estimated glomerular filtration rate (eGFR) and NT-proBNP values between the 2 cohorts upon admission. No differences among cardiovascular medications at admission were observed, except for a higher percentage of LF-LG AS patients receiving anticoagulation therapy ($p<0.023$) and diuretics ($p<0.035$) compared to those with HG (**Table 1**).

In the LF-LG AS subgroup, LV dimensions and masses were significantly elevated ($p<0.05$ for all). As expected, patients with LF-LG AS exhibited significantly lower LVEF and MG ($p<0.001$ for both). Moreover, this subgroup demonstrated higher filling pressures and compromised longitudinal right ventricular function compared to patients with HG AS ($p<0.03$ for both).

Table 1. Baseline characteristics of study population, stratified in those with high gradient (NF-HG), low flow-low gradient (LF-LG) aortic stenosis and controls.

	Controls (N = 10)	HG AS (N =34)	LF-LG AS (N =11)	P value
Age, years	65.1 ± 10	79 ± 8.9	63.3 ± 8.7	0.001
Male Sex, n (%)	5 (50)	16 (47.1)	6 (54.5)	0.909
BMI, kg/m^2	26.5 ± 3.7	27.8 ± 5.7	25.0 ± 3	0.268
AH, n (%)	8 (80)	29 (85.3)	10 (90.9)	0.777
Diabetes Mellitus, n (%)	1 (10)	8 (23.5)	2 (18.2)	0.634
Dyslipidemia, n (%)	5 (50)	27 (79.4)	9 (81.8)	0.142
Known AF, n (%)	2 (20)	4 (11.8)	4 (36.4)	0.182
CKD, n (%)	0 (0)	3 (8.8)	1 (9.1)	0.619
CAD history, n (%)	1 (10)	4 (11.8)	3 (27.3)	0.404
Prior HF hospitalization, n (%)	0 (0)	1 (2.9)	2 (18.2)	0.108
Clinical presentation				
Angina, n (%)	2 (20)	5 (14.7)	2 (18.2)	0.909
Syncope, n (%)	1 (10)	2 (5.9)	1 (9.1)	0.877
Dyspnea, n (%)	8 (80)	33 (97.1)	11 (100)	0.445
NYHA Class III-IV, n (%)	0 (0)	11 (32.4)	6 (54.5)	0.074
EuroSCORE II, (%)	1.71 ± 0.9	1.66 ± 0.9	1.83 ± 1.2	0.923
Laboratory tests				
GFR, ml/min	78.3 ± 9.8	72 ± 14.8	83.3 ± 13.6	0.069
BNP, pg/ml	1.37 ± 0.21	1.90 ± 0.87	2.14 ± 0.76	0.073
Medications				
Diuretics, n (%)	3 (30)	23 (67.6)	9 (81.8)	0.035*
MRA, n (%)	1 (10)	8 (23.5)	2 (18.2)	0.634
ACE-I/ARBs, n (%)	4 (40)	16 (47.1)	7 (63.6)	0.517
Beta blockers, n (%)	5 (50)	9 (26.5)	5 (45.5)	0.270
Statins, n (%)	4 (40)	23 (67.6)	9 (81.8)	0.120
Antiplatelets, n (%)	4 (40)	18 (52.9)	5 (45.5)	0.744
Anticoagulants, n (%)	2 (20)	3 (8.8)	5 (45.5)	0.023**
Oral antidiabetic drugs, n (%)	0 (0)	4 (11.8)	2 (18.2)	0.397
Insulin, n (%)	1 (10)	3 (8.8)	1 (9.1)	0.994

Continuous variables are presented as mean ± SD or median [LQ-UQ], when indicated; categorical ones as n (%).
χ^2 test was used for categorical variables; ANOVA for normally distributed and the Kruskal-Wallis test for non-normally distributed continuous variables.
Post-hoc significant comparisons were carried out with the Bonferroni-corrected test.
*p-value<0.05 for LF-LG versus control.
** p-value<0.05 for LF-LG versus HF-HG.
Abbreviations: NF-HG: Normal Flow – High Gradient; LF-LG: Low Flow – Low Gradient; AS: Aortic stenosis; BMI: Body Mass Index; BSA: Body Surface Area; AH: Arterial Hypertensions; AF: Atrial Fibrillation; CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; HF: Heart Failure; eGFR: estimated Glomerular Filtration Rate; BNP: Brain Natriuretic Peptide; MRA: Mineralocorticoid Receptor Antagonists; ACE-I: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin-receptor blockers.

Tissue biomarkers of cardiac metabolism

A progressive increase in gene expression of both SGLT2 and SGLT1 was observed across the three study groups (p<0.001) (**Figure 2, Panel A**). Particularly, in patients with LF-LG AS, both SGLT1 and SGLT2 gene expressions were notably high, whereas they were nearly absent in the control group (**Figure 2, Panels A**). Consistently, LF-LG AS patients displayed higher protein levels compared to both HG AS and control group (**Figure 2, Panel B**). These differences remained significant even after adjusting for age, gender, body mass index (BMI), diabetes mellitus (DM), arterial hypertension (AH), and coronary artery disease (CAD). Similarly, NHE gene expression demonstrated a significant and progressive increase across the three groups, reaching its peak in patients with LF-LG AS (p for trend <0.001) (**Figure 2, Panel C**). In contrast, NHE protein expression levels were higher in patients with AS compared to control group (**Figure 2, Panel D**), but no significant trend was found among the groups. These differences remained significant after adjusting for age, gender, BMI, DM, AH, and CAD.

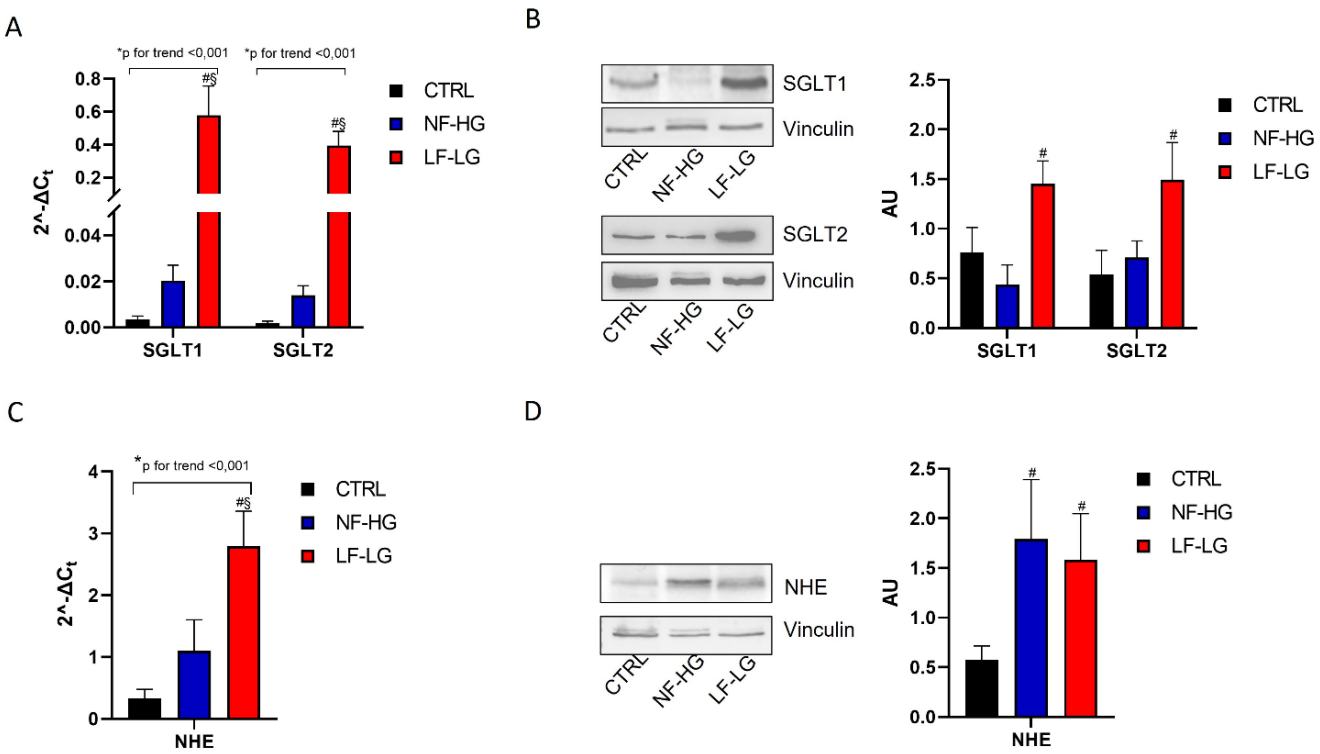


Figure 2. Detection of tissue cardiac metabolism biomarkers according to aortic stenosis phenotypes: A, C) Tissue relative mRNA levels of SGLT1, SGLT2 and NHE were determined by real-time reverse transcription-polymerase chain reaction. GAPDH was used as the internal control. The fold increase of mRNA expression was calculated using the $2^{-\Delta Ct}$ method; B, D) Western blot analysis for myocardial SGLT1, SGLT2 and NHE. The histograms show the densitometric analysis and values are expressed as arbitrary units (AU).

Data are mean ± SD. When adjusted for age, gender, BMI, presence of DM, AH, and CAD history p for trend <0.05*. # $p < 0.05$ for NF-HG and LF-LG versus control. § $p < 0.05$ for LF-LG versus NF-HG.

A gradual increase in both gene and protein myocardial expressions of GLUT4 and PPAR-γ, along with a progressive decrease in protein myocardial expression of PPAR-α was observed across the three study groups (p<0.001 for all) (**Figure 3**). However, there were no significant differences in gene and protein expression levels of GLUT1 among the three groups (**Figure 3, Panels A-B**). Notably, both gene and protein expressions of GLUT4 were significantly elevated in AS patients, without differences between HG and LF-LG AS (**Figure 3, Panels A-B**). Myocardial gene and protein expressions of PPAR-γ were significantly higher in LF-LG AS patients compared to both control group (p<0.05) and HG group (p<0.05). While no significant differences in PPAR-α gene expression were observed among the three study groups, LF-LG AS patients exhibited significantly

lower PPAR-α protein expression (**Figure 3, Panels C-D**). These differences remained significant after adjusting for age, gender, BMI, DM, AH, and CAD.

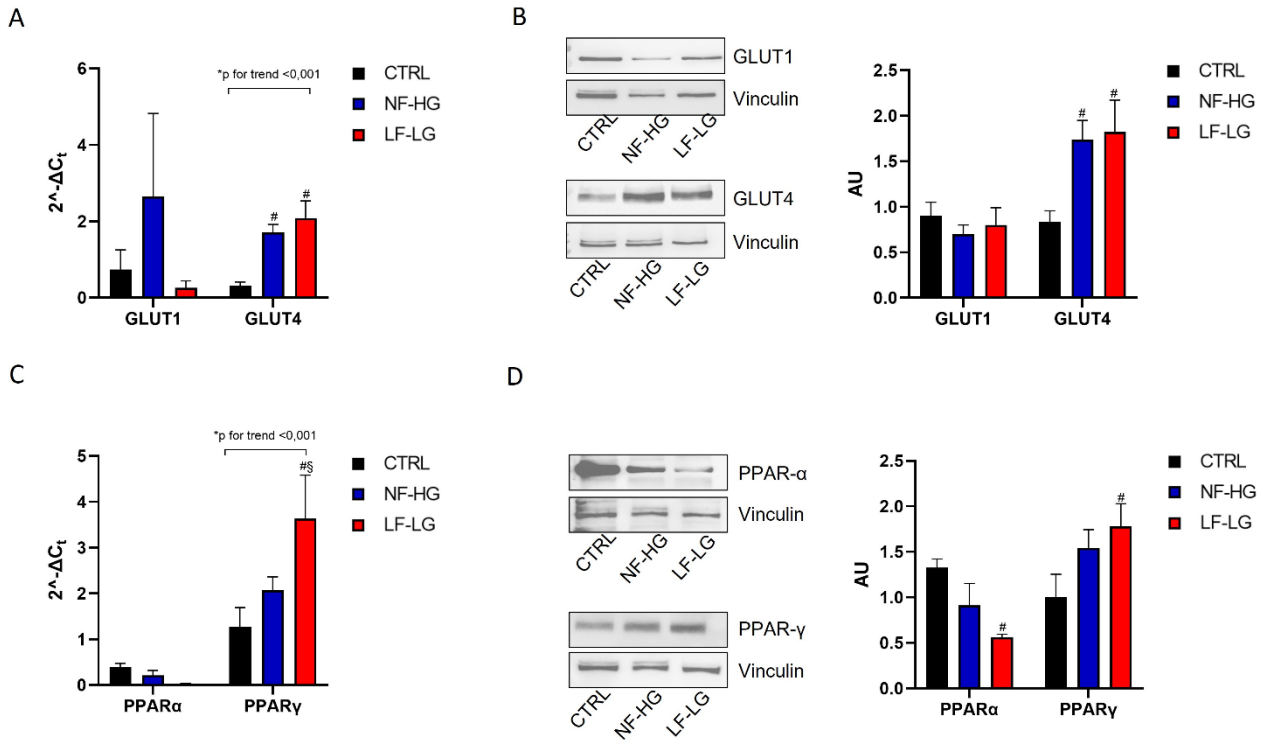


Figure 3. Detection of tissue cardiac metabolism biomarkers according to aortic stenosis phenotypes: A, C) Tissue-relative mRNA levels of GLUT1, GLUT4, PPARα, and PPARg, were determined by real-time reverse transcription-polymerase chain reaction. GAPDH was used as the internal control. The fold increase of mRNA expression was calculated using the $2^{-\Delta Ct}$ method; B, D) Western blot analysis for myocardial GLUT1, GLUT4, PPARα, and PPARg. The histograms show the densitometric analysis, and values are expressed as arbitrary units (AU).
Data mean ± SD When adjusted for age, gender, BMI, presence of DM, AH, and CAD history p for trend <0.05*. # p < 0.05 for NF-HG and LF-LG versus control. § p < 0.05 for LF-LG versus NF-HG.

Association of SGLT2, SGLT1, and NHE1 with cardiac remodeling in patients with AS

Gene expression of SGLT2 (r=-0.58, p<0.001), SGLT1 (r=-0.37, p<0.01), and NHE (r=-0.34 p<0.01) was significantly and inversely correlated with LVEF. Gene expression of SGLT2 was also inversely and significantly correlated with AVA (r=-0.29, p<0.045), and positively correlated with LV mass index (r= 0.42, p<0.003). Regarding plasma biomarkers of cardiac remodeling, both SGLT1 and SGLT2 gene expression showed a positive correlation with plasma soluble suppression of

tumorigenicity 2 (sST2) (r=0.30 p<0.04; r=0.34 p<0.018, respectively) and Serpin-4 (r=-0.55 p<0.001; r=-0.64 p<0.001, respectively). NHE1 gene expression had a positive correlation with plasma Serpin-4 (r=-0.51 p<0.001) but not with sST2 levels (r=0.25 p<0.08). Multivariate regression analyses, adjusting for age, gender, BMI, AH, DM, CAD revealed the independent association of SGLT1, and SGLT2 gene expression with plasma sST2 and Serpin-4 levels as well as the independent association of NHE1 with Serpin-4. When including in the model also LVEF as a covariate, only Serpin-4 plasma levels were significantly associated with SGLT1 and SGLT2. A model that included AS phenotypes as a covariate, and tested the independent association of SGLT1, SGLT2, and NHE gene expression, showed that only the AS phenotype was independently associated with plasma sST2 and Serpin-4 levels.

Association of SGLT2 with inflammatory, fibrosis, and oxidative stress biomarkers.

Both SGLT1 and SGLT2 gene expressions were positively correlated with TGF-β (r=0.42 p<0.002; r=0.72 p<0.001, respectively) and collagen (r=0.65 p<0.001; r=0.73 p<0.001, respectively) gene expression as markers of fibrosis. They also showed positive correlations with NF-kB (r=0.37 p<0.009; r=0.36 p<0.01, respectively) and myocardial IL-6 (r=0.52 p<0.001; r=0.68 p<0.001, respectively) gene expression as inflammatory markers, and SOD2 (r=-0.35 p<0.01; r=-0.38 p<0.006, respectively) gene expression as a marker of oxidative stress. Furthermore, SGLT2 gene expression had a positive correlation with GLUT4 (r=0.33 p<0.02) and PPAR-α (r=0.36 p<0.01) gene expressions, thus supporting the metabolic relationship between them. NHE1 gene expression was positively correlated with NF-kB (r=0.38 p<0.005) and SOD2 (r=-0.32 p<0.01) gene expression.

Multivariate analyses, including age, gender, BMI, AH, DM, CAD, AS phenotypes, and gene expressions of SGLT2, SGLT1, and NHE, revealed that both SGLT2 (b=0.52; t =2.49; p<0.01) and NHE1 gene expressions (b=0.45; t =2.25; p<0.05) were independently associated with NF-kB gene expression. Only SGLT2 gene expression was independently associated with myocardial IL-6

(b=0.53; t=2.81; p<0.001), TGF- β (b=0.59; t =3.22; p<0.001), and collagen (b=0.62; t =3.62; p<0.001) gene expression.

Discussion

Our study demonstrates, for the first time, the hyper-expression of SGLT2 gene and protein level in patients with LF-LG AS. In contrast, controls and HG AS patients showed undetectable or negligible SGLT2 expression. Additionally, correlations were observed between SGLT2 expression and plasma and tissue biomarkers related to fibrosis, inflammation, and oxidative stress. These findings provide further evidence for the potential molecular involvement of SGLT2 in cardiac functional impairments of LF-LG AS patients.

The available treatments for severe AS include surgical replacement (SAVR) or trans-catheter aortic valve implantation (TAVI). So far, medical therapy has not been proven effective in delaying disease progression, and AVR is recommended once symptoms or LV dysfunction develop (21). The presence, extent, and reversibility of cardiac damage, particularly fibrosis, play a major role in the prognosis of these patients and could even impact the benefits of AVR (32,33). Despite procedural success of AVR/TAVI, a substantial number of TAVI recipients face heart failure-related hospitalization within the first year post-TAVI, leading to a notable increase in long-term mortality and health care costs. Therefore, there is an urgent need for pharmacological strategies aiming at mitigating or slowing down irreversible cardiac remodeling and its associated LV dysfunction (34,35). In large, randomized trials, SGLT2i significantly improved cardiovascular and renal outcomes in diabetic patients, extending benefits to non-diabetic patients with HF (32,36-38). Moreover, SGLT2i have shown promising effects in patients with acute myocardial infarction, with less robust evidence, as randomized clinical trials are still ongoing (39-42).

While SGLT2 expression in the kidney is well established, its presence in the myocardium is still debated (43-46). Recent experiments have demonstrated the expression of SGLT2 in cardiomyocytes of patients with HF, regardless of diabetic status (43). However, no study has investigated changes in myocardial SGLT2 gene and protein expression in patients with AS and whether these changes correlate with fibrosis, inflammation, and oxidative stress, leading to a gradual and progressive deterioration of cardiac metabolism and impaired cardiac function.

Our data showed, for the first time, the SGLT2 hyper-expression in LF-LG AS patients, which is associated with critical molecular changes in cardiac metabolism, oxidative stress, inflammatory damage, fibrosis, and cardiac remodeling pathways (**Figure 4**). These findings align with previous research linking SGLT2 protein hyper-expression to increased activity in the inflammation and oxidative stress pathways (47).

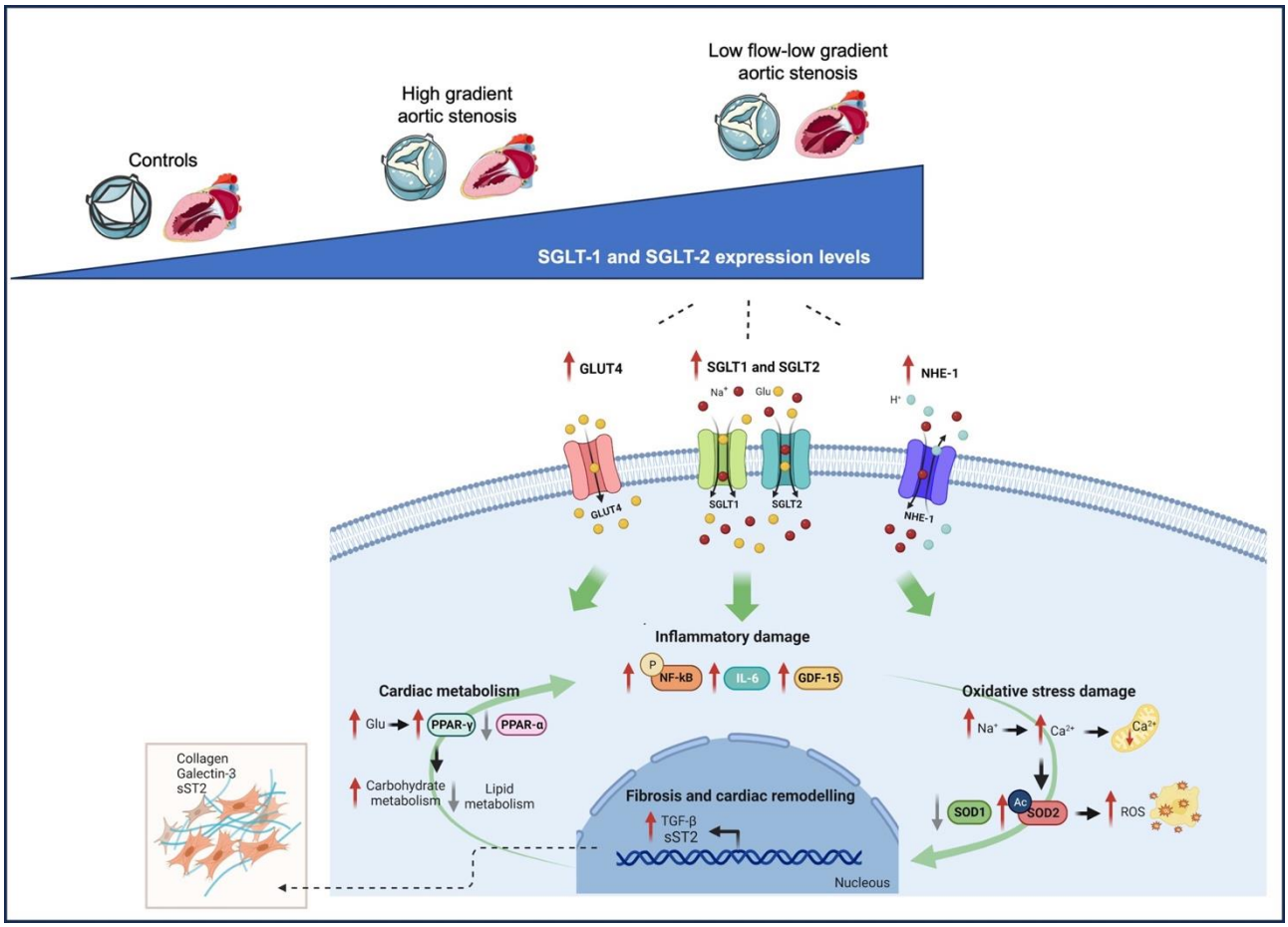


Figure 4. SGLT1 and SGLT2 expression and intracellular pathways in patients with severe AS. Patients with low-flow low-gradient (LF-LG) aortic stenosis (AS) showed: i) SGLT1 and SGLT2 hyper-expression; ii) elevated levels of GLUT4 and NHE-1, leading to increased intracellular concentrations of glucose (Glu), sodium (Na+), along with a reduction in H+ levels. This intracellular perturbation promotes: a) alterations in cardiac metabolism by increasing PPAR-γ and decreasing PPAR-α expression, promoting carbohydrate over lipid metabolism; b) cardiac remodeling and fibrosis, through over-expression of sST2 and TGF- β which leads to increased synthesis of Collagen, Galectin-3, and sST2 by fibroblasts; c) inflammation, marked by elevated levels of GDF-15 and phosphorylated NF-kB (S276) (active form) levels, which in turn increases IL-6 gene expression; d) oxidative stress damage through increased mitochondrial Ca+ concentrations, followed by a reduction in the antioxidant enzyme SOD1 and an increase in the acetylated form of SOD2 (inactive form).

Pressure overload in severe AS involves both structural and metabolic remodeling and increases the risk of progression to HF (48). Continuous pressure overload in AS intensifies myocardial wall stress, resulting in increased wall thickness and mass, ultimately leading to left ventricular hypertrophy and related fibrosis. Cardiac remodeling in AS represents a typical phenotypic response to stress, culminating in impaired myocardial metabolism and energetics. Metabolism in healthy cardiomyocytes during mechanical overload involves 3 stages (48): i) substrate utilization, primarily through beta-oxidation, supported by glycolysis for additional requirements such as exercise or long-term increased myocardial stress ("myocardium metabolic flexibility"); ii) oxidative phosphorylation in the mitochondrial membrane, the preferred pathway for ATP generation; iii) ATP transfer and utilization for myofibril contraction. From a biomolecular perspective, as AS severity advances and structural myocardial remodeling evolves toward HF, significant metabolic derangement emerges. Specifically, this leads to abnormal cardiac substrate utilization, characterized by a down-regulation of fatty acid oxidation, increased reliance on glucose metabolism, and consequent myocardial lipid accumulation. This creates a metabolic condition resembling energy deprivation where there is an imbalance between cardiomyocytes' energy requirements and contractile performance (48). This energy imbalance might trigger increased SGLT2 expression, precipitating a metabolic shift from primarily lipid-based to carbohydrate-based metabolism, resulting in reduced ATP synthesis and functional inefficiency (49). In this context, our study reveals that in patients with LF-LG AS, GLUT4 and NHE-1 levels are elevated, causing an increase in intracellular concentrations of glucose (Glu), sodium (Na^+), and a reduction in H^+ levels. This intracellular perturbation promotes: a) metabolic shift by upregulating PPAR-γ while downregulating PPAR-a expression, favoring carbohydrate over lipid metabolism; b) fibrosis and cardiac remodeling, by sST2 and TGF-b over-expression, leading to increased synthesis of Collagen, Galectin-3, and sST2 by fibroblasts; c) inflammation, by rising GDF-15 and phosphorylated NF-kB (S276) (active form) levels, subsequently increasing IL-6 gene expression; d) oxidative stress damage

facilitated by heightened mitochondrial Ca^{+} concentrations, followed by a reduction in the antioxidant enzyme SOD1 and an increase in the acetylated form of SOD2 (inactive form) (**Figure 4**). Our data corroborate the previously established role of SGLT1 and NHE in the molecular remodeling process as we observed a progressive increase in their expression from controls to LF-LG AS patients (26). Of particular interest is the role of NHE, which, when hyper-expressed, has been associated with increased expression of phosphorylated phospholipase (PLC) and inositol triphosphate (IP3). This leads to enhanced release of Ca^{++} from the endoplasmatic reticulum, increased entry of extracellular Ca^{++}, and activation of profibrotic activities in atrial fibroblasts (50). In line with these findings, empagliflozin has been shown to inhibit cardiac fibrogenesis by inhibiting the NHE, and modulating calcium homeostasis (50).

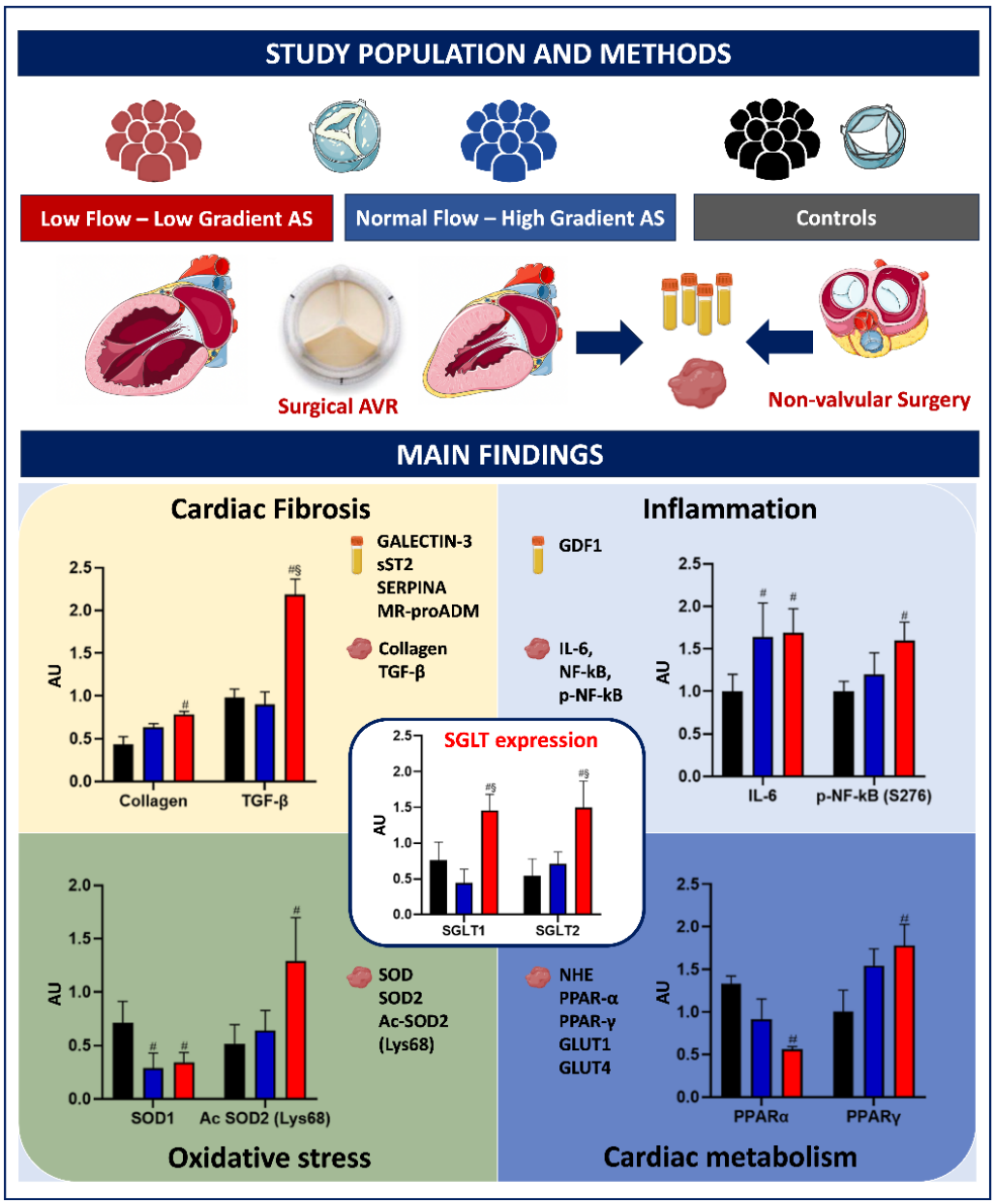
Remarkably, all the above-mentioned pathways interact with each other, creating a harmful vicious cycle (**Figure 4**). Over time, this structural-metabolic imbalance increases the risk of reduced LVEF and the development of HF.

An unresolved question is whether the progression of metabolic damage corresponds to the clinical progression of the disease. Interestingly, Amat-Santos et al. have recently started a clinical trial in TAVI patients evaluating the clinical usefulness of dapagliflozin to prevent re-hospitalization (51). Our data, demonstrating the overexpression of SGLT2 in LF-LG AS patients and its association with unfavorable cardiac remodeling, supports the rationale of this trial. It also highlights the possibility of initiating the SGLT2i before AVR (SAVR/TAVI), particularly in cases of LF-LG AS to minimize the development of fibrosis, inflammation, and metabolic derangements.

Conclusions

Our findings indicate that the overexpression of SGLT2 in LF-LG AS patients is associated with unfavorable cardiac remodeling and impaired cardiac function. The hyper-expression of SGLT2 gene and protein in patients with LF-LG might pave the way to the use of SGLT2-Is in this subset

population. This approach has the potential to improve the outcomes of AVR and reduce the likelihood of re-hospitalization within one year.



Graphical abstract. Central Illustration. Main findings of the study. Abbreviations: AS – aortic stenosis; AVR – aortic valve replacement; AU - arbitrary units. Bar plots: in red, patients with low-flow low-gradient aortic stenosis; in blue, patients with normal flow – high gradient AS; in black: controls. # $p < 0.05$ for NF-HG and LF-LG versus control. § $p < 0.05$ for LF-LG versus NF-HG.

PART II

Multimodality imaging in the diagnostic work-up of patients with aortic stenosis: from valve to cardiac damage.

CHAPTER 3

MULTI-MODALITY IMAGING IN AORTIC STENOSIS

AN EACVI CLINICAL CONSENSUS DOCUMENT

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Introduction

Non-invasive imaging, in combination with clinical assessment, has played a central role in the assessment and management of AS for many decades. In this EACVI clinical scientific update, we explored the current use of multi-modality imaging in the diagnosis, risk-stratification and follow-up of patients with AS, with a particular focus on recent developments and future directions. Echocardiography is and will likely remain the key method of diagnosis and surveillance of aortic stenosis providing detailed assessments of valve hemodynamics and the cardiac remodelling response. Other imaging modalities are now increasingly being used, providing complementary information that is improving our understanding of the underlying biology, and helping to guide clinical decision-making. CT is already widely used in the planning of transcutaneous aortic valve implantation. We anticipate its increased use as an anatomical adjudicator to clarify disease severity in patients with discordant echocardiographic measurements. CT calcium scoring is currently used for this purpose, however contrast computed tomography techniques are emerging that allow identification of both calcific and fibrotic valve thickening. Additionally, improved assessments of myocardial decompensation with echocardiography, cardiac magnetic resonance and computed tomography will become more commonplace in our routine assessment of AS. Underpinning all of this will be the widespread application of artificial intelligence. In combination we believe this new era of multi-modality imaging in aortic stenosis will improve the diagnosis, follow-up and timing of intervention in aortic stenosis as well as potentially accelerate the development of the novel pharmacological treatments required for this disease.

Echocardiography

Echocardiography is the key primary imaging modality for the diagnosis, assessment, and follow-up of AS. The purpose of the echocardiographic examination in a patient with suspected AS is: i) to confirm valve morphology and a diagnosis of AS; ii) to grade severity; iii) to assess the cardiac remodeling response.

Aortic valve morphology

Transthoracic echocardiography is able, in the majority of cases, to determine the valve phenotype (tricuspid, bicuspid, unicuspid or other) according to Sievers classification (Type 0: No raphe; Type 1: 1 raphe; Type 2: 2 raphe) or a new classification recently proposed by an international group of experts (52). Transoesophageal echocardiography (TOE) or cardiac magnetic resonance (CMR) can be helpful to clarify aortic valve morphology when transthoracic echocardiography is not diagnostic.

Hemodynamic severity of AS

The main echocardiographic parameters to define AS severity are the peak aortic jet velocity, peak and mean transvalvular gradients, aortic valve area, and Doppler velocity index (DVI) (53). Aortic valve area can be indexed for body surface area to account for differences in height, particularly in those of shorter stature. It should be avoided in obese or very thin patients when indexing to height may be superior. Based on these echocardiographic parameters, we can differentiate severe from non-severe AS (**Table 1**).

The aortic valve area, calculated from the continuity equation, is widely used as a "less flow-dependent" parameter of AS severity that can be employed to assess AS severity even in low flow states. It should be noted that the aortic valve area can be prone to measurement error, related predominantly to inaccuracies in assessing the left ventricular outflow tract (LVOT) area and the simplistic assumption that the LVOT is circular rather than oval (54). Alternatives include the velocity time integral (VTI) ratio, which provides a ratio of the VTI at the aortic valve and the left ventricular outflow tract and, therefore, avoids measurement of the left ventricular outflow tract area completely (55).

Table 1 **Echocardiographic parameters of severe and very severe AS**

	Non-severe AS	Discordant AS (with low flow defined as SVI < 35 mL/m^2)	Severe AS	Very severe AS
Peak jet velocity (m/s)	<4.0	3.0–4.0	≥4.0	≥5.0
Mean gradient (mmHg)	<40	20–40	≥40	≥60
AVA (cm^2)	>1.0	≤1.0	≤1.0	<0.6
Indexed AVA (cm^2/m^2)	>0.6	≤0.6	≤0.6	<0.4

Patients may have discordant echocardiographic assessments where the above parameters do not agree on the true severity of AS. Most commonly, this is encountered in patients with an AVA < 1.0 cm^2 and a peak velocity of <4.0 m/s).
AVA, aortic valve area; AS, aortic stenosis.

Discordant grading of AS severity at echocardiography

Up to 40% of patients with severe AS have an apparent discordance between the peak velocity/mean gradient and aortic valve area: most commonly where the aortic valve area indicates severe disease and the peak velocity or mean gradient suggests otherwise Berthelot-Richer (56). "Discordant grading" includes 3 main categories:

i) "classical" low-flow, low-gradient AS with stroke volume index <35 mL/m^2 and with reduced left ventricular ejection fraction (<50%);

ii) "paradoxical" low-flow, low-gradient AS with stroke volume index <35 mL/m^2 but with preserved left ventricular ejection fraction (≥50%);

iii) normal-flow, low-gradient AS with stroke volume index ≥35 mL/m^2 and preserved left ventricular ejection fraction (≥50%).

In cases of low-flow low-gradient AS with low ejection fraction, dobutamine stress echocardiography is recommended (57,58). True severe aortic stenosis is characterized by a fixed aortic valve area (≤1.0cm^2) in the face of an increased flow rate. This will result in higher gradients and velocities across the stenotic valve (transaortic velocity ≥ 4m/s and mean pressure gradient across the valve of > 40 mmHg at any stage of dobutamine stress echocardiography). Another important parameter to assess is the change in stroke volume with dobutamine administration. An increase in stroke volume of < 20% is a marker of reduced LV reserve and is associated with a worse prognosis and higher peri-

operative risk (59). The alternative that is being increasingly used in patients with discordant echocardiography and which is recommended in the ESC guidelines is CT calcium scoring (58).

Assessment of the myocardium and cardiac remodeling

Besides grading AS severity, echocardiography is useful in assessing the structure and function of the left ventricle as well as the other cardiac chambers. Assessment of left atrial dilatation, pulmonary artery pressure, right ventricular dysfunction and tricuspid regurgitation provides incremental information on the stage of disease and may have important prognostic implications in patients with AS (10). On this basis, a classification for staging the extent of extra aortic valve cardiac damage and heart failure associated with AS has recently been proposed integrating progressive involvement of the chambers of the heart (11-14). This echo assessment of cardiac chamber remodeling may also be useful in selecting the optimal type and timing of aortic valve replacement with transcatheter aortic valve implantation (TAVI) potentially preferred in patients with more advanced damage.

Developing techniques in the echocardiographic assessment of AS

Other echocardiographic techniques are emerging to provide more sensitive assessments of left ventricular function in AS. Speckle tracking echocardiography provides an assessment of myocardial strain. In particular, global longitudinal strain appears to provide a more sensitive marker of systolic dysfunction than ejection fraction. A threshold of < 15% is associated with AS patients who have a higher risk of adverse outcomes (60).

Computed Tomography

CT calcium scoring

Discordant echocardiographic measurements are common and governed by complex interactions between the ventricle, the valve, and systemic arterial compliance (61). It is therefore valuable to have an alternative, anatomical assessment of disease severity that is truly flow-independent, reliable,

inexpensive and reproducible. Non-contrast CT aortic valve calcium scoring fulfils this role. As an anatomical measure of both valve calcium density and volume, a standardised method of assessment has been validated in multiple international cohorts, with established sex-specific thresholds for severe AS: 1200 AU in women (positive predictive value of 93% and negative predictive value of 79%) and 2000 AU in men (positive predictive value of 88% and negative predictive value of 82%) (61,62). CT aortic valve calcium scoring is now recommended by both European Society of Cardiology and American Heart Association/ American College of Cardiology Guidelines to help clarify stenosis severity when discordant echocardiographic assessments remain inconclusive (16).

CT angiography

An accurate pre-TAVI multimodality imaging assessment is pivotal not only to determining patient's eligibility for TAVI but also for precise procedure planning. Imaging is needed to obtain a degree of "controlled" oversizing (target of 10-15% annular area oversized), resulting in a radial force between the prosthetic valve and aortic valve complex, to ensure adequate anchoring and sealing and to avoid complications linked to incorrect valve selection (63-66). During the last years, cardiac computed tomography (CCTs) has become the gold standard imaging modality for TAVI procedure planning. Specific acquisition requirements depend on the local imaging acquisition protocol and CT scanner, but some general principles should be considered, according to the Society of Cardiac Computed Tomography (SCCT) consensus document (67):

- Scanner system: multi-slice scanner systems (at least a 64-detector technology) should be used, providing an optimal reconstructed slice width of 0.6 mm.
- Patient preparation: premedication with beta-blocker or nitrates should be avoided, despite higher heart rates, considering that evaluation of the coronary arteries is not the primary goal of the examination and the clinical concern regarding the severe aortic stenosis.
- Acquisition: the best approaches would be to combine, during the same intravenous contrast material injection, the EKG-gated data acquisition of the aortic root structures and a faster

non-EKG gated CT angiography of the vascular bed for simultaneous assessment of the vascular access routes (66,68-70). Retrospective EKG-gated synchronization should be preferred and, to avoid under-sizing, annulus measurements should be performed in the systolic phase (typically 20% to 45% of the R-R interval), during which it manifests its intrinsically largest dimensions (66,71,72). Tube voltage and settings should be chosen according to patient's weight and size.

Native axial slices can be easily transferred, reconstructed and post-processed using dedicated semi-automated TAVI workstation software (4). Post-processing platforms facilitate annular segmentation by manual placement of each aortic cusp nadir. Once the appropriate plane has been generated, the following dimensions are used to guide the prosthetic valve selection, in terms of type and size, combined with the best access route, with high intra- and inter-observer reproducibility (73-75):

- annular size and left-ventricular outflow tract (LVOT) diameter (the aortic annulus is defined as the virtual basal ring, formed by joining the three most caudal connection points of the valvar aortic leaflets (76,77). CCT, with its multiplanar reconstructions, provide a comprehensive definition of the annular geometry and avoid the systematic underestimation by TTE);
- sinotubular junction and ascending aorta diameters;
- coronary ostium heights (≤12 mm is a risk factor for coronary occlusion);
- fluoroscopic projection angles (identifying proper angulations for fluoroscopy that allow the appropriate coaxial positioning of the prosthesis along the centerline of the aorta and orthogonal to the native valve plane, reducing the aortogram numbers required during the implantation, procedural timings and contrast medium volume) (73);
- calcifications amount and distribution in the valvular apparatus and contiguous critical areas, using a semiquantitative score or quantitively Agatson score (>3000 was correlated with an increased incidence of paravalvular regurgitation) (73,78,79);
- vascular access.

Cardiac magnetic resonance

The ability of CMR to characterise the aortic valve, the myocardium and the aorta make it an attractive imaging modality in AS. The major limitations of CMR compared to echocardiography include its lack of portability, length of scan and relative expense although rapid image acquisition protocols have already improved the latter two issues (80).

Assessment of the Myocardium

CMR provides reference standard assessments of left ventricular structure (wall thickening, hypertrophy dilatation, mass-volume-ratio) and function (ejection fraction and myocardial strain using feature-tracking) and should be used in cases where echocardiographic windows are poor and ventricular assessments uncertain (81).

Myocardial fibrosis

The unique strength of CMR is myocardial tissue characterization. Non-infarct patterns of late gadolinium enhancement (LGE) can be identified in patients with AS as a marker of focal replacement fibrosis, demonstrating a close association with increased collagen deposition and microscars on histology (82). The prevalence of non-infarct LGE in severe AS ranges from 27% to 51% (30) and is associated with multiple other markers of left ventricular decompensation, including impairment in systolic and diastolic function, the ECG-strain pattern, elevated serum biomarkers (e.g. B-type natriuretic peptide and cardiac troponin) reduced exercise capacity and symptomatic status (83). Once established, further LGE appears to accumulate rapidly over time and to be irreversible following aortic valve replacement (27,29). The myocardial scar burden that patients develop whilst waiting for aortic valve replacement, therefore, persists into the long term, an important observation given that it also serves as a powerful independent predictor of long-term outcomes (30). The ongoing EVOLVED randomized controlled trial is investigating whether prompt valve replacement in

asymptomatic patients with severe AS and myocardial scarring improves patient outcomes (Clinicaltrials.gov identifier: NCT03094143) (84). Furthermore, distinct patterns of non-ischaemic LGE make it possible to identify concomitant pathology such as cardiac amyloidosis, which is also associated with a higher risk of all-cause mortality (85).

Beyond LGE, T1 mapping and extracellular volume fraction (ECV) quantification can identify extracellular matrix expansion: a surrogate for fibrosis (both replacement and diffuse interstitial fibrosis) or infiltration (e.g. amyloidosis). Diffuse fibrosis increases with more severe AS and left ventricular hypertrophy (27). Unlike the focal fibrosis detected by LGE, diffuse fibrosis is largely reversible after aortic valve replacement. Indeed, patients with more extensive diffuse fibrosis derive a larger benefit in symptoms and left ventricular function following aortic valve replacement (86). Several recent large multicentre studies of patients with severe AS imaged prior to AVR, demonstrated ECV% was associated with markers of left ventricular decompensation and both cardiovascular and all-cause mortality (87,88).

Reverse left ventricular remodeling after aortic valve replacement

Reverse remodeling after aortic valve replacement is associated with early normalization in left ventricular function within 6 months and 20-30% left ventricular mass regression in the first 6 to 12 months (89,90). Mass decreases most in those with more left ventricular hypertrophy and no scar(89). ECV quantification is able to discern cellular from matrix volume regression, although more research into this area is required (29,88).

Integrating current clinical modalities

Echocardiography remains the mainstay of diagnosis and monitoring in patients with AS. It provides vital information on the valve and myocardium and is both widely available and cost-effective. In many patients no further imaging is required. However, in certain patient groups additional imaging

approaches can improve patient assessment and should be given due consideration. An integrated approach, facilitated by a dedicated Heart Valve Team is proposed in **Figure 1**.

In patients with discordant echocardiography, additional imaging using either CT calcium scoring or stress echocardiography in patients with a low flow state, helps clarify AS severity and aids decision-making. In patients with suspected aortopathy, CT or CMR should be used to provide a comprehensive assessment of the thoracic aorta. In patients with suspected concomitant amyloidosis, CMR or bone scintigraphy (both with the exclusion of light chain disease) is recommended in the latest ESC guidelines. Similarly, in patients with left ventricular systolic dysfunction, CMR can clarify whether the impairment is due to the valve disease (and might therefore improve following aortic valve replacement) or other irreversible processes, including myocardial infarction. This can help decision-making around the need for valve intervention. Finally in those patients being considered for valve intervention, CT angiography is now routinely used to assess the suitability and access options for the majority of patients prior to TAVI.

Valve and Myocardial Assessments

The anatomic assessment provided by CT may come to play a greater role in how we assess and track AS severity, particularly in patients with discordant echocardiography or suboptimal echo windows. As has been observed in coronary artery disease, there is a natural progression from non-contrast to contrast CT angiography, allowing more detailed assessment of fibrotic as well as calcific valve thickening. As novel medical therapies emerge targeting valve calcification or fibrosis these contrast CT assessments may allow us to tailor optimal therapies for individual patients and provide an imaging technique able to track the effects of new therapies on anatomic disease progression in phase 2 clinical trials. This can then inform which therapies should proceed to phase 3 clinical end-point trials (91).

Advanced multi-modality myocardial assessments by echocardiography, CMR and CT may also be increasingly used to track mild to moderate AS and the effects of AS on the myocardium and to

identify more precisely when the left ventricle is starting to decompensate in the face of AS, thereby optimising the timing of aortic valve replacement. Finally, the impact of artificial intelligence is likely to be felt in daily clinical practice across all the imaging modalities, optimising and standardising cardiac imaging (87,92).

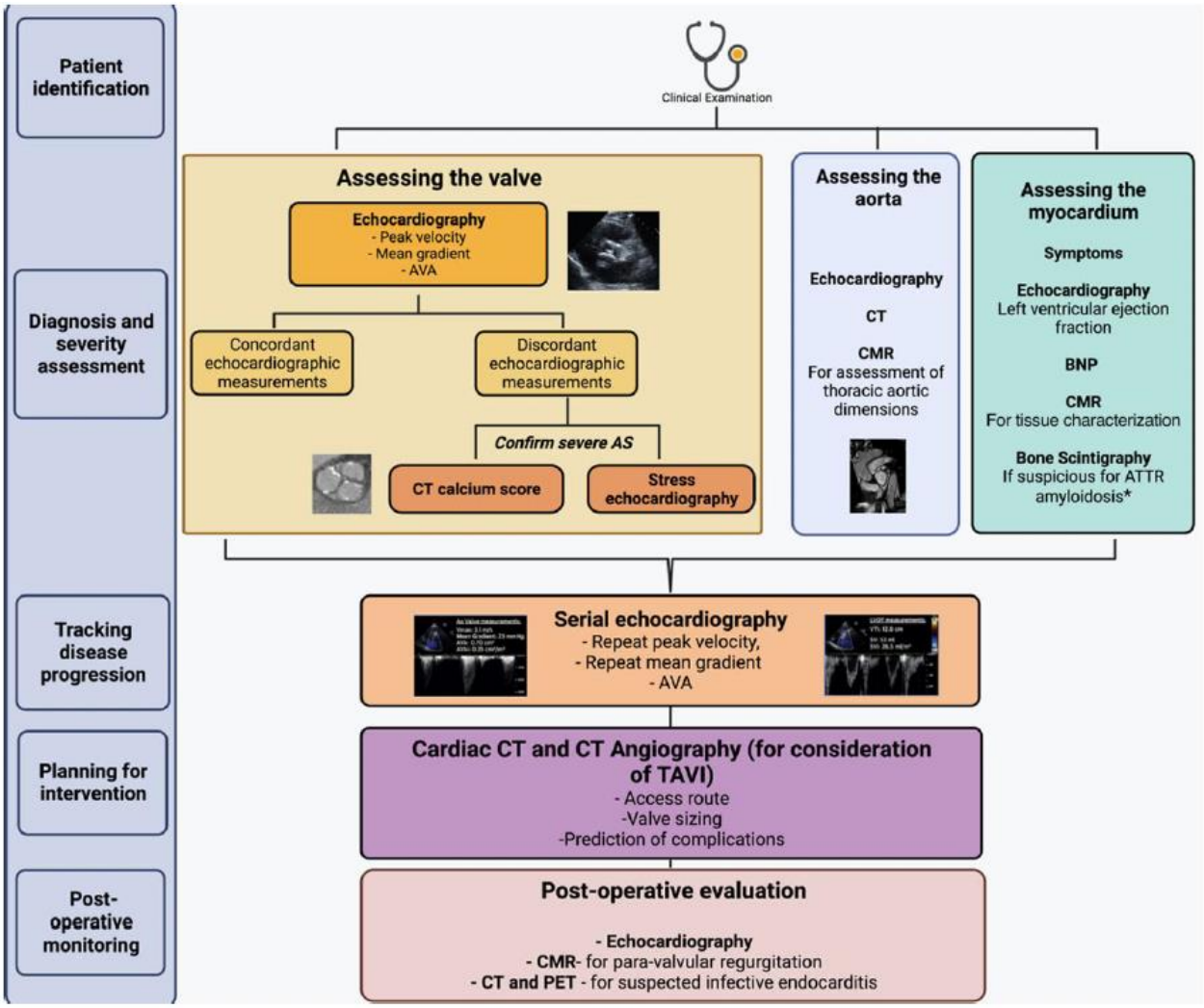

Figure 1. The current patient pathway in diagnosing and monitoring AS with the use of multi-modality imaging. AVA, aortic valve area; AS, aortic stenosis; ATTR, transthyretin; BNP, beta-natriuretic peptide; CMR, cardiac magnetic resonance; CT, computed tomography; LV, left ventricular; TAVI, transcatheter aortic valve implantation. *Features of amyloidosis including but not limited to features of heart failure, carpal tunnel syndrome, neuropathy, low-voltage QRS complex on ECG, left ventricular hypertrophy, left ventricular diastolic dysfunction, and granular speckling effect of myocardium on echocardiography.

Conclusions

The diagnosis and management of AS continues to evolve and to improve. Echocardiography remains the most important imaging test, playing an indispensable role in the diagnosis and monitoring of patients with this condition and in clinical decision-making. Other imaging modalities provide complementary information and are increasingly being used in complex patients where echocardiographic assessments are inconclusive or in the planning of TAVI procedures. A multidisciplinary approach with a Heart Valve Team is recommended to ensure the appropriate use of multimodality imaging and to optimize the care provided to our AS patients.

CHAPTER 4

MYOCARDIAL WORK PREDICTS OUTCOME IN ASYMPTOMATIC AORTIC STENOSIS: SUBANALYSIS OF RANDOMIZED AVATAR TRIAL

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Introduction

In patients with severe AS, LV myocardial damage induced by pressure overload is associated with adverse outcomes (27,60,93-98). Current guidelines recommend using LVEF to assess myocardial impairment in aiding the decision-making (96,98). However, several studies have demonstrated the low sensitivity of LVEF to detect ongoing myocardial damage, diminishing its value regarding the prognostic implications in the severe AS setting (60,93,96,98-100). This limitation may be overcome by implementing other echocardiographic techniques to provide more sensitive assessments of left ventricular function in AS. In particular, speckle-tracking echocardiography with global longitudinal strain (GLS) appears to provide a more sensitive marker of systolic dysfunction than ejection fraction. In severe AS, GLS often appears impaired at baseline or shows further deterioration over time, while LVEF remains within the normal range (60,101). Impaired GLS has been shown to be associated with the development of symptoms, the need for AVR, and increased morbidity and mortality despite preserved LVEF (60,100,101). However, afterload dependency of GLS may limit its accuracy in AS, as GLS may be reduced not only due to myocardial dysfunction but also due to increased LV afterload.

Recently, non-invasive LV myocardial work (MW) has been validated as an echocardiographic index of LV systolic performance incorporating afterload (102-104). Therefore, the assessment of MW might provide more accurate information on myocardial status than GLS in the conditions characterized by variable LV afterload between visits or clinical settings such as AS.

In symptomatic patients with severe AS, LV global work index (GWI) has been associated with NYHA III/IV heart failure symptoms, while GLS did not (105). However, the clinical implications of GWI assessment in asymptomatic patients with severe AS are unknown. In the present subanalysis of the AVATAR trial, we investigated the association between GWI and outcome in asymptomatic patients with severe AS and preserved LVEF, who were randomized to early AVR versus conservative treatment.

Methods

This was a retrospective subanalysis of echocardiographic data performed in patients of the AVATAR randomized clinical trial (NCT02436655) (93,106). In brief, this was an international, multicenter (9 centers) trial in patients with asymptomatic severe AS and preserved LVEF, who were randomly assigned to early AVR versus conservative management. The absence of symptoms was validated using exercise testing.

The final study population consisted of 86 patients (55% of the original AVATAR cohort) mainly due to the unavailability of echocardiographic images, recording by ultrasound system or in a format not allowing MW analysis (n=56; 80%) as, at this moment, only one ultrasound vendor provides MW analysis. Additional reasons were poor echocardiographic image quality for speckle-tracking or absence of simultaneous blood pressure measurement (n=7; 10%) and others (n=7; 10%). There were no significant statistical differences in baseline characteristics between the original AVATAR cohort and the patients included in this analysis. Each patient underwent transthoracic echocardiography at baseline and, if alive, at 12 months following early AVR or at 12 months following randomization to conservative treatment. Follow-up information was obtained from all included patients.

All analysed echocardiographic images were recorded using Vivid E9, 95 or S70 machine (GE Healthcare Horten, Norway) and analyzed offline using dedicated software (EchoPAC, version 202, Milwaukekee, WI, USA). All baseline and follow-up analyses were performed by operators blinded to clinical data and outcome. GLS was calculated using a 17-segment model at the time in systole when the value peaked. MW was assessed by the combination of LV strain data and a non-invasively estimated LV pressure curve, calculated by entering the sum of the subject’s brachial cuff systolic blood pressure and mean pressure gradient across the aortic valve into the measurement tool as well as setting valvular event timing. This non-invasive method of MW calculation in AS (adding transaortic P mean to the systolic blood pressure) showed excellent correlation and high agreement with MW calculation using invasive LV pressure (105,107). The area of the pressure strain loop is used to derive segmental and global MW. The segmental distribution of MW is displayed in a bull's

eye plot. Global work index (GWI) was calculated as the average of segmental values. The clinical endpoints consisted of all-cause mortality and its composite with HF hospitalization.

Results

This analysis included 86 patients (mean age 67 ± 11 years, 57% males), out of whom 41 (48%) were randomly allocated to early AVR and operated within a median of 50 days (IQR, 33-65 days). Among 45 patients allocated originally to the conservative management, a total of 16 (18%) patients underwent late AVR after a median of 383 days (IQR, 224-583 days), while 29 (34%) individuals were asymptomatic and had no AV intervention during the entire follow-up.

The majority of patients (88%) had degenerative etiology of AS, while the bicuspid aortic valve was noted in 12% of individuals. All included patients had severe AS (AVA 0,69 ± 0,17 cm^2), with 21 (24%) individuals having a low flow (SVI ≤ 35 ml/m^2). Average LV GLS showed significant impairment (-14 ± 5%), while GWI was within the normal range (1986 ± 279 mmHg%) despite the high afterload imposed by severe AS. During median follow-up of 1305 days (IQR 931-1655 days), a total of 12 (14%) patients died from any cause, while cardiovascular cause of death was recorded in 7 (8%) individuals. An additional 8 (9%) subjects were admitted for HF decompensation.

Table 1. Baseline and 12-month follow-up characteristics, functional and clinical outcome.

	All patients (n=86)	GWI ≤ 2000 mmHg% (n=42)	GWI > 2000 mmHg% (n=44)	P value
Age, years	67 ± 11	68 ± 10	67 ± 11	0.66
Sex (female), n (%)	37 (43)	18 (43)	19 (43)	1.00
Etiology of aortic stenosis, n (%)				
Degenerative	74 (88)	36 (86)	38 (86)	1.00
Bicuspid	12 (12)	6 (14)	6 (14)	
STS score, %	2,1 ± 1,6	2.1±1.7	2,1 ± 1,5	0.86
Diabetes mellitus, n (%)	25 (29)	12 (29)	13 (30)	1.00
Hypertension, n (%)	75 (87)	36 (86)	39 (89)	0.75
History of CAD	0	0	0	NA
History of stroke, n (%)	2 (2)	1 (2)	1 (2)	1.00
BNP pg/ml	121 ± 88	134 ± 82	110 ± 94	0.35
Creatinine µmol/L	82 ± 21	81 ± 21	83 ± 20	0.70
Echocardiography				
LVEDd mm	51 ± 4	51 ± 5	52 ± 4	0.35
LVEF≥ 60%, n (%)	76 (88)	38 (90)	38 (86)	0.73
LV mass index g/m^2	129 ± 29	129 ± 32	129 ± 26	0.88
SVI ml/m^2	41 ± 10	41 ± 10	41 ± 1	0.99
V_{max} m/s	4,5 ± 0,3	4.6 ± 0.3	4,4 ± 0,3	0.012
P_{mean} mmHg	53 ± 12	56 ± 11	50 ± 12	0.06
AVA cm^2	0,69 ± 0,17	0.70 ± 0.15	0,69 ± 0,20	0.65
AVAi cm^2/m^2	0,36 ± 0,08	0.36 ± 0.07	0,35 ± 0,09	0.79
HR, bpm				
Baseline	75 ± 13	78 ± 13	72 ± 13	0.053
12-month follow up	74 ± 14	76 ± 14	71 ± 13	0.12
Systolic blood pressure, mmHg				
Baseline	135 ± 13	134 ± 15	136 ± 12	0.68
12-month follow up	131 ± 25	130 ± 24	131 ± 26	0.72

SBP+Pmean, mmHg				
Baseline	185 ± 20	187 ± 22	183 ± 18	0.43
12-month follow up	137 ± 66***	146 ± 61***	127 ± 71***	0.25
LVEF, %				
Baseline	69 ± 7	68 ± 8	69 ± 6	0.32
12-month follow-up	68 ± 7	67 ± 7	70 ± 6	0.16
LV GLS, %				
Baseline	-14 ± 5	-13 ± 4	-16 ± 3	P < 0.001
12-month follow-up	-16 ± 3**	-15 ± 5**	-17 ± 3	0.038
LV GWI, mmHg%				
Baseline	1986 ± 279	1788 ± 199	2194 ± 176	P < 0.001
12-month follow-up	1827±292***	1679 ± 238***	2005 ± 262***	P < 0.001
Clinical Outcomes				
All-cause mortality, n (%)	12 (14)	11 (26)	1 (2)	0.001
Cardiovascular mortality, n (%)	7 (8)	7 (17)	0	0.005
HF hospitalization, n (%)	8 (9)	7 (17)	1 (2)	0.023
Composite of all-cause death and HF hospitalization, n (%)	18 (21)	16 (42)	2 (5)	< 0.001
Composite of cardiovascular death and HF hospitalization, n (%)	14 (16)	13 (31)	1 (2)	< 0.001
Stroke, n (%)	3 (3)	2 (4)	1 (2)	0.61
Acute myocardial infarction, n (%)	4 (2)	3 (7)	1 (2)	0.35

** p<0,01, ***p<0,001 Baseline versus 12-month follow-up

AVA - aortic valve area; AVAi - AVA index, AVR – aortic valve replacement, BNP - brain natriuretic peptide; EDd - end-diastolic diameter; GLS – global longitudinal strain, GWI – global work index, LV - left ventricular, P_{mean} - mean transaortic valvular gradient; STS - Society for Thoracic Surgeons; SVI - stroke volume index; V_{max} - maximal velocity across the aortic valve

To assess the relationship between GWI and clinical outcome, spline curves were constructed (**Figure 1**). An increase in risk (HR>1) was observed in individuals with GWI ≤ 2000 mmHg% for all-cause mortality or its composite with HF hospitalization (**Figure 1A-B**). At baseline, patients with lower (≤2000 mmHg%) versus higher GWI showed similar clinical, routine echocardiographic and hemodynamic characteristics with the exception of higher transaortic V max and lower GLS (both p<0.05) in patients with lower GWI (**Table 1**).

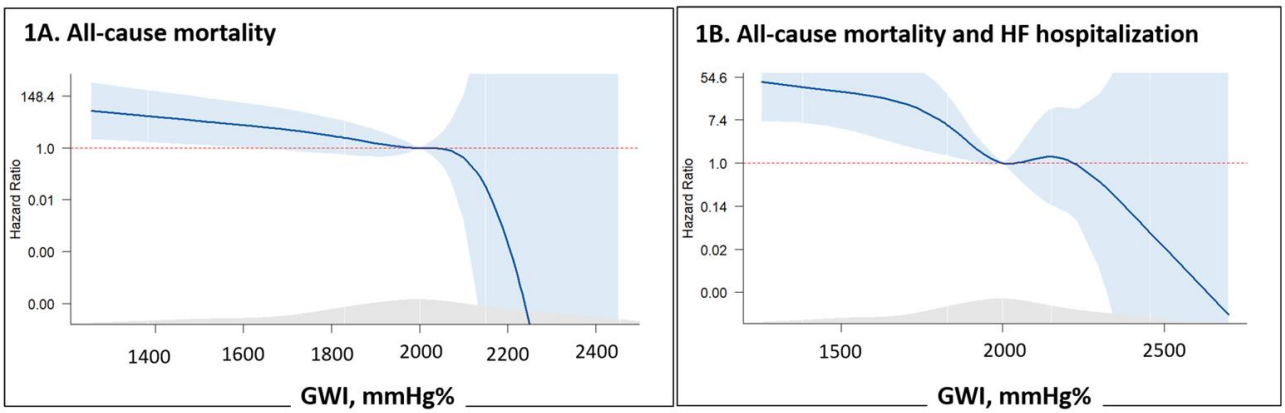

Figure 1. Association between left ventricular global work index (GWI) and all-cause mortality (1A) or GWI and a composite of all-cause mortality and HF hospitalization (1B). Risk (hazard ratio) of mortality or its composite with HF hospitalization increased with GWI ≤ 2000 mmHg%.

Figure 2 shows individual examples of GWI at baseline in four different categories of patients according to the randomization assignment and clinical outcome. Patients with lower GWI showed significantly higher all-cause mortality (26% vs. 2%) or its composite with HF hospitalization (42% vs. 5%) (**Figure 3A-B**), higher cardiovascular mortality (17% vs. 0%) or its composite with HF hospitalization (31% vs 2%) (all p<0.05) (**Table 1**). In a multivariable Cox regression analysis, GLS and GWI emerged as independent predictors of all-cause mortality and its composite with HF hospitalization (all p<0.05).

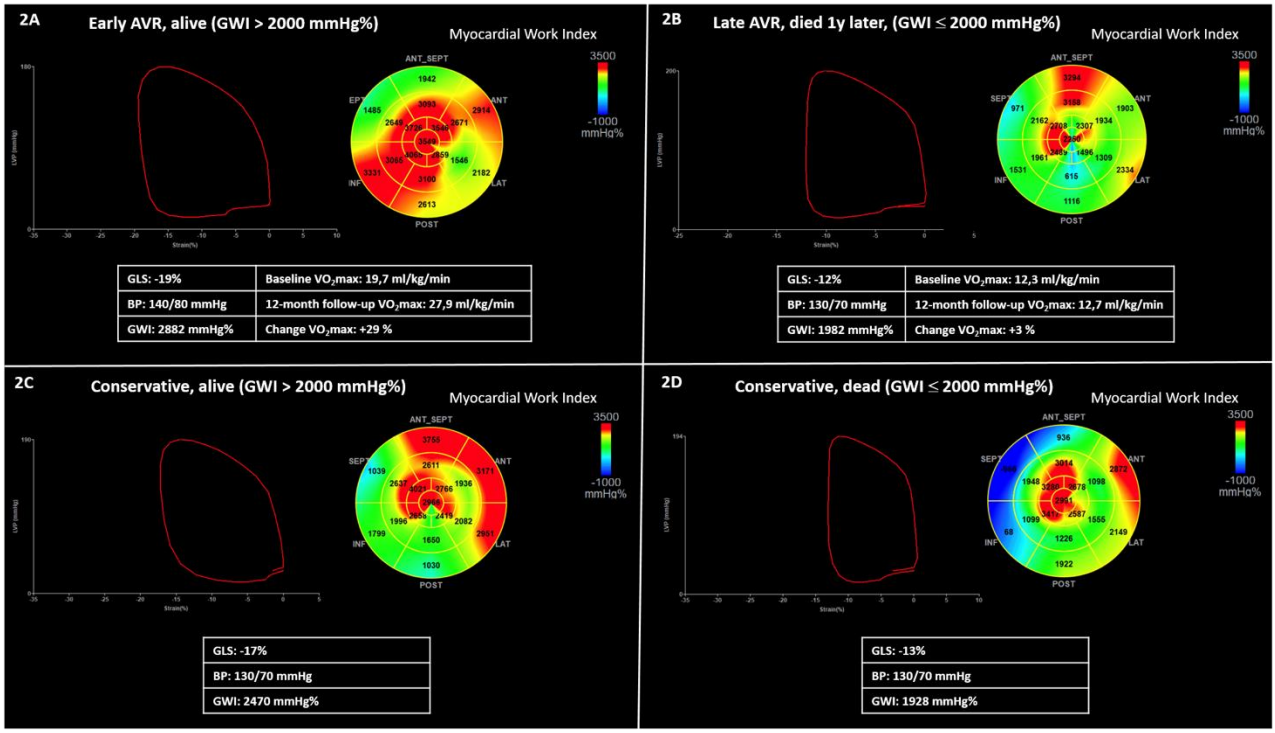

Figure 2. Individual examples of GWI in four patients: 2A Early AVR with GWI > 2000 mmHg%: A 73-year old man who underwent AVR 53 days post randomization and was alive at the end of follow up. Note, relatively preserved VO2max at baseline with significant improvement after AVR. 2B Late AVR with GWI ≤ 2000 mmHg%: A 64-year old man, originally randomized to the conservative group, who developed an indication to AVR and was operated 873 days post randomization. He died 1 year after AVR. Note, consistently low VO2max both at baseline and 12 months later. 2C Conservative alive with GWI > 2000 mmHg%: A 78-year old woman, who was asymptomatic and was managed conservatively for the entire follow up. 2D Conservative dead with GWI > 2000 mmHg%: A 71-year old woman who died 14 months after randomization to the conservative arm. Abbreviations: BP: blood pressure, GLS: global longitudinal strain, GWI: global work index, VO2max: maximal myocardial oxygen consumption.

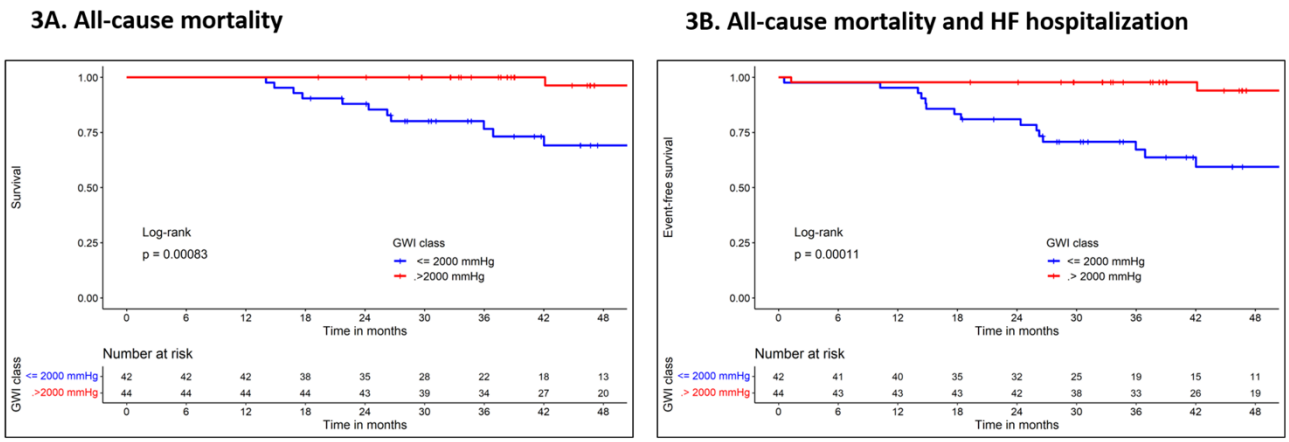

Figure 3. Kaplan-Meier curves for left ventricular global work index (GWI) using cutoff value (≤ 2000 mmHg% versus > 2000 mmHg%). 2A shows all-cause mortality. 2B shows a composite of all-cause mortality and HF hospitalization.

However, in a time-dependent ROC analysis, GWI showed a larger AUC than GLS both for all-cause mortality and its composite with HF hospitalizations (**Figure 4**). In patients originally assigned to the conservative group, lower GWI (≤ 2000 mmHg%) was also independently associated with a higher likelihood of "late" AVR (32% vs. 7%; p<0.05) during follow-up (HR: 0.77; 95% CI 0.64-0.93; p = 0.007), while GLS did not show significant association.

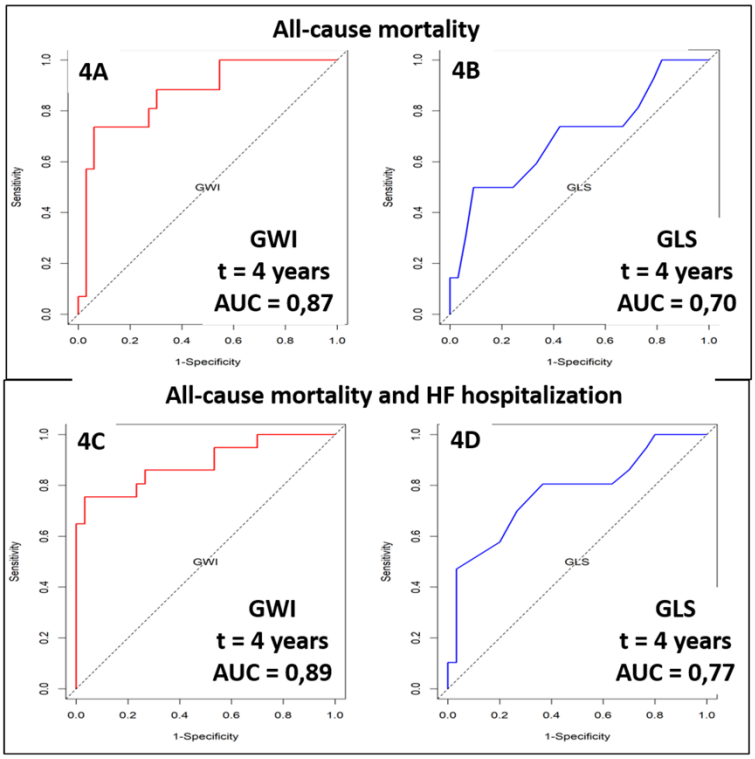

Figure 4. Time-dependent ROC curve for global work index (GWI) and global longitudinal strain (GLS), respectively, to predict all-cause mortality (4A, 4B) and its composite with HF hospitalization (4C, 4D) at 4-year follow-up.

Discussion

Timing of AVR in asymptomatic patients with severe aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF) is challenging. In the present subanalysis of the AVATAR trial, in asymptomatic patients with severe AS and preserved LVEF, normal or impaired global work index was independently associated with higher all-cause mortality and its composite with HF hospitalization as compared with "supranormal" global work index while yielding higher predictive

power than GLS. In contrast, GLS showed impaired values with only minor differences between asymptomatic versus mildly symptomatic versus severely symptomatic patients (105,107).

The new findings of the present study are that patients with a “supranormal” global work index had better clinical outcomes than patients with normal or reduced myocardial work. Furthermore, the global work index showed higher predictive power to identify patients with adverse clinical outcomes than the GLS. Thus, it seems that in patients with severe AS and preserved LVEF, the global work index may more accurately reflect the extent of myocardial damage than the GLS, being promising to guide clinical decision-making.

CHAPTER 5

PROSPECTIVE EVALUATION OF THE LEARNING CURVE AND DIAGNOSTIC ACCURACY FOR PRE-TAVI CARDIAC COMPUTED TOMOGRAPHY ANALYSIS BY CARDIOLOGISTS IN TRAINING: THE LEARN-CT STUDY.

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Introduction

In recent years, cardiac CT (CCT) has become the gold standard imaging modality for TAVI procedure planning, guiding the choice of the most suitable prosthetic valve (type and size) and the best access route (73,74). So far, imaging evaluation has been performed by radiologists and/or industry specialists, but considering the increase in TAVI procedures and the number of qualified centers, cardiologists have started gaining experience in CCT analysis in order to achieve an independent decision-making process. Although the cardiac CT analysis software is user-friendly and provides intuitive workflow, an error in valve selection might cause serious peri and post-procedural complications due to either valve under or over-sizing (108-110). Therefore, cardiologists must be well-trained before performing pre-TAVI CCT analysis independently.

The pre-TAVI CCT-analysis has been validated by several studies, which showed high sensitivity, specificity, and very good overall accuracy values among the readers (67). However, these studies showed several limitations: most of them were carried out only by experienced radiologists (not directly involved in the valve selection and implantation process), presented a low number of readers selected for the comparison, had a retrospective study design, none of them compared the reader performance with semi-automatic software, which are currently available on the market, and no adjudication of image quality was performed (111-113). Furthermore, only a single study evaluated measurements of an inexperienced observer with lower reliability, suggesting the need to set a standard learning curve (111). No data about the learning curve and number of cases required for a beginner cardiologist to perform an accurate pre-TAVI CCT assessment are available. It is reasonable to assume an improvement in the analytical capacity directly proportional to the number of cases performed. Therefore, in the present study, we sought to investigate the effective learning curve prospectively and the minimum number of cases required for a trainee cardiologist to acquire the skill to perform accurate pre-TAVI CCT analysis using semi-automatic software.

Methods

This is a prospective observational study performed from March 1st to September 30th, 2021. The institutional review board approved this study. Four cardiology fellows (readers: R1, R2, R3, R4) without prior experience in CCT analysis were divided into two groups (cardiac interventional fellows [R1 and R2] and non-invasive cardiac imaging fellows [R3 and R4]). After a comprehensive training in pre-TAVI CT evaluation, each reader performed an independent analysis of the same 40 cases twice. The readings were completed in the same order for each fellow. The fifth reader was a certified TAVI CT specialist with >5 years of experience in pre-operative CT evaluation, validated by an experienced interventional cardiologist involved in TAVI program. The latter was referred as the reference reader (RR) (**Figure 1**). All readers performed the complete analysis of aortic root and ascending aorta with a semi-automatic software (3-Mensio Structural Heart software, version 9.1.SP3, Pie Medical Imaging, Maastricht, The Netherlands) based on the recommendation of the expert consensus document of the Society of Cardiovascular Computed Tomography (4) (**Figure 2**). Image quality was adjudicated using the 4-point Likert scale by an independent CT image quality committee. All analyses were independently performed by each reader, blinded to the results of the other readers. All cases were analyzed in blocks of 5 according to the chronological order in which patients were consecutively scheduled for TAVI (the same for each reader) and repeated a second time after 48 hours. Thereafter, the readers proceeded to the next series of 5 cases. The time to complete each case analysis was recorded. At the end of each examination, the reader was asked to select the appropriate valve size, both for self-expandable and balloon-expandable valves, according to the standard cut-off (75,114,115). The first measurement was used to assess the readings accuracy of each reader compared to the RR. The second measurement of each observer was used to evaluate intra-observer reliability. The analyses performed by the cardiology fellows were not used for clinical decisions.

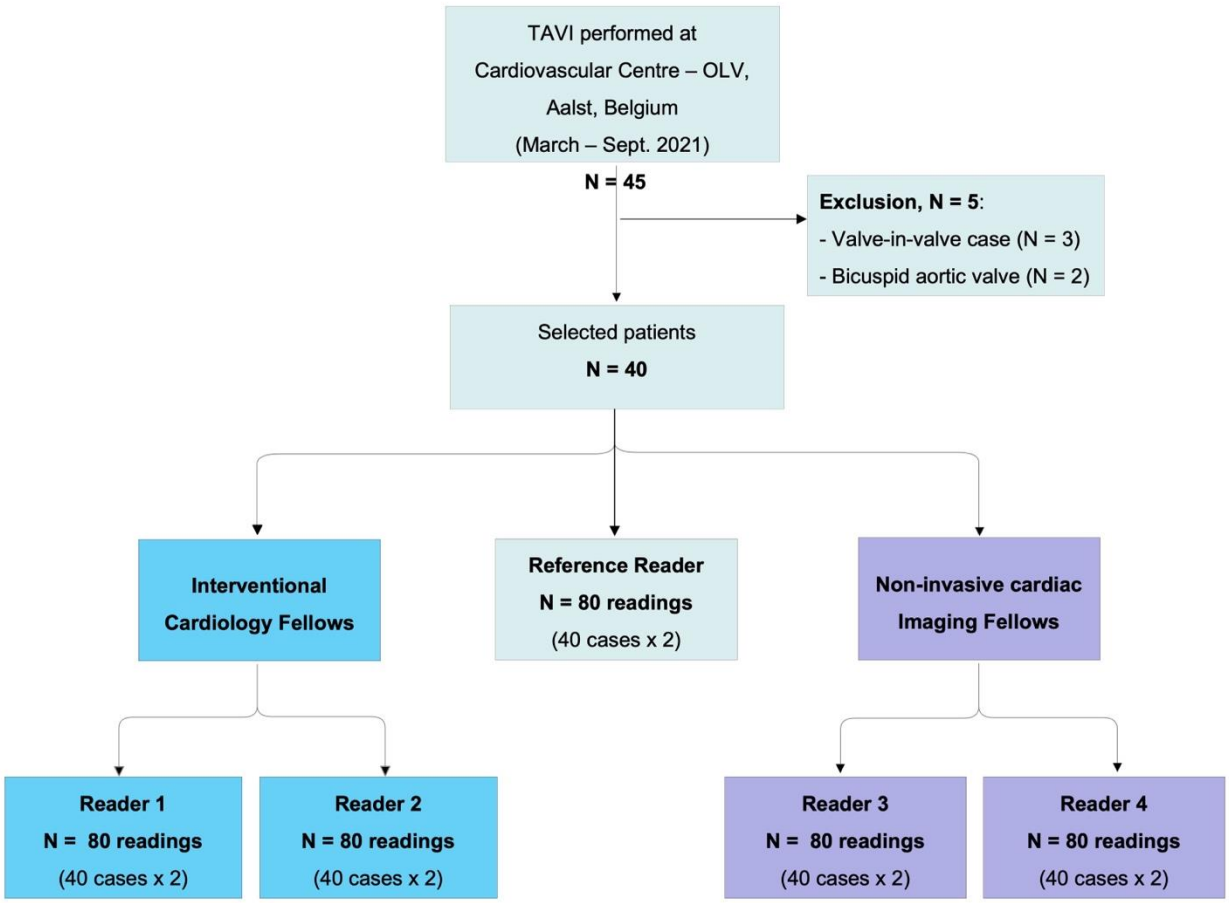

Figure 1: Study Flow chart.

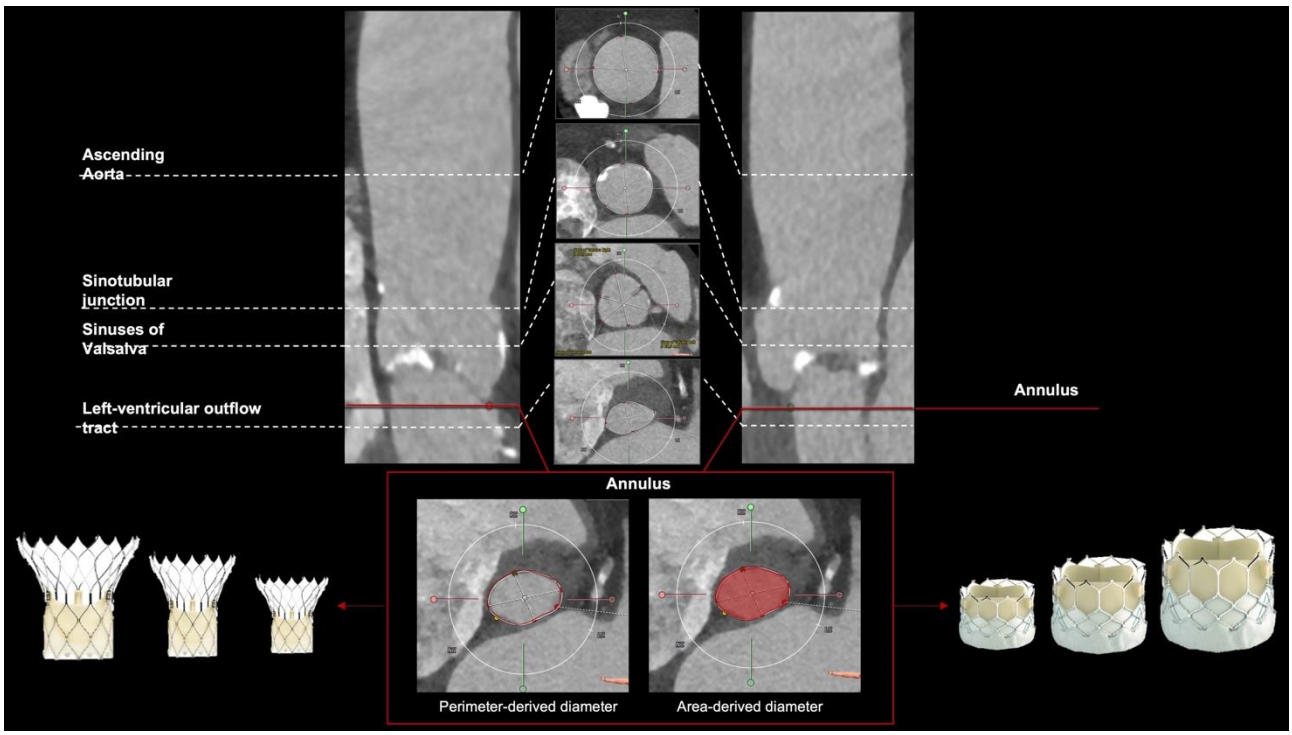

Figure 2: Schematic representation of the analysis performed using 3-Mensio Structural Heart software (version 9.1.SP3, Pie Medical Imaging, Maastricht, The Netherlands). Measurements of the aorta are performed at the level of the left-ventricular outflow tract, aortic annulus, sinuses of Valsalva, Sino-tubular junction, and the ascending aorta. Based on the perimeter-derived annulus diameter, the size of the self-expandable valve was selected, while the size of the balloon-expandable valve was selected based on the area-derived annulus diameter.

The study aimed to evaluate and describe the learning curve and diagnostic accuracy of the pre-TAVI CCT assessment obtained by 4 different cardiology fellows (2 non-invasive imaging and 2 interventional) after adequate training. Interpretation accuracy was defined as the agreement between a reader and the RR in both balloon- and self-expandable valve size selection and was considered achieved only when the same valves size, for both types, were selected by the reader and the RR. The study's primary outcome was the minimum number of cases required to achieve an interpretation accuracy $\geq 80\%$. The secondary outcomes were: i) an inter-observer intraclass correlation coefficient (ICC) > 0.80 between each reader and the gold standard for both the perimeter and area evaluated at the CCT; ii) a comparable intra-observer variability between the first and the second measurement among the cardiology fellows and the RR for both the perimeter and area evaluated.

Results

Study population

During the study period, a total of 45 patients underwent TAVI. The final study sample size consisted of 40 patients, as 3 of them were excluded because of a valve-in-valve procedure and 2 for a bicuspid aortic valve (**Figure 1)**.

The mean age was 83.3 ± 5.7 years, and there were 20 female patients (50%). The mean left ventricular ejection fraction was 48 ± 11%, with a mean transaortic pressure gradient of 49 ± 14 mmHg and a mean peak aortic jet velocity of 4.1 ± 0.7 cm/sec. The mean aortic valve area was 0.6 ± 0.2 cm^2, and 34 patients (85%) received a self-expandable prosthesis (Portico Valve®, Abbott Vascular) by a retrograde transfemoral approach. CCT image quality was assessed as acceptable or good/excellent in 52.5% of cases, with an optimal slice thickness in 72.5%. No cases were excluded for non-diagnostic image quality (**Table 1**).

Table 1: Baseline clinical and CT acquisition characteristics.

	Patients undergoing TAVI N = 40
Female gender, n (%)	20 (50)
Age, years (mean ± sd)	83.3 ± 5.7
BMI, kg/m^2 (mean ± sd)	25.2 ± 4.4
Echocardiography	
LVEF, % (mean ± sd)	48 ± 11
Grad. Mean, mmHg (mean ± sd)	49 ± 14
V max, cm/sec (mean ± sd)	4.1 ± 0.7
AVA, cm^2 (mean ± sd)	0.6 ± 0.2
CT acquisition	
Total DLP (mean ± sd)	533 ± 240
Total mAs, (mean ± sd)	2847 ± 836
Kv (mean ± sd)	120 ± 12
Optimal slice thickness, n (%)	29 (72.5)
Image quality score (4-point-rating scale) (mean ± sd)	2.75 ± 0.7
Quality score > 2, n (%)	21 (52.5)

Continuous variables are presented as mean ± SD; categorical ones as n (%). Abbreviations: BMI: body mass index, LVEF: left ventricle ejection fraction; AVA: aortic valve area; DLP: total dose length product; mAs: milliampere-seconds; Kv: tube Voltage.

Learning curve

The readers' learning curves were calculated based on a consecutive series of 5 cases. The mean complexity score for each series was 19 ± 2.4, ranging from 14 of the second series (case 6-10, **Figure 3 green bar**) to 22 of the fifth series (case 21-25), which appeared to be the most difficult to analyze, together with the seventh series (**Table 2** and **Figure 3**). Borderline cases were 14 (35%).

Table 2. CT complexity score (*upper panel*) and estimation according to number of cases (*lower panel*).

Parameters	**Score (points)**
Slice thickness	0 = Optimal (0.6 mm) 1 = Sub-optimal (> 0.6 mm)
Image quality score	1 = good/excellent image quality 2 = acceptable image quality 3 = poor image quality 4 = non-diagnostic
Aortic valve calcification	1 = mild 2 = moderate 3 = severe

Number of cases	**1-5**	**6-10**	**11-15**	**16-20**	**21-25**	**26-30**	**31-35**	**36-40**
CT slice thickness	4/5	1/5	1/5	1/5	0/5	2/5	1/5	1/5
CT quality	5/20	4/20	7/20	8/20	10/20	5/20	4/20	4/20
CT calcium	10/15	9/15	11/15	11/15	12/15	12/15	13/15	13/15
Average score	19/40	14/40	19/40	20/40	22/40	19/40	21/40	18/40

The total complexity score for each series of 5 cases was calculated based on the points obtained from each parameter evaluated in each case.

After 5 series examined, corresponding to 50 CTs readings (i.e. 25 cases analyzed twice), cardiology fellows were able to select the valve size with ≥ 80% of accuracy with a significant improvement between the first 5 series of cases and the following 3 (diagnostic accuracy=51% vs 81.66%, p=0.023). Each of the 4 readers completed 80 readings in 40 cases, for a total of 320 readings in 160 cases. A complete agreement regarding prosthesis size selection was reached in 100 out of 160 cases

(63%), ranging from 60 to 65% according to the specific reader. The average interpretation accuracy was 45 % for cases 1 to 5, 50% for cases 6 to 10, 60 % for cases 11 to 15, 55 % for cases 16 to 20, 45% for cases 21 to 25, 80% for cases 26 to 30, 80% for cases 31 to 35 cases and 85% for the last series from 36 to 40 cases (**Table 3**). Furthermore, by analyzing borderline and non-borderline cases, an agreement was observed in 28 (50%) and 69 (66.3%) cases, respectively. As for the curve obtained in the overall population, also in borderline cases, a significant improvement in diagnostic accuracy was achieved in the last 3 groups of cases compared to the first 5 ($p=0.047$). Conversely, for the non-borderline cases, an initial improvement can be noticed with the achievement of a learning plateau, without significant differences between the first 5 blocks (25 cases) and the following 3 ($p=0.063$) (**Figure 3, panel B**).

Learning curves of interventional cardiology and non-invasive cardiac imaging fellows showed a similar trend, and both categories of fellows got a diagnostic accuracy $\geq$ 80% after 50 readings (25 cases analyzed twice), reaching a plateau, without significant differences ($p=0.44$, **Figure 3, panel C**).

Table 3. Interpretation accuracy (total and divided into borderline and non-borderline cases) in valve size selection according to the number of CCTs performed for pre-TAVI screening.

Number of cases	**1-5**	**6-10**	**11-15**	**16-20**	**21-25**	**26-30**	**31-35**	**36-40**
Reader 1	40 (2/5)	40 (2/5)	40 (2/5)	60 (3/5)	40 (2/5)	100 (5/5)	80 (4/5)	100 (5/5)
Reader 2	40 (2/5)	60 (3/5)	60 (3/5)	80 (4/5)	20 (1/5)	60 (3/5)	80 (4/5)	80 (4/5)
Reader 3	40 (2/5)	80 (4/5)	80 (4/5)	40 (2/5)	60 (3/5)	60 (3/5)	80 (4/5)	80 (4/5)
Reader 4	60 (3/5)	20 (1/5)	60 (3/5)	40 (2/5)	60 (3/5)	100 (5/5)	80 (4/5)	80 (4/5)
Average score	**45 (9/20)**	**50 (10/20)**	**60 (12/20)**	**55 (11/20)**	**45 (9/20)**	**80 (16/20)**	**80 (16/20)**	**85 (17/20)**
Borderline cases	**3/5**	**2/5**	**0/5**	**2/5**	**2/5**	**1/5**	**2/5**	**2/5**
Reader 1	33.3 (1/3)	50 (1/2)	-	50 (1/2)	50 (1/2)	100 (1/1)	100 (2/2)	100 (2/2)
Reader 2	33.3 (1/3)	50 (1/2)	-	50 (1/2)	0 (0/2)	60 (0/1)	50 (1/2)	100 (2/2)
Reader 3	33.3 (1/3)	50 (1/2)	-	50 (1/2)	50 (1/2)	60 (1/1)	100 (2/2)	50 (1/2)
Reader 4	33.3 (1/3)	0 (0/2)	-	50 (1/2)	50 (1/2)	100 (1/1)	100 (2/2)	100 (2/2)
Average score	**33.3 (4/12)**	**37.5 (3/8)**	**-**	**50 (4/8)**	**37.5 (3/8)**	**75 (3/4)**	**87.5 (7/8)**	**87.5 (7/8)**
Non-borderline case	**2/5**	**3/5**	**5/5**	**3/5**	**3/5**	**4/5**	**3/5**	**3/5**
Reader 1	50 (1/2)	33.3 (1/3)	40 (2/5)	33.3 (1/3)	33.3 (1/3)	100 (4/4)	66.6 (2/3)	100 (3/3)
Reader 2	50 (1/2)	66.6 (2/3)	60 (3/5)	66.6 (2/3)	33.3 (1/3)	75 (3/4)	100 (3/3)	66.6 (2/3)
Reader 3	50 (1/2)	100 (3/3)	80 (4/5)	100 (3/3)	66.6 (2/3)	50 (2/4)	66.6 (2/3)	100 (3/3)
Reader 4	100 (2/2)	33.3 (1/3)	60 (3/5)	66.6 (2/3)	66.6 (2/3)	100 (4/4)	66.6 (2/3)	66.6 (2/3)
Average score	**62.5 (5/8)**	**58.3 (7/12)**	**60 (12/20)**	**58.3 (7/12)**	**50 (6/12)**	**81.3(13/16)**	**75 (9/12)**	**83.3 (10/12)**

Values are presented as % (number of correct readings/total readings). Borderline cases: number of borderline cases present into each group of 5 cases; non-borderline cases: number of non-borderline cases present into each group of 5 cases.

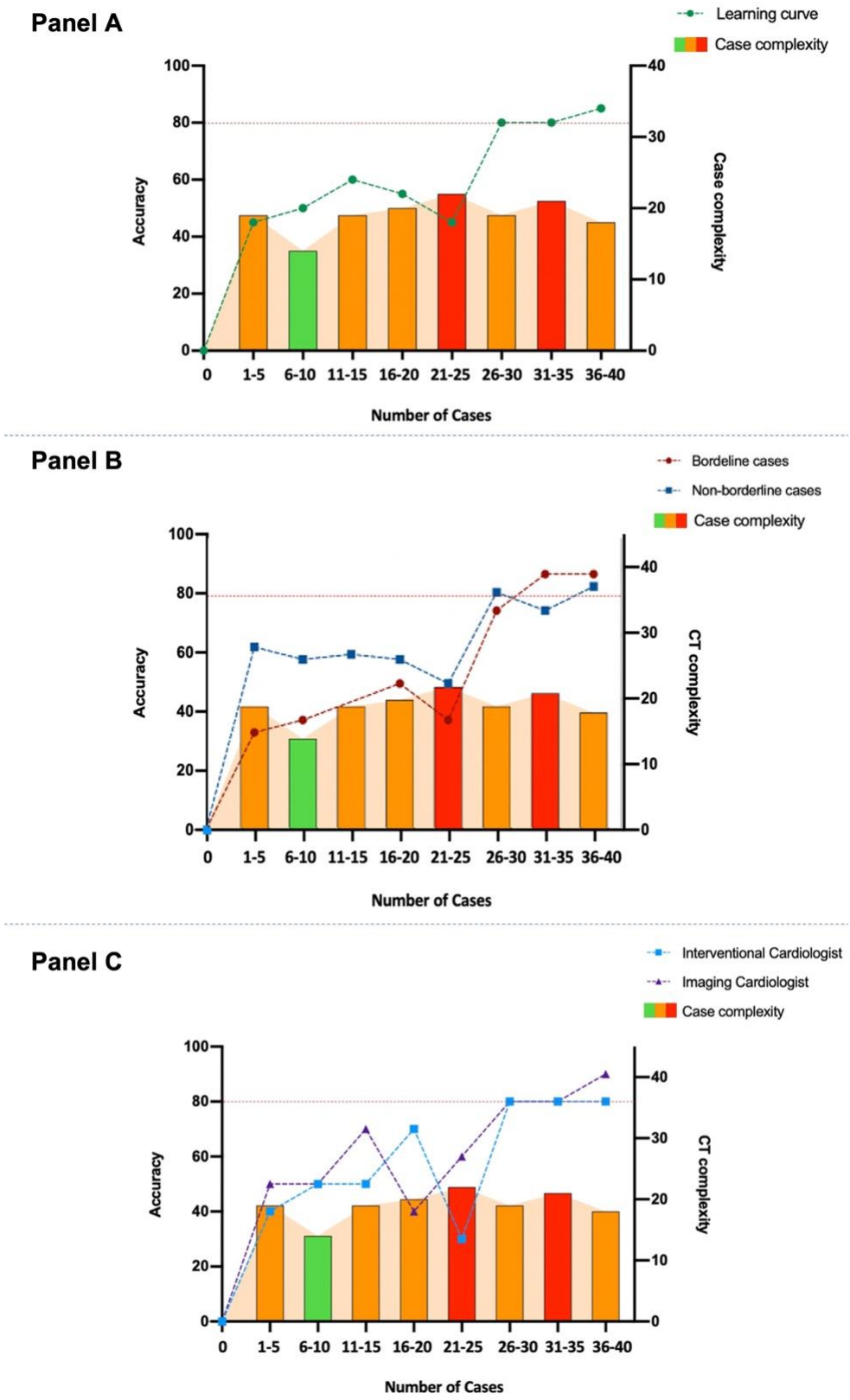

Figure 3: Learning curves according to the number of cases and CT case complexity, with a grading colour scale from green for the lowest complexity to red for the most complex series. Panel A: learning curve plotted based on the number of cases performed by each reader, considering the complexity of each series. Panel B: learning curve plotted based on the number of cases performed divided between borderline and non-borderline cases; Panel C: learning curve plotted based on the number of cases performed divided between interventional cardiology and cardiac imaging fellows.

Total agreement between the readers and the RR for coronary height assessment was 91% (291 correct evaluation out of 320), ranging from 88.5% for the first 25 cases (177/200) to 95% for the last 3 series (114/120). Thus, the coronary height learning curve showed a similar trend with a significant improvement in terms of the agreement after the first 25 cases (23 out of 29 total disagreements in the first 5 series compared to 6 out of 29 in the next 3, p=0.04). The mean reading time, over the 40 cases, was 8.5 ± 2.3 minutes. The mean time for the complete analysis per patient was 8.5 min (±2.9), 9.3 min (±2.4), 7.5 min (±1.3), 8.9 min (±2.3), for each reader, respectively. The readers' skill at performing CCT analyses in less than 10 minutes improved rapidly and significantly after the first four blocks (**Figure 4**). Reading time for each reader decreased significantly from 10.2 (±2.1) to 6.9 (±1) minutes after 20 cases and continuously improved thereafter for every 5 consecutive series for all cases (p<0.001, **Figure 4**).

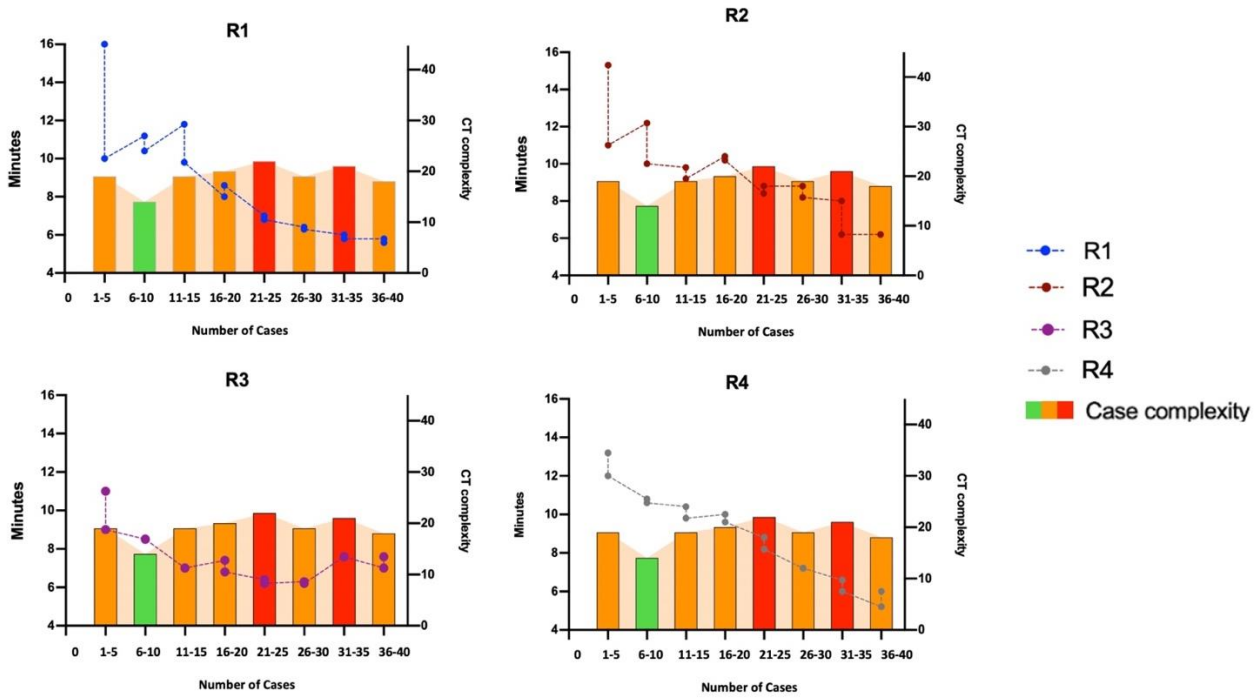

Figure 4: Reading times according to the number of cases and CT case complexity. R1, R2, R3, R4: cardiology readers.

Results: Inter-observer variability

ICC for annulus perimeter assessment ranged from 0.96 (95% CI 0.50-0.99) for the first 25 cases to 0.99 (95% CI 0.71-0.99) of the last 15. The same trend was observed for area measurements, with a marked improvement in precision between the first 25 and the last 15 cases [ICC 0.96 (95% CI 0.63-0.99) and 0.99 (95% CI 0.74-0.99) respectively]. Thus, after 50 readings (25 cases repeated twice) of CT analyses, cardiology fellows could reach a very high accuracy in both perimeter and area assessment, with an ICC ranging from 0.98 to 0.99.

Results: Intra-observer variability

Bland–Altman analysis revealed a mean difference between the two measurements of the RR of 0.02 (ULA= 0.73, LLA= -0.78) mm for the perimeter derived, and -0.005 (ULA= 0.67, LLA= -0.68) mm for the area derived. The mean bias of the first and second measurements of the same cases calculated for the readers 1, 2, 3 and 4, are reported in **Figure 5** and **6** and did not significantly differ as compared to the RR (p=0.89, p=0.052, p=0.96, p=0.22 for the perimeter and p=0.55, p=0.42, p=0.32 and p=0.17, for the area, respectively). An excellent intra-observer agreement for both perimeter and area measurements were also demonstrated by the ICC, ranging from 0.96 and 0.99 in all the readers (**Figure 5-6**).

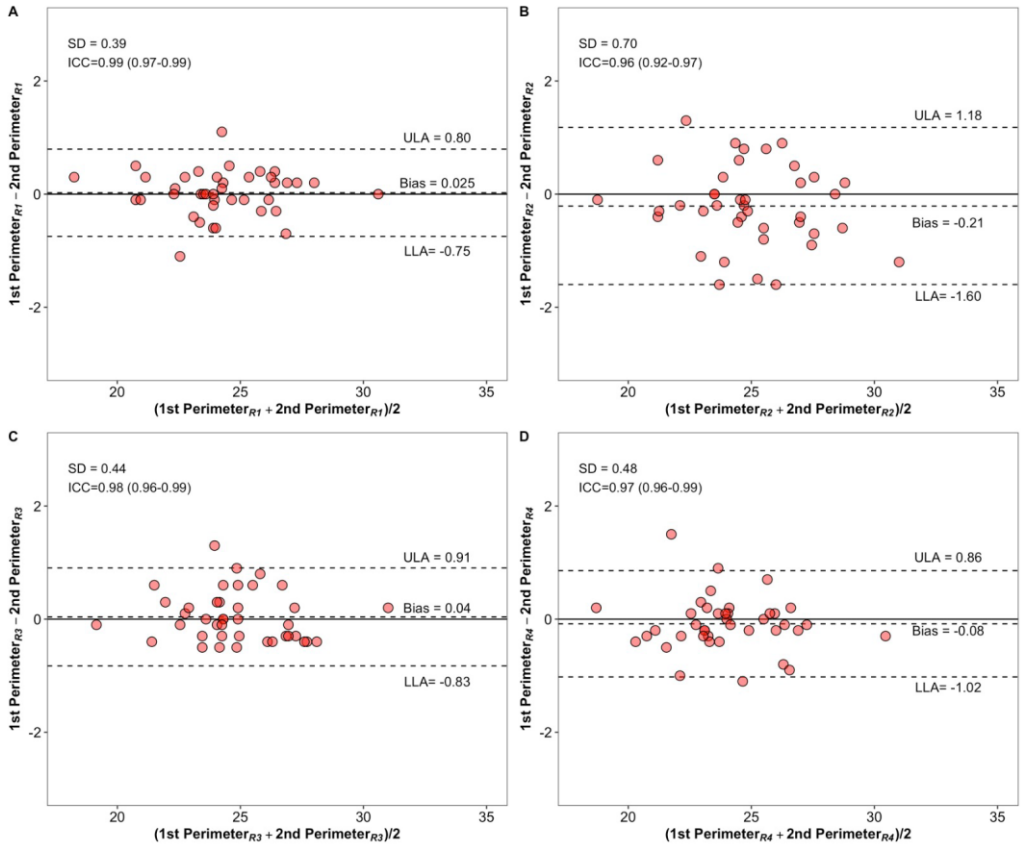

Figure 5. Four readers Bland Altman plots for intra-observer variability of the perimeter-derived.

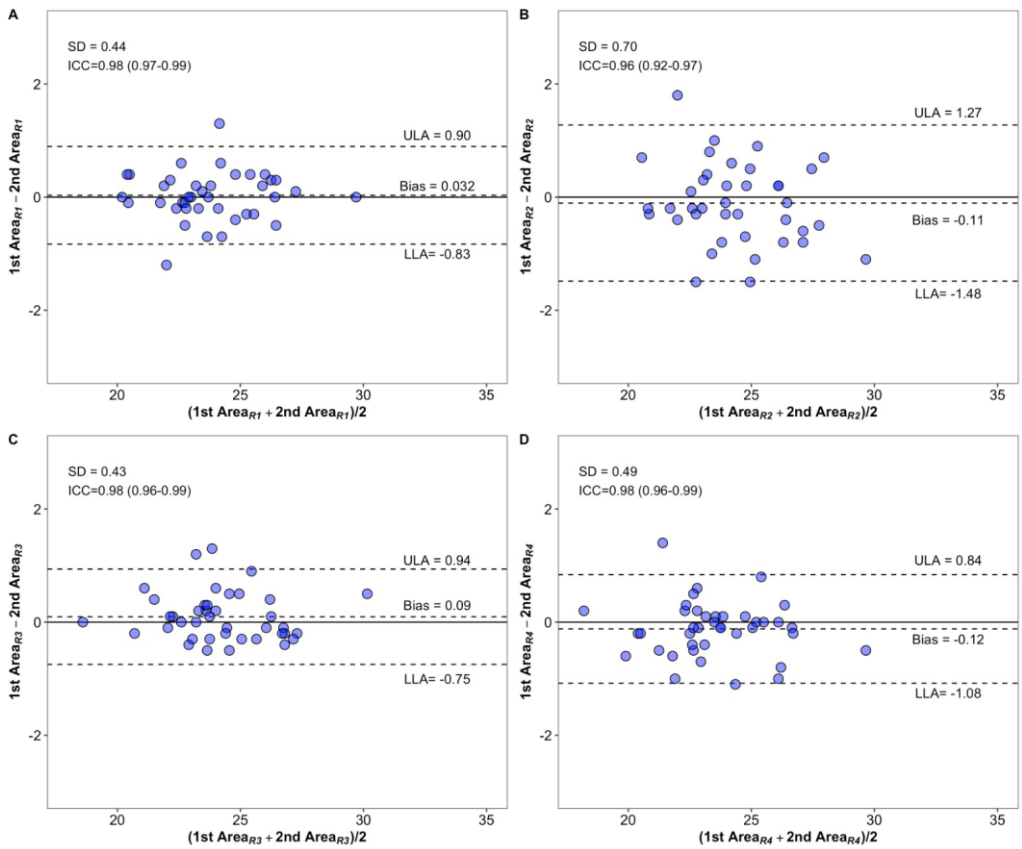

Figure 6. Four readers Bland Altman plots for intra-observer variability of the area derived.

Discussion

This prospective observational study investigated for the first time the effective learning curve with number of cases required to acquire the skills to perform an accurate pre-TAVI CCT analysis. The main novelties of our study are: i) after 50 readings (25 cases repeated twice), cardiology fellows could select the valve size with ≥ 80% of accuracy compared to the RR, regardless of aortic valve calcification, image quality and slice thickness; ii) the learning curves of both interventional and non-invasive cardiac imaging cardiologist showed a similar trend reaching the diagnostic accuracy ≥ 80% after 50 readings (25 cases repeated twice); iii) each reader achieved a very high precision in both annulus perimeter and diameter assessment by CCT analysis as demonstrated by the excellent agreement in the inter- and intra-observer reliability analysis; iv) after 40 readings (20 cases repeated twice) each reader could perform CCTs analyses in less than 10 minutes.

Unlike the SAVR, direct visualization of the aortic valve and adaptation of the prosthesis size is not possible during TAVI procedure, and incorrect valve selection might cause severe complications. Valve under-sizing might be associated with paravalvular regurgitation, an independent predictor of long-term mortality, or valve migration. On the other side, valve over-sizing might obstruct coronary ostia, atrioventricular block, or rupture of the aortic root (63-65). Thus, an accurate pre-procedural multimodality imaging assessment is pivotal not only to determine patient's eligibility to TAVI but also for precise procedural planning and the proper training of the cardiologists to perform an independent pre-TAVI CCT analysis is crucial.

So far, all studies assessing the reliability and reproducibility of pre-TAVI CCT measurements were carried out by experienced radiologists using manual post-processing software. Importantly, in our study, we focused on cardiologists in training without prior experience in pre-TAVI CCT analysis, divided into 2 groups (cardiac interventional fellows and cardiac imaging fellows), comparing their performance to that of a professional CT reader. The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have established minimum requirements in terms of number of cases interpreted and learning hours needed to guarantee a high level of accuracy

in analyzing coronary CT scan images (116-120). However, for pre-TAVI assessment, only one study suggested a learning curve comprised between one and six months based on a single inexperienced reader (111). Nevertheless, neither a minimum number of cases required to achieve good diagnostic accuracy, nor a learning curve were provided. Moreover, the temporal criteria alone, without reporting the number of cases analyzed by the reader in that time, is necessary but insufficient to define a training program. So far, our study is the first to investigate the gradual improvement of the operator's experience as the number of cases increases, suggesting a precise number of cases (readings) needed for an accurate pre-TAVI CT reading. Importantly, our findings support competency of the readers, generally achievable with a minimum number of CT readings, rather than large volumes in structural CCT imaging, providing evidence on the recommendations based on expert opinion provided by the SCCT Guidelines (120).

The choice of the 80% diagnostic accuracy set as primary target of the learning curve stems from considerations related to the intra-observer variability of the RR. Here, in fact, the RR reports an intra-observer variability in the valve size selection leading to an internal diagnostic accuracy of 87.5%, i.e. 6 disagreements at the repeated measurement out of 40 total cases. Thus, considering this latter intra-observer diagnostic accuracy, we deemed acceptable to set the threshold for the cardiologist in training > 80%. Please also notice that in the last series, the accuracy of the cardiologists in training reaches 85%, almost overlapping the one of the RR. Therefore, if we set the diagnostic accuracy of the RR as our reference value, after 50 cases the cardiologists in training were able to reach a diagnostic accuracy between 91 and 97% compared to the RR one.

A minimum of 50 readings (25 cases repeated twice) is required to achieve and hold a diagnostic accuracy above 80% regardless of the case complexity. The last 4 series (from 21-25 to 36-40) were those with the most significant aortic valve calcifications (**Table 2** and **Figure 3**). Considering the trend of the learning curve “normalized” for the case complexity, we can conclude that after 50 readings (25 cases repeated twice), the impact of aortic valve calcification burden is

largely offset by the increased reader's experience, which translates into limited (if any) impact on diagnostic accuracy of valve sizing.

For borderline cases high accuracy was achieved after analyzing 25 CT (50 readings) as for non-borderline ones but with a different trend of the learning curves. For non-borderline cases, proficiency rapidly increased exponentially, reaching the first plateau after the first 5 cases (10 reading) and the second one, above the threshold of diagnostic accuracy, after 25 (50 readings); for borderline cases, instead, the learning curve resembled more a sigmoid function with slowly accumulating small steps at first, followed by larger steps and then smaller steps again till the curve reaches its plateau (**Figure 3, Panel B**). There are two explanations for the different trends of the 2 curves:

1. Valve size selection is based on the annulus measurements according to industry's recommendations. Thus, for borderline cases, it could happen that a slight change in annulus measurement would lead to an erroneous valve size selection, which explains the lower accuracy for the first borderline cases compared to non-borderline, in the early phase of the investigation.
2. In clinical practice, valve selection is based not only on the industry's recommendations but also on patients' clinical and morphological characteristics. This integration of information might be at times challenging in case of limited experience, especially in patients with borderline annulus size that may easily be associated with a wrong selection of the valve size by the cardiologist in training. Therefore, the latter improvement in the accuracy for the borderline cases over time might be related to the fellows' participation in the weekly TAVI meetings and procedural planning discussions, which helped for better understanding of patients' clinical and morphological factors that may influence the valve size selection.

Hence, we believe that TAVI meeting should be an integral part of the learning curve of a trainee cardiologist approaching this field. It is also interesting to note a negligible deflection of the learning

curve in the series between cases 20-25, which can be partly explained by the greater complexity of that series and partly to the Dunning–Kruger effect, which is a hypothetical cognitive bias stating that people with low ability at a task, tend to overestimate their skills (121).

Previous studies assessed the intra- and inter-observer variability, all of them with similar results, reporting an excellent inter-observer correlation with calculated ICCs and correlation coefficients greater than 0.90 (112,113). Similarly, in our study, the readers reached an excellent inter- and intra-observer variability, which constantly increased across different CT blocks. Thus, reproducibility is a function of both reader's expertise and software's characteristics. Notably, we used for our study a semi-automatic software that provides automatic segmentation of the ascending aorta after a manual assignment of the "virtual ring", which includes the most caudal hinge points of all three aortic cusps. The automatic imaging selection for the analysis, the intuitive workflow and user-friendly interface might affect the excellent inter- and intra-observer reliabilities data for the aortic annulus dimensions compared to the previous studies. Remarkably, compared to the previous studies, in which the maximum number of observers included was 3, in our study, 5 readers were involved in the analysis, making our data more reliable and consistent. Based on these findings, we demonstrate that, after 50 readings (25 cases repeated twice), reader’s diagnostic performance reached the plateau and remained high regardless of the extent of aortic valve calcification, image quality and slice thickness.

CHAPTER 6

COMBINED CARDIAC DAMAGE STAGING IN PATIENTS WITH CLINICALLY SIGNIFICANT AORTIC STENOSIS

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Introduction

Irreversible myocardial damage occurring during the progression of AS has been associated with poor outcomes in patients with ssAS despite AVR (12,122). On the other side, the decision-making process regarding the timing of intervention in patients with moderate/asymptomatic severe aortic stenosis (m/asAS) is still debated (16). Recent randomized clinical trials suggest that early intervention strategy may improve the survival of patients with asymptomatic severe AS (123,124). Thus, ad-hoc risk stratification systems able to identify patients who may benefit from elective intervention are needed.

The cardiac damage staging is a multiparametric system that characterizes and quantifies the extent of extra-valvular (extra-aortic valve) cardiac damage. It includes 5 stages (stage 0 to 4) associated with incremental risk of poor outcomes (11). Patients were hierarchically classified in each stage (worst stage) if at least one of the above-mentioned criteria was met within that stage.

The prognostic value of this staging classification has been shown for the first time in patients with ssAS undergoing TAVR and confirmed in broader cohorts of patients with m/asAS (13,125,126). The variables included in this staging system could be evaluated non-invasively by transthoracic echocardiogram (TTE) or invasively by right heart catheterization (RHC) (127,128). While TTE provides a non-invasive estimation of right heart chambers and pulmonary pressures, RHC remains the gold standard for the assessment of pulmonary hypertension (PH), which has been shown to be a strong predictor of mortality in patients with ssAS undergoing AVR (127,129-131).

We aimed to i) assess the prognostic value of RHC compared to TTE in the characterization of cardiac damage at long-term follow-up in patients with clinically significant AS, divided into those with m/asAS and ssAS; ii) to explore the reclassification rate between TTE- and RHC-derived cardiac damage staging; iii) to identify patients that would benefit of RHC for accurate prognostic risk stratification. Moreover, we proposed a “combined” cardiac damage staging including variables derived from both TTE and RHC to stratify m/asAS and ssAS patients and tested its prognostic value.

Methods

The study population was derived from an observational registry of patients with valvular heart disease (VHD) managed in the Heart Valve Clinic (HVC) of Cardiovascular Center OLV, Aalst (Belgium) between January 2017 and December 2021. Patients with moderate to severe AS, defined as aortic valve area <1.5 cm^2 at TTE, were deemed eligible for inclusion. Among these, consecutive patients undergoing RHC for clinical indication with a comprehensive TTE performed within 1 month from RHC were included in the study population. Exclusion criteria were history of rheumatic valve disease, endocarditis, more than mild aortic regurgitation or mitral stenosis, previous valve repair or replacement. Based on the TTE closest to the RHC and the clinical status, patients were divided into those with m/asAS and those with ssAS (58).

Patients were categorized into five stages according to the presence and extent of extra-aortic valve cardiac damage as detected by the TTE closest to the RHC (Stages 0-4) (**Figure 1**).

A "combined" cardiac damage staging was elaborated according to the following criteria: i) stages 3-4 were hierarchically assigned according to RHC; ii) stages 0 to 2 were hierarchically assigned according to TTE; iii) the cases in which the right chambers damage was shown by TTE but not confirmed by RHC were reclassified according to hierarchical echocardiographic left chamber involvement stages (stages 0 to 2).

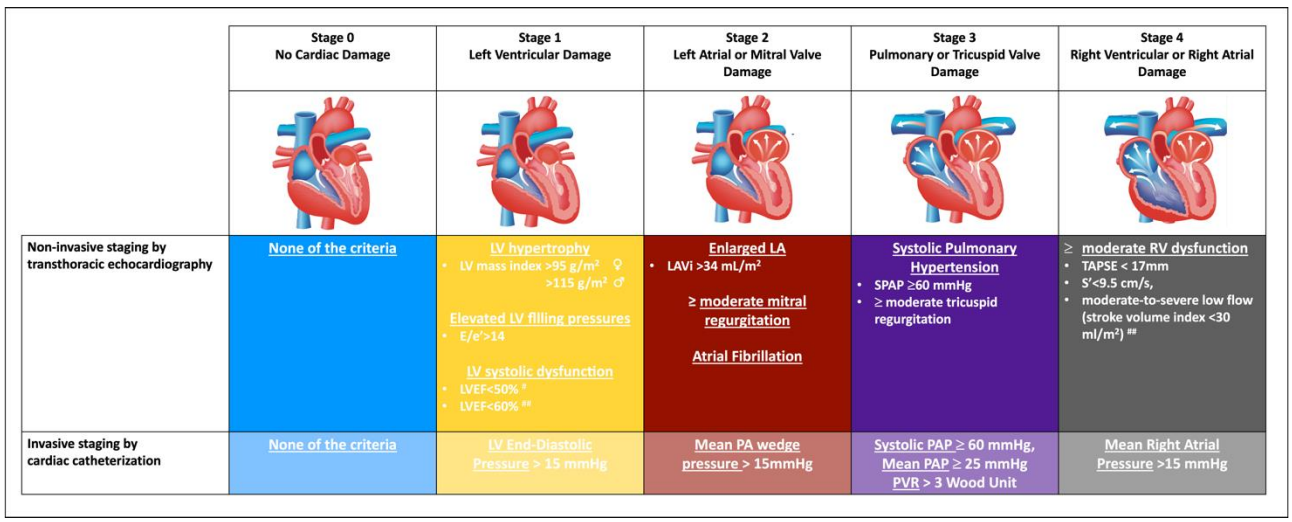


Figure 1. Extra-aortic valve cardiac damage staging of aortic stenosis according to transthoracic echocardiography and right heart catheterization. Abbreviations: LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; LA: Left

Atrium; LAVi: Left Atrial Volume Indexed; SPAP: Systolic Pulmonary Artery Pressure; PAP: Pulmonary Artery Pressure; PVR: Pulmonary Vascular Resistance; RV: Right Ventricle; TAPSE: Tricuspid Annular Plane Systolic Excursion. Symbols: ♀: in females; ♂: in males; #: in patients with symptomatic severe aortic stenosis; ##: in patients with moderate/asymptomatic severe aortic stenosis.

Results

The study population included 432 patients, divided into 183 (42.4%) patients with m/asAS and 249 (67.6%) with ssAS. Baseline clinical characteristics, echocardiographic, and RHC data of both cohorts stratified by TTE-derived stage of cardiac damage are shown in **Tables 1-2.**

Patients with moderate/asymptomatic severe AS

Patients with m/asAS had a mean age of 74.6±10.8 years; almost half of them had arterial hypertension, dyslipidemia, or coronary artery disease. The distribution of patients in each stage according to TTE criteria is shown in **Table 1** and **Figure 2** (**Panel A**). Patients in higher stages had lower estimated glomerular filtration rate (eGFR) and more often used MRA; patients in Stage 3 showed the highest NT-proBNP (**Table 1**). The median LVEF was 58% [55-65], the mean LV mass index 107.1±29.2 g/m^2, mean aortic valve gradient 38±12 mmHg, peak aortic jet velocity 3.9±0.6 m/s, and AVA 1±0.3 cm^2. The median time between TTE and RHC was 5 [1-27] days. At RHC, patients with m/asAS showed a median SPAP of 35 [30-44] mmHg, and a median PAWP of 14 [11-19] mmHg.

Patients with symptomatic severe AS

Patients with ssAS had a mean age of 78±9 years; most patients (86.3%) were symptomatic for dyspnea (**Table 2**). The distribution of patients in each stage according to TTE criteria is shown in **Table 2** and **Figure 2** (**Panel C**). Patients in Stage 3 were older, more frequently diabetic, and had lower eGFR. There was a gradual increase in the NT pro-BNP values across the different stages, with more frequent use of diuretics in Stages 3-4 (**Table 2**). The median LVEF was 55% [52-63], the mean

LV mass index 117.6±35 g/m^2, mean aortic valve gradient 49±10 mmHg, peak aortic jet velocity 4.5±0.5 m/s, and AVA 0.83±0.18 cm^2. As expected, patients with ssAS had more advanced extra-aortic valve damage compared to m/asAS. The median time between TTE and RHC was 2 [1-20] days. At RHC, the median SPAP was 38 [32-45] mmHg, and the median PAWP was 15 [12-20] mmHg.

Long-term outcomes

The clinical outcomes during follow-up per stage of cardiac damage in both cohorts are presented in **Table 3**. In the overall study population, the median follow-up was 3.1 [2-5] years. The rate of AVR in each cohort is reported in **Table 3**. At long-term follow-up, among patients with mas/asAS, 11 (6%) patients were admitted to the hospital for HF; 32 patients (17.5%) died, among which 15 (46.9%) for a cardiovascular cause, with an increasingly higher mortality rate in Stages 3-4. Among patients with ssAS, 19 (7.6%) patients were admitted to the hospital for HF; 75 patients (30.1%) died, among which 43 (57.3%) for a cardiovascular cause, also in this case with an increasingly higher mortality rate in Stages 3-4 (**Table 3**).

Table 1. Baseline characteristics of patients with moderate and asymptomatic severe aortic stenosis.

	Total (N = 183)	Stage 0 (N = 19)	Stage 1 (N = 46)	Stage 2 (N = 61)	Stage 3 (N= 30)	Stage 4 (N= 27)	P value*
Age, years	74.6 ± 10.8	70 ± 17.2	72.3 ± 8	75.7 ± 9.8	80.4 ± 8.4‡†§	75.8 ± 9.7	<0.001
Female gender, n (%)	70 (38.3)	12 (63.2)	9 (19.6)	21 (34.4)	18 (60)†	10 (37)	0.001
BMI, kg/m^2	26.9 ± 4.2	26.6 ± 3.4	27.7 ± 4.4	27.2 ± 4.8	25.9 ± 3.8	26.2 ± 3.2	0.436
BSA	1.85 ± 0.20	1.83 ± 0.2	1.93 ± 0.2°°	1.85 ± 0.2	1.74 ± 0.2	1.85 ± 0.2	<0.001
Hypertension, n (%)	119 (65)	12 (63.2)	24 (52.4)	45 (73.8)	20 (66.7)	18 (66.7)	0.241
Dyslipidemia, n (%)	141 (77)	11 (57.9)	35 (76.1)	50 (82)	22 (73.3)	23 (85.2)	0.196
Diabetes Mellitus, n (%)	52 (28.4)	3 (15.8)	11 (23.9)	22 (36.1)	8 (26.7)	8 (29.6)	0.438
CAD, n (%)	106 (57.9)	6 (31.6)	22 (47.8)	42 (68.9)‡	16 (53.3)	20 (74.1)‡	0.009
AF, n (%)	63 (34.4)	0 (0)	0 (0)	37 (60.7)‡†°	18 (60)	8 (29.6)	<0.001
HF, n (%)	12 (6.6)	0 (0)	0 (0)	3 (4.9)	5 (16.7)‡†	4 (14.8)	0.012
COPD, n (%)	41 (22.4)	3 (15.8)	10 (21.7)	12 (19.7)	10 (33.3)	6 (22.2)	0.589
Cancer, n (%)	32 (17.5)	2 (10.5)	10 (21.7)	10 (16.4)	6 (20)	4 (14.8)	0.821
CABG, n (%)	8 (4.4)	0 (0)	0 (0)	4 (6.6)	0 (0)	4 (14.8)‡†°°	0.017
Symptoms, n (%)	-	-	-	-	-	-	-
Laboratory Tests							
eGFR	64 ± 19.4	67 ± 20	74.4 ± 12.2§°° °	63.3 ± 21	52.3 ± 17.4	58.7 ± 18.9	<0.001
NT pro-BNP	615 [232 – 1725]	290 [56 – 755]	208 [100 – 375]	1121 [513 – 2382]	1842 [557 – 6085]†	634 [316 – 1601]	<0.001
Medications							
ARB, n (%)	97 (53)	11 (57.9)	21 (45.7)	34 (55.7)	13 (43.3)	18 (66.7)	0.341
ACEi, n (%)	67 (36.6)	9 (47.4)	12 (26.1)	26 (42.6)	7 (23.3)	13 (48.1)	0.095
MRA, n (%)	72 (39.3)	3 (15.8)	10 (21.7)	28 (45.9)	17 (56.7)‡†	14 (51.9)	0.002
BB, n (%)	116 (63.4)	12 (63.2)	31 (67.4)	40 (65.6)	15 (50)	18 (66.7)	0.577

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%).

χ^2 test was used for categorical variables; ANOVA for normally distributed and the Kruskal-Wallis test for non-normally distributed continuous variables.

*Post-hoc significant comparisons were carried out with the Bonferroni-corrected test:

‡ p significant versus Stage 0; † p significant versus Stage 1; § p significant versus Stage 2; °° p significant versus Stage 3; ° p significant versus Stage 4.

Abbreviations: BMI: Body Mass Index; BSA: Body Surface Area; CAD: Coronary Artery Disease; AF: Atrial Fibrillation; HF: Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CABG: Coronary Artery Bypass Grafting; eGFR: estimated Glomerular Filtration Rate; NT pro-BNP: N-terminal (NT)-pro hormone Brain Natriuretic

Peptide; ARB: Angiotensin-receptor blockers; ACE-i: Angiotensin-converting enzyme inhibitors; MRA: Mineralocorticoid Receptor Antagonists; BB: Beta Blockers.

Table 2. Baseline characteristics of patients with symptomatic severe aortic stenosis.

	Total (N = 249)	Stage 0 (N = 23)	Stage 1 (N = 53)	Stage 2 (N = 99)	Stage 3 (N= 38)	Stage 4 (N= 36)	P value*
Age, years	77.9 ± 9	74 ± 11.7	75.8 ± 9.3	79.3 ± 8.3‡†	81 ± 7.5‡†	77 ± 9	0.010
Female gender, n (%)	112 (45)	16 (69.6)	21 (39.6)	42 (42.2)	19 (50)	14 (38.9)	0.115
BMI, kg/m^2	27.2 ± 4.6	24.6 ± 3.9	28 ± 4.5‡	26.9 ± 4	28.1 ± 5.5	27.8 ± 5	0.023
BSA	1.83 ± 0.21	1.78 ± 0.3	1.85 ± 0.2	1.81 ± 0.2	1.80 ± 0.22	1.88 ± 0.25	0.163
Hypertension, n (%)	153 (61.4)	12 (52.2)	26 (49.1)	66 (66.7)	28 (73.7)	21 (58.3)	0.093
Dyslipidemia, n (%)	171 (68.7)	13 (56.5)	32 (60.4)	74 (74.7)	28 (73.7)	24 (66.7)	0.241
Diabetes Mellitus, n (%)	75 (30.1)	1 (4.3)	15 (28.3)	26 (26.3)	16 (42.1)‡	17 (47.2)‡	0.004
CAD, n (%)	130 (52.2)	9 (39.1)	21 (39.6)	51 (51.5)	21 (55.3)	28 (77.8)‡†	0.006
AF, n (%)	87 (34.9)	0 (0)	0 (0)	53 (53.5)	17 (44.7)	17 (47.2)	<0.001
HF, n (%)	22 (8.8)	0 (0)	0 (0)	8 (8.1)	5 (13.2)	9 (25)§	<0.001
COPD, n (%)	50 (20.1)	2 (8.7)	7 (13.2)	26 (26.3)	8 (21.1)	7 (19.4)	0.214
Cancer, n (%)	50 (20.1)	3 (13)	8 (15.1)	23 (23.2)	8 (21.1)	8 (22.2)	0.686
CABG, n (%)	10 (4)	1 (4.3)	0 (0)	5 (5.1)	2 (5.3)	2 (5.6)	0.579
Symptoms, n (%)	249 (100)	23 (100)	53 (100)	99 (100)	38 (100)	36 (100)	0.999
Dyspnea, n (%)	215 (86.3)	21 (91.3)	40 (75.5)	85 (85.9)	37 (97.4)†	32 (88.9)	0.042
NYHA Class, n (%)							0.005
I		4 (17.4)	5 (9.4)	2 (2)	0 (0)	1 (28)	
II		15 (65.2)	29 (54.7)	53 (53.5)	24 (63.2)	14 (38.9)	
III		3 (13)	7 (13.2)	29 (29.3)	12 (31.6)	14 (38.9)	
IV		0 (0)	3 (5.7)	2 (2)	1 (2.6)	3 (8.3)	
Angina, n (%)	64 (25.7)	4 (17.4)	14 (26.4)	25 (25.3)	10 (26.3)	11 (30.6)	0.860
Syncope, n (%)	23 (9.2)	0 (0)	9 (17)	12 (12.1)	1 (2.6)	1 (2.8)	0.028
Labo Test							
eGFR	60 ± 21.1	70.8 ± 15.6°°	65.2 ± 17.7	57.1 ± 22	55.6 ± 20.5	55 ± 21	0.007
NT pro-BNP	1036 [367 – 3322]	277 [187 – 897]	474 [225 – 1209]	1342 [433 – 3355]	1651 [817 – 3162]	4741 [695 – 10005]‡†§	<0.001
Medications							
ARB, n (%)	131 (52.6)	6 (26.1)	25 (47.2)	61 (61.6)§	18 (47.4)	21 (58.3)	0.024
ACEi, n (%)	87 (34.9)	3 (13)	17 (32.1)	43 (43.4)°°	9 (23.7)	15 (41.7)°°	0.026
MRA, n (%)	108 (43.4)	3 (13)	20 (37.7)	44 (44.4)	20 (52.6)‡	21 (58.3)‡	0.007
BB, n (%)	159 (63.9)	14 (60.9)	28 (52.8)	66 (66.7)	24 (63.2)	27 (75)	0.271

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%).

χ^2 test was used for categorical variables; ANOVA for normally distributed and the Kruskal-Wallis test for non-normally distributed continuous variables.

*Post-hoc significant comparisons were carried out with the Bonferroni-corrected test:

‡ p significant versus Stage 0; † p significant versus Stage 1; § p significant versus Stage 2; °° p significant versus Stage 3; ° p significant versus Stage 4.

Abbreviations: BMI: Body Mass Index; BSA: Body Surface Area; CAD: Coronary Artery Disease; AF: Atrial Fibrillation; HF: Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CABG: Coronary Artery Bypass Grafting; NYHA class: New York Heart Association class; eGFR: estimated Glomerular Filtration Rate; NT pro-BNP: N-terminal (NT)-pro hormone Brain Natriuretic Peptide; ARB: Angiotensin-receptor blockers; ACE-I: Angiotensin-converting enzyme inhibitors; MRA: Mineralcorticoid Receptor Antagonists; BB: Beta Blockers.

Table 3. Long-term outcomes stratified by cardiac damage staging in both cohorts of patients with moderate/asymptomatic severe aortic stenosis and symptomatic severe aortic stenosis.

Moderate/asymptomatic severe aortic stenosis	Total (N = 183)	Stage 0 (N = 19)	Stage 1 (N = 46)	Stage 2 (N = 61)	Stage 3 (N= 30)	Stage 4 (N= 27)	P value*
AVR, n (%)	42 (23)	6 (31.6)	14 (30.4)	9 (14.8)	6 (20)	7 (25.9)	0.302
SAVR, n (%)	36 (85.7)	4 (66.7)	13 (92.9)	9 (100)	4 (66.7)	6 (85.7)	
TAVR, n (%)	6 (14.3)	2 (33.3)	1 (7.1)	0 (0)	2 (33.3)	1 (14.3)	
CABG, n (%)	14 (7.7)	0 (0)	6 (13)	5 (8.2)	2 (6.7)	1 (3.7)	0.389
Re-admission for HF, n (%)	11 (6)	0 (0)	0 (0)	4 (6.6)	4 (13.3)	3 (11.1)	0.082
All-cause of death, n (%)	32 (17.5)	0 (0)	2 (4.3)	14 (23)‡†	8 (26.7)‡†	8 (29.6)‡†	0.002
Cardiovascular death, n (%)	15 (46.9)	0 (0)	0 (0)	6 (42.8)	4 (50)	5 (62.5)	0.445
Symptomatic severe aortic stenosis	**Total (N = 249)**	**Stage 0 (N = 23)**	**Stage 1 (N = 53)**	**Stage 2 (N = 99)**	**Stage 3 (N= 38)**	**Stage 4 (N= 36)**	**P value***
AVR, n (%)	123 (49.4)	10 (43.5)	34 (64.1)	50 (50.5)	15 (39.5)	14 (38.9)	0.089
SAVR, n (%)	51 (41.4)	5 (50)	21 (61.8)	17 (34)	4 (26.7)	4 (28.6)	
TAVR, n (%)	72 (58.6)	5 (50)	13 (38.2)	33 (66)	11 (73.3)	10 (71.4)	
CABG, n (%)	21 (8.4)	1 (4.3)	4 (7.5)	13 (13.1)	1 (2.6)	2 (5.6)	0.247
Re-admission for HF, n (%)	19 (7.6)	1 (4.3)	1 (1.9)	10 (10.1)	4 (10.5)	3 (8.3)	0.384
All-cause of death, n (%)	75 (30.1)	2 (8.7)	14 (26.4)	25 (25.3)	17 (44.7)‡	17 (47.2)‡	0.004
Cardiovascular death, n (%)	43 (57.3)	1 (50)	3 (21.4)	14 (56)	12 (70.6)	13 (76.5)	0.024

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%).

χ^2 test was used for categorical variables; ANOVA for normally distributed and the Kruskal-Wallis test for non-normally distributed continuous variables.

*Post-hoc significant comparisons were carried out with the Bonferroni-corrected test:

‡ p significant versus Stage 0; † p significant versus Stage 1; § p significant versus Stage 2; °° p significant versus Stage 3; ° p significant versus Stage 4.

Abbreviations: AVR: Aortic Valve Replacement (including surgical and transcatheter); SAVR: Surgical Aortic Valve Replacement; TAVR: Transcatheter Aortic Valve Replacement. CABG: Coronary Artery Bypass Grafting. HF: Heart Failure.

TTE versus RHC-derived cardiac damage staging: reclassification rate

For each cohort, the proportion of patients assigned to each stage according to the TTE and RHC-derived staging is shown in **Figure 2**. In both cohorts, TTE assigned the higher proportion of patients in Stage 2, while RHC in Stages 1 and 3 (**Figure 2**). Thus, we explored how these patients were reclassified between TTE and RHC in both cohorts (**Figure 2 – Panels B** and **D**). The Cohen's Kappa between the TTE and RHC cardiac damage staging was 0.49 for patients with m/asAS and 0.51 for patients with ssAS, denoting overall a moderate agreement. In details, no patients in TTE-derived Stage 0 were classified in Stages 3-4 based on RHC in both cohorts. The stage with the higher reclassification rate was Stage 2. Interestingly, RHC showed right chambers damage (Stage 3-4) in around 40-50% of patients classified in TTE-derived Stage 2 in both cohorts (**Figure 2 – Panels B** and **D**).

"Discordant" versus "concordant" cases

Among patients included in TTE-derived Stage 1-2, 35 patients (33%) with m/asAS and 65 (43%) with ssAS presented right heart chambers damage (Stage 3-4) at RHC. Thus, we compared baseline and TTE characteristics of those patients ("discordant" cases) versus patients in TTE-derived Stage 1-2 for which also the RHC excluded the presence of right heart chambers damage ("concordant" cases). In both cohorts, "discordant" patients were significantly older, with a higher prevalence of AF and markedly elevated NT pro-BNP ($p<0.05$ for all). At TTE, discordant patients showed higher LAVi, E/e' and SPAP.

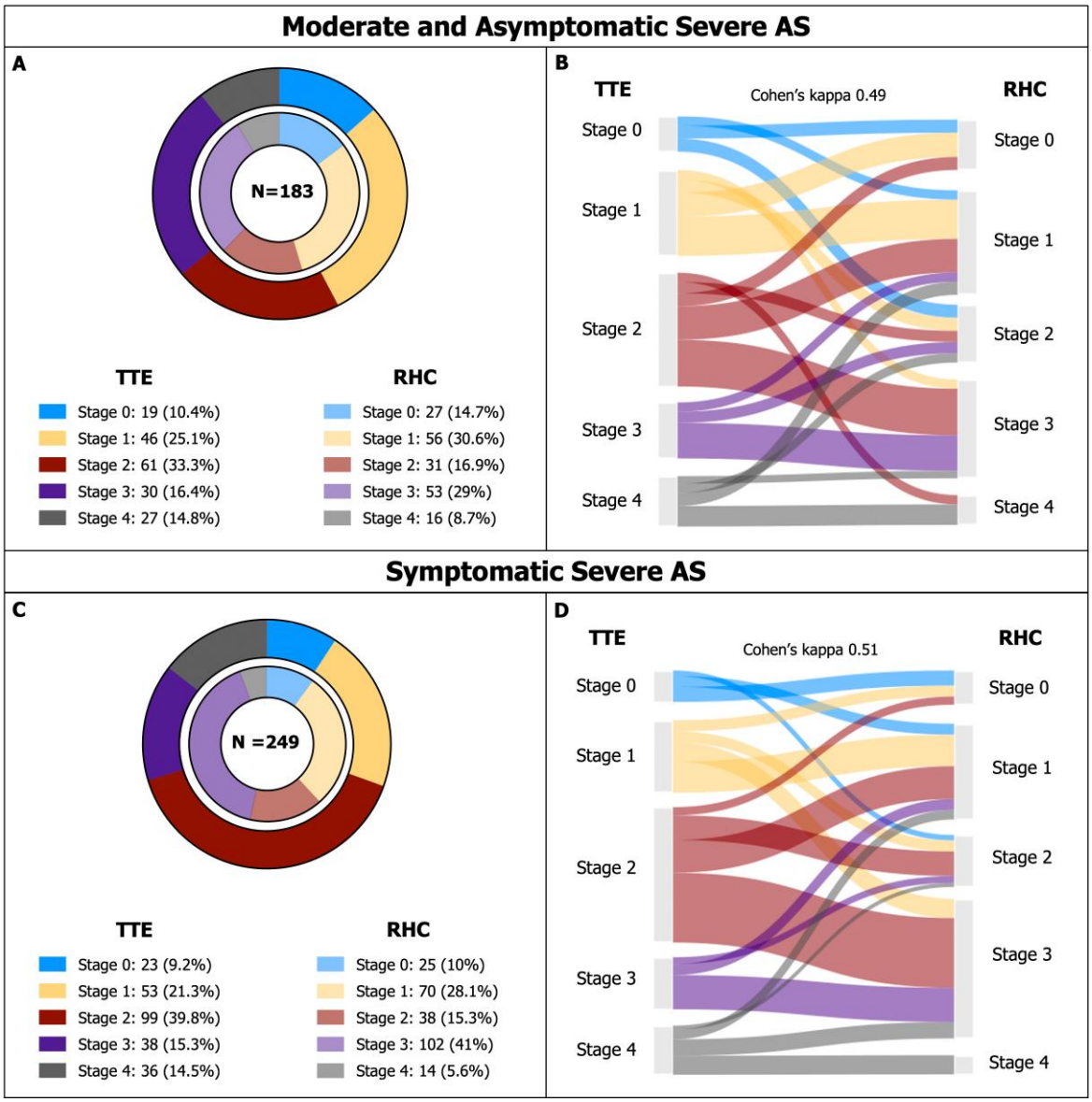


Figure 2. Panels A and **C:** distribution of patients in each stage of cardiac damage derived from TTE and RHC in both patients with moderate/asymptomatic severe and severe symptomatic aortic stenosis, respectively. **Panels B** and **D**: Sankey diagram showing the reclassification of patients between TTE and RHC in both cohorts of patients. Abbreviations: AS: Aortic Stenosis; TTE: Transthoracic Echocardiography; RHC: Right Heart Catheterization.

Prognostic value

Kaplan-Meier curve analysis confirmed that all-cause death significantly increased along with each stage of cardiac damage evaluated both by TTE and RHC at 6-year follow-up in patients with m/asAS (log-rank chi-square 18.56; p=0.001 and log-rank chi-square 42.34; p<0.001, respectively) (**Figure 3 – Panels A** and **B**). This was confirmed also for patients with ssAS (log-rank chi-square 13.56; p=0.008 and log-rank chi-square 45.08; p<0.001, respectively) (**Figure 3 – Panels C** and **D**). Compared to TTE, RHC-derived staging showed better discrimination in the mortality curves between Stage 4 versus 3 in both patients with m/asAS (HR 3.25, CI95% 1.5–7.1, p<0.003) and ssAS (HR 2.46, CI95% 1.2–4.9, p=0.010) (**Figure 3**). In patients with ssAS, RHC better discriminated prognosis between patients in Stage 3 versus 2 (HR 2.23, CI95% 1.1–4.6, p=0.029). Overall, the accuracy of RHC-derived cardiac damage staging for predicting all-cause mortality was numerically higher than the TTE-derived one in both cohorts (AUC 0.79, CI 0.70-0.87 versus AUC 0.70, CI 0.62-0.78 in patients with m/asAS; AUC 0.71, CI 0.65-0.78 versus AUC 0.63, CI 0.56-0.71 in patients with ssAS). However, the difference didn't reach significance neither for m/asAS (p=0.153) nor for ssAS (p=0.090) (**Figure 4**).

The "combined" cardiac damage staging

In both cohorts, the "combined" cardiac damage staging showed a stepwise increase in all-cause mortality at 6-year follow-up (log-rank chi-square 53.17 for patients with m/asAS, p<0.001 and log-rank chi-square 52.38; p<0.001, respectively) (**Figure 5**). The accuracy of the "combined" cardiac damage staging in predicting all-cause mortality was higher than the TTE-derived one (AUC 0.82, CI 0.74-0.89, p=0.041 in m/asAS and AUC 0.74, CI 0.67-0.80, p=0.034 in ssAS) and comparable to the RHC-derived one (p=0.158 in m/asAS and p=0.175 in ssAS) (**Figure 5**).

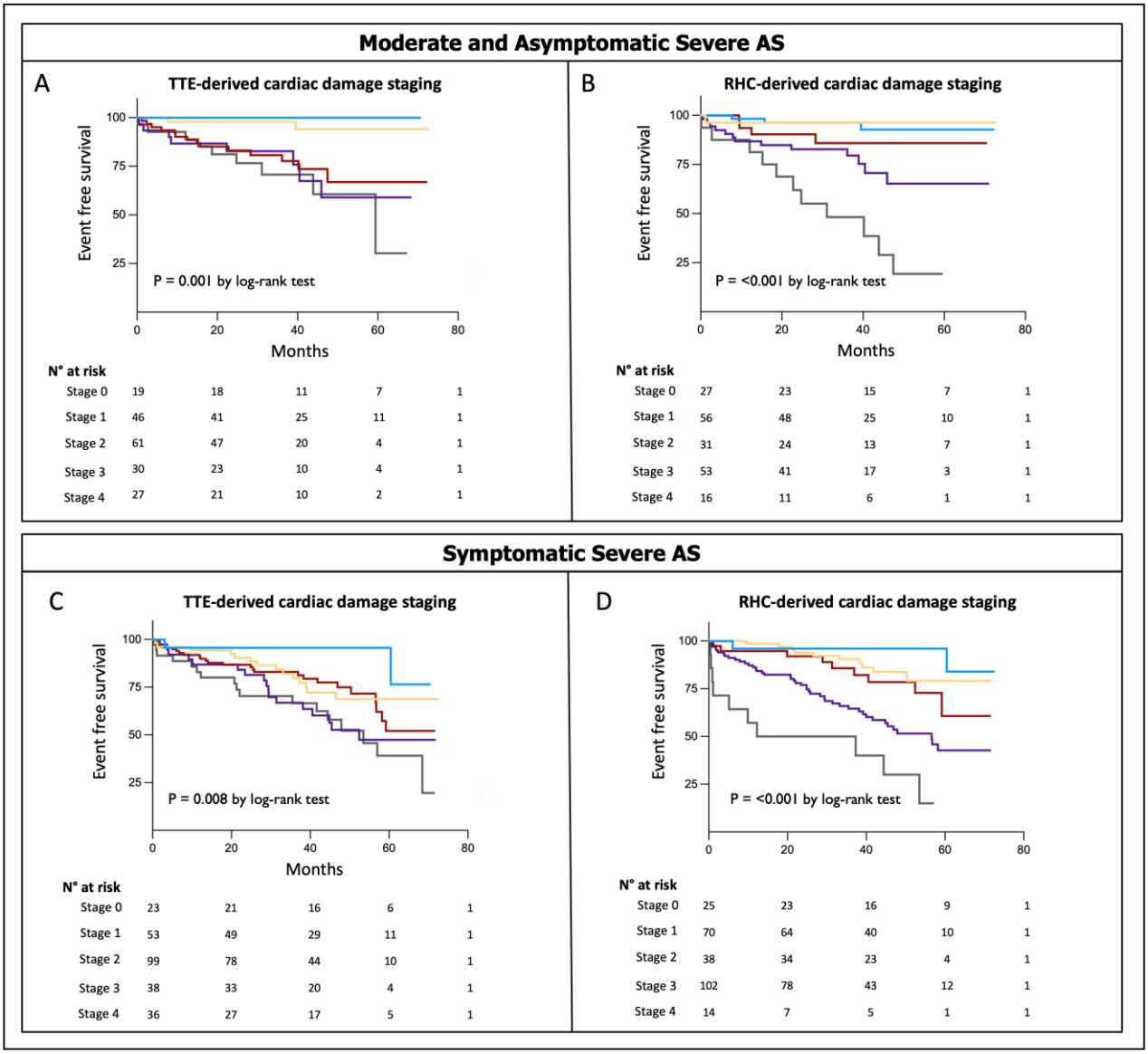
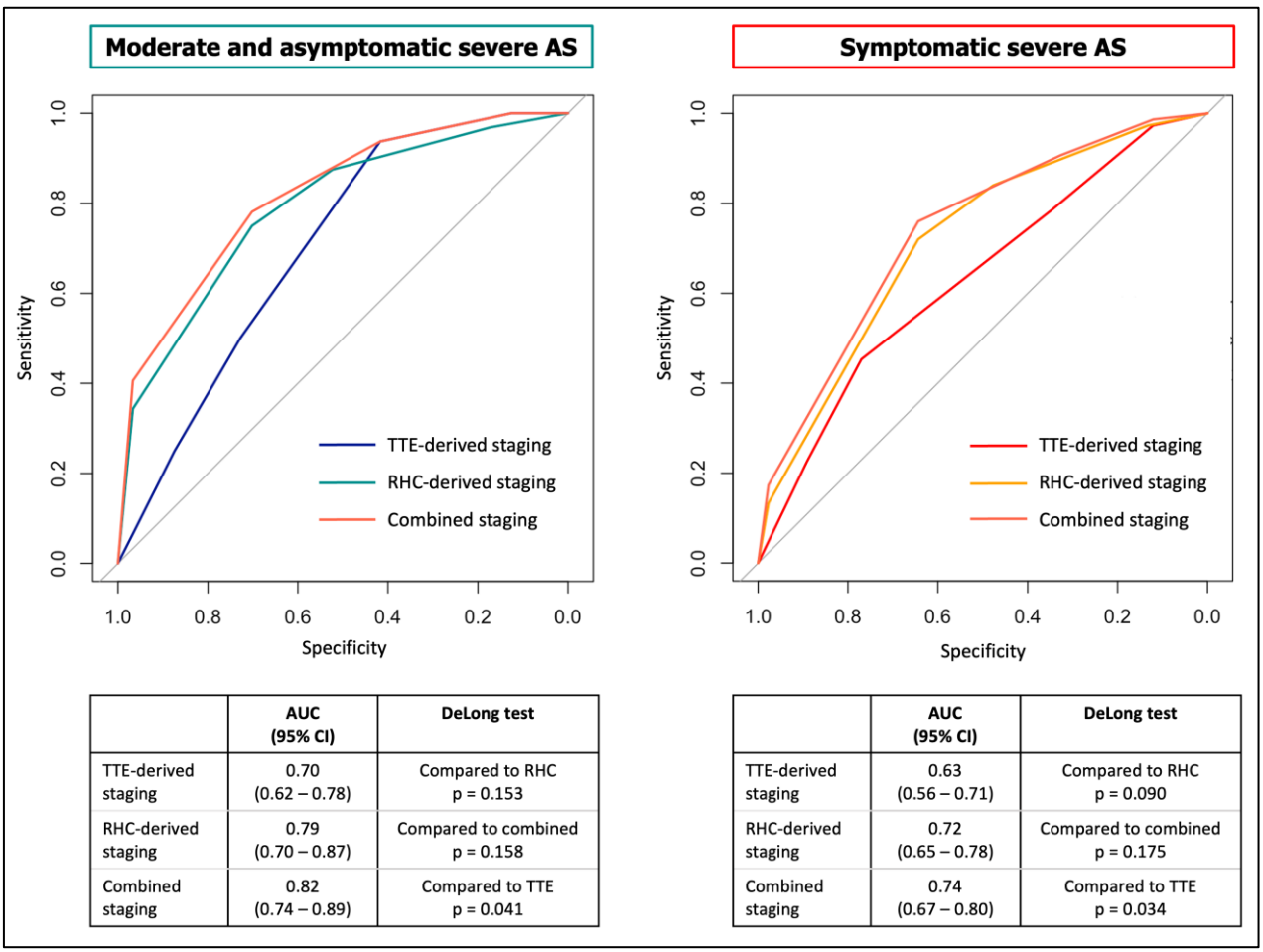


Figure 3 – Kaplan-Meier curves of all-cause mortality according to the TTE- and RHC-derived cardiac damage staging in patients with moderate/asymptomatic severe aortic stenosis (**Panel A** and **B**, respectively) and in those with symptomatic severe aortic stenosis (**Panel C** and **D**, respectively). Abbreviations: AS: Aortic Stenosis; TTE: Transthoracic Echocardiography; RHC: Right Heart Catheterization.



	AUC (95% CI)	DeLong test
TTE-derived staging	0.70 (0.62 – 0.78)	Compared to RHC p = 0.153
RHC-derived staging	0.79 (0.70 – 0.87)	Compared to combined p = 0.158
Combined staging	0.82 (0.74 – 0.89)	Compared to TTE p = 0.041

	AUC (95% CI)	DeLong test
TTE-derived staging	0.63 (0.56 – 0.71)	Compared to RHC p = 0.090
RHC-derived staging	0.72 (0.65 – 0.78)	Compared to combined p = 0.175
Combined staging	0.74 (0.67 – 0.80)	Compared to TTE p = 0.034

Figure 4 – ROC curve analysis comparing the accuracy in predicting all-mortality among the cardiac damage staging derived from TTE, RHC and the "combined" staging. Abbreviations: AS: Aortic Stenosis; TTE: Transthoracic Echocardiography; RHC: Right Heart Catheterization; AUC: Area Under the Curve; CI: Confidence Interval.

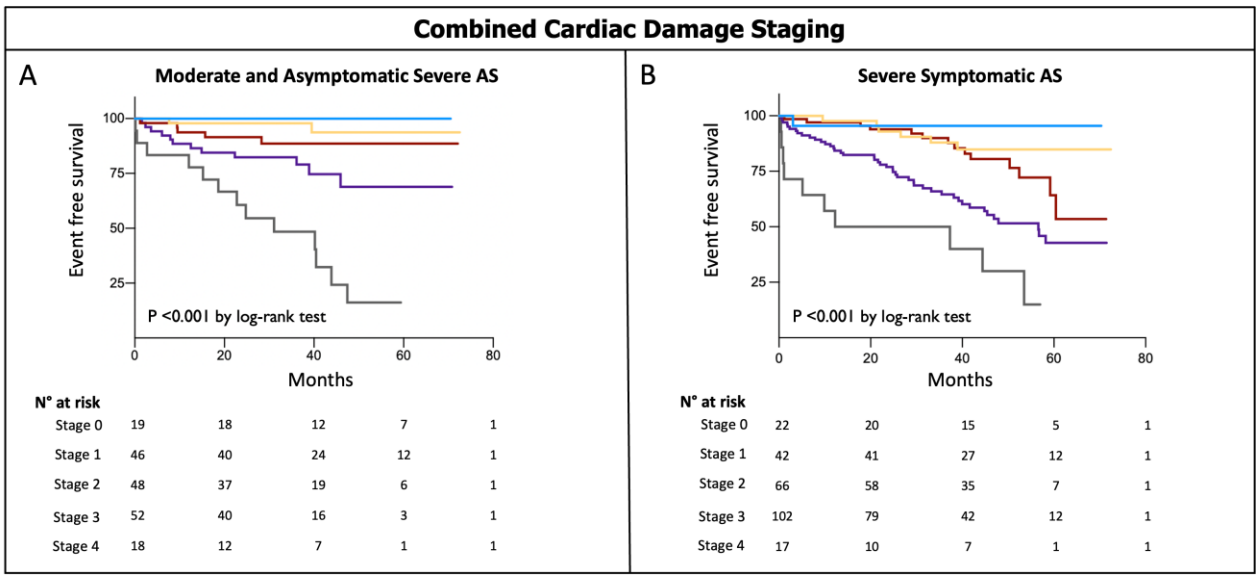


Figure 5 – Kaplan-Meier curves of all-cause mortality according to the "combined" cardiac damage staging in patients with moderate/asymptomatic severe aortic stenosis (**Panel A**) and in those with symptomatic severe aortic stenosis (**Panel B**). Abbreviations: AS: Aortic Stenosis.

Discussion

In this study, we investigated the added value of RHC compared to TTE in characterizing the extra-aortic valve damage in patients with m/asAS and ssAS. The main findings are: i) in both cohorts, a higher proportion of patients were assigned in Stage 2 and a lower proportion in Stage 1 and 3 by TTE, as compared to the RHC-derived cardiac damage staging; ii) patients in TTE-derived Stage 2 had a high rate of reclassification with 40-50% of them presenting with right chambers involvement (stages 3-4) at RHC; iii) these “discordant” cases were significantly older, had a higher prevalence of AF, markedly elevated NT pro-BNP, higher LAVi, E/e’ and SPAP versus “concordant” cases; iv) in both cohorts, the TTE- and RHC-derived staging system had prognostic value for estimating cardiac damage, although the agreement between the individual scores appeared moderate; v) in patients with clinically significant AS, the "combined" cardiac damage staging, integrating TTE and RHC, was more accurate in predicting mortality than the TTE-derived system (and comparable to the RHC-derived one).

Cardiac damage staging: a pathophysiology-based approach

Cardiac damage staging is emerging as a clinical tool that assist clinicians in outlining the management and treatment of patients with ≥moderate AS, whether symptomatic or not. The risk scores recommended by current guidelines (i.e., the STS-PROM and EuroSCORE II score) focus mainly on the general condition and comorbidities of the patient and only assess the "procedural" risk related to AVR itself. Unfortunately, they are unable to predict the mortality risk related to the "global cardiac health" of AS patients (58). However, the presence, extent and reversibility of extra-aortic cardiac involvement were found to be one of the most important prognostic factors that may even interfere with the potential benefits of AVR (12,132). Thus, a pathophysiology-based assessment that takes into account the natural history of AS and the progressive heart damage caused by the disease is crucial to identify the best timing for intervention, both in patients with ssAS, for whom AVR may be "overdue" as well as in those with m/asAS, for whom AVR may be "premature" (133).

Overall, our data confirmed that both TTE and RHC can reliably map cardiac damage in patients with m/asAS and ssAS and provide important prognostic information, as evidenced by the progressively higher mortality at the more advanced stages. However, compared to TTE-, RHC-derived staging showed better discrimination in the mortality curves, mainly between stages assessing RV damage (stage 3 and 4), which was also evident by the AUC curve.

Cardiac damage staging: the role of TTE and RHC

In both m/asAS and ssAS patients, TTE was found to be highly accurate in ruling out the presence of cardiac damage (stage 0), as well as in assessing LV function (stage 1-2), which is an important discriminator in the timing and choice of intervention (134-136). In addition to LV dysfunction, PH and the associated RV dysfunction are not uncommon and impact mortality in patients with AS (129,130). Our study corroborates previous observations that, compared to ultrasound, RHC is more accurate in evaluating the presence and extent of PH and RV dysfunction (130,137). Indeed, we

showed that RHC could detect pulmonary vasculature damage in approximately 40-50% of TTE-derived Stage 2 patients, reclassifying them in Stage 3 and 4. The median time difference between TTE and RHC measurements ranged between 2-5 days, which excludes that the discrepancies were due to changes in hemodynamic status and/or pharmacological treatment.

Reclassification rate: discordant vs concordant patients

Although the TTE- and RHC-derived staging *per se* showed prognostic value, the agreement between them was moderate. Indeed, up to 50 % of Stage 1-2 patients had either elevated pulmonary pressures or RV dysfunction by RHC and were reclassified in Stage 3-4. Several mechanisms may account for this observation. First, the TTE-derived staging score considers clinical parameters such as AF, which are not being used in the RHC-derived one. Second, it is well established that the non-invasive echocardiographic assessment of RV function is often complicated by the presence of concomitant pulmonary disease, the specific location of the RV in the thoracic cavity, and the complex structure and distinct contraction pattern of the RV itself (138). Finally, the ultrasound assessment of pulmonary pressures is indirect and depends not only on the filling status of the patient but also on the detection of a measurable TR signal, which is not the case with RHC where pressures are measured directly (137). The estimation of RA pressure for the calculation of SPAP by inspection of the inferior vena cava is also an indirect estimation and not a precise measurement. In line with these observations, we found that at TTE Stage 1-2, especially older patients with AF were reclassified to a higher Stage, probably due to the underestimation of pulmonary pressure by the variability of TTE measurements. In addition, these discordant cases were characterized by higher NT proBNP and elevated filling pressures with higher E/e', suggesting the presence of congestion and/or pulmonary vasculature damage by RHC.

RHC in AS: clinical implications

The comparison of both staging systems highlights the possible complementary role of RHC in risk stratification of patients with m/asAS and ssAS. From our results it can be inferred that: patients in TTE stage 0 do not need additional RHC and those in stage 3-4 can be referred for an RHC to confirm the diagnosis of PH and RV impairment. However, based on our observations, it is the patient in Stages 1 and 2, mainly the elderly with AF and elevated filling pressure at TTE, who may benefit the most from RHC, since in this patient group elevated pulmonary pressure and RV dysfunction are often missed by ultrasound.

The "combined" cardiac damage staging, integrating both TTE and RHC measurement, aids to stratify better the severity of cardiac damage and allows to determine the prognosis of patients with m/asAS and ssAS more accurately compared to TTE alone. This does not imply that RHC should be performed in all patients with moderate to severe AS. Our data suggest that the integration of RHC to TTE in the diagnostic work-up might improve prognostic stratification, especially in case of the elderly with AF and elevated filling pressure at TTE.

Unfortunately, our data are not sufficiently powered to determine the stage at which the benefit of an AVR is the greatest, but they can add a piece to the puzzle of understanding which parameters should be considered in decision-making and how to interpret them. Ongoing randomized clinical trials (EASY-AS trial, NCT04204915 and PROGRESS trial, NCT04889872) will be conclusive for the best treatment strategy in this challenging population.

Conclusions

Our results should be interpreted considering some limitations. First, this was an observational study, thus, so far, it should be considered hypothesis-generating. Moreover, more sensitive TTE parameters that define the LV and RV systolic function like global left and right ventricular longitudinal strain, myocardial work have not been considered; however, so far, none of them have widespread application in routine clinical practice nor have been included in guidelines (60,139).

PART III

Role of Heart Valve Clinics in the management of patients with aortic stenosis.

CHAPTER 7

OUTCOMES IN PATIENTS WITH MODERATE AND ASYMPTOMATIC SEVERE AORTIC STENOSIS FOLLOWED UP IN HEART VALVE CLINICS

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Introduction

The management of patients with moderate AS (mAS) and asymptomatic severe AS (asAS), particularly the choice between early intervention versus watchful waiting, is still debated (140). A delay in reporting symptoms is common; once symptoms develop, early recognition and timely referral to intervention are critical (15,141). In this setting, the RECOVERY and AVATAR trials supported the benefit of early aortic valve replacement (AVR) versus conventional watchful waiting strategy for patients with asAS and normal left ventricular ejection fraction (LVEF)(93,99). These trials are in line with the evolving clinical decision-making paradigm regarding the management of this challenging population. Similarly, no strong recommendations have been established yet for the treatment of patients with mAS, who do not have a favorable prognosis, especially in case of concomitant reduced LVEF (142-144). The benefit of early detection of AS progression and left ventricle dysfunction prompts the interest to evaluate the outcome benefit of dedicated health-care pathways and educational programs.

Recently, an increasing number of patients with VHD have been managed in Heart Valve Clinics (HVCs), which offer multidisciplinary services and fast and easy referral towards other necessary disciplines, enhancing the quality of patient care (15). However, due to the high prevalence of VHD, most patients with AS are still followed in routine cardiac care consultations. This condition allowed a direct comparison in the same institution between usual ambulatory cardiac care (standard-of-care, SOC) and HVC approach. Therefore, we aimed to evaluate the outcome benefit of a HVC approach compared to SOC in patients with mAS and asAS. Moreover, a subgroup analysis was performed to assess the benefit of HVC care separately in patients with mAS and asAS.

Methods

The study population included in our single-center, observational registry was identified according to the following criteria: i) patients with mAS or asAS, diagnosed according to current ESC Guidelines (98), ii) good quality trans-thoracic echocardiography (TTE) to assess AS grade, iii) at least one cardiac ambulatory consultation at our Cardiovascular Center. Exclusion criteria included: i) class I indications for surgical/transcatheter aortic valve replacement (SAVR/TAVR) (98), ii) concomitant more than moderate aortic regurgitation and/or mitral valve disease at the time of the first echocardiography, iii) prior valve surgery or percutaneous procedure of the aortic valve, iv) severe extracardiac comorbidity limiting survival (life expectancy <12 months). Based on the type of outpatient strategy, patients were divided into the HVC group, if they underwent at least one visit in the HVC, and the SOC group, if they were followed with routine cardiac care consultations (performed by interventional cardiologists, electrophysiologists, heart failure specialists, and clinical cardiologists). These patients were referred to HVC or SOC by general practitioners, outpatient care specialists in cardiology, internal medicine and resident cardiologists according to current guidelines and availability of ambulatory slots (16). Once included in the HVC program, the patients followed the cardiological schedule provided by this setting. The indication for AVR (SAVR/TAVR) has been assigned following the Guidelines and confirmed by the Heart Team according to symptoms onset and, in case of asymptomatic patients, in presence of any among: abnormal exercise test, LVEF<50%, markedly elevated biomarkers, rapid progression of AS severity, severe valve calcification assessed by computed tomography (CT) (98).

The HVC organization

Since 2014, a Heart Valve Center (HVCe) has been set up in our Cardiovascular Center according to the ESC/AHA Guidelines, including: i) availability of the entire spectrum of surgical and transcatheter valve procedures with 24/7 services, ii) weekly Heart Team meetings; iii) organization of a HVC for ambulatory management; iv) use of multimodality imaging including

echocardiography, cardiac CT, cardiac magnetic resonance (CMR) and nuclear medicine, v) yearly evaluation of patients outcomes with quality check and planning of educational programs (16,17). The HVC involves cardiologists with expertise in VHD, cardiac imaging specialists, cardio-anesthesiologists, cardiac surgeons, and dedicated nurses. Specifically, the cardiologists involved have the following competencies: i) more than 10-year experience in VHD; ii) performance of high volume of TTE/transesophageal echocardiograms per year, with official certifications for echocardiographic guidance of percutaneous structural valve intervention (MitraClip/TriClip); iii) continuous update on the field of VHD by periodical training courses, lead of research projects and participation in national/international congresses; iv) weekly attendance of Heart Team meetings; v) some of them, experience in cardiac CT and CMR. The organization of the HVC includes a reduced number of patients per session of consultations (6-8 patients versus 12-14 patients in SOC), with an average of 40 minutes per visit, resulting in more time dedicated for patients' education and supplementary TTE image acquisitions if necessary. The HVC program provides a tailored schedule of follow-up according to the severity of VHD and the overall patient clinical status. Specifically, patients with clinically significant AS managed in the HVC are followed-up at least every 6 months with physical examination, electrocardiogram, and TTE. Patients who develop symptoms or experience a significant worsening of symptoms/quality of life between scheduled HVC consultations could communicate with the HVC physician by telephone/email. Moreover, a dedicated team of nurses adequately trained and skilled for managing patients with VHD is available to answer to HVC patients' calls and reschedule consultations with the help of secretaries, if necessary (15,145).

Study endpoints

The primary endpoint of the study was all-cause mortality. The vital status was validated in the Belgian Population Register. We also assessed cardiovascular death, hospitalization for heart failure (HF) and a composite of all-cause death and non-fatal hospitalization due to worsening HF.

Results

The study population consisted of 2129 patients with mAS and asAS, divided into those followed in the SOC (n=1878) and those in the HVC (n=251). The mean age was 76.5±12.4 years, and 992 (44.2%) were females (**Table 1**). A total of 919 (43.2%) patients had asAS (773 [41.2%] in SOC and 146 [58.2%] in HVC, p<0.001), while the remaining 1210 (56.8%) patients had mAS (1105 [58.8%] in SOC and 105 [41.8%] in the HVC) (**Table 2**).

Baseline, clinical and echocardiographic characteristics

Baseline characteristics, cardiovascular risk factors, comorbidities and medical therapy are reported in **Table 1**. Patients in SOC were older (p<0.001), with a higher prevalence of arterial hypertension (p=0.041), CAD (p=0.003) and lower GFR (p<0.001) (**Table 1**–**unmatched columns**). Medical therapy was also similar between the two cohorts (**Table 1**). At echocardiogram, LVEF and Vmax were lower in the SOC group (p<0.01 for both, **Table 2**). After 1:1 PSM, no differences were observed in baseline and echocardiographic characteristics between the two groups (**Table 1 and 2–matched columns**).

Outcomes in the unmatched population

Mean follow-up was 4.8±1.8 years (4.8±1.7 years in HVC and 4.7±2 years in SOC, p=0.123). During the study period, a total of 822 patients (38.6%) died, 307 (14.4%) had HF hospitalization and 596 patients (28%) underwent AVR, of whom 85.1% SAVR and 14.9% TAVR. Compared to SOC, Kaplan-Meier estimates showed a lower rate of unadjusted all-cause death and the composite endpoint in the HVC cohort (p<0.001 for both – **Figure 1**, ***Panels A*** and ***C***).

Table 1. Baseline characteristics, comorbidities and medical therapy of matched and unmatched patients with moderate and asymptomatic severe AS, divided into Heart Valve Clinic versus Standard-of-Care.

	Unmatched				Matched		
	Total (N = 2129)	**Heart Valve Clinic (N = 251)**	**Standard of Care (N = 1878)**	**P-value**	**Heart Valve Clinic (N = 156)**	**Standard of Care (N = 156)**	**P-value**
Age, n (%)	76.5 ± 12.4	71 ± 13.3	77.2 ± 12.2	<0.001	72.8 ± 11.3	72 ± 13.5	0.559
Female Sex, n (%)	942 (44.2)	99 (39.4)	843 (44.9)	0.118	58 (37.2)	53 (34)	0.636
BMI, (Kg/m^2)	26.3 [23.7 - 29.6]	26.9 [24.1 - 29.7]	26.3 [23.7 - 29.6]	0.228	27.1 [24.5 - 29.4]	26.4 [23.6 - 29.3]	0.321
HBP, n (%)	720 (33.8)	70 (27.9)	650 (34.6)	0.041	52 (33.3)	49 (31.4)	0.809
T2DM, n (%)	559 (26.2)	55 (21.9)	504 (26.8)	0.112	40 (25.6)	43 (27.6)	0.798
AF, n (%)	731 (34.3)	80 (31.9)	651 (34.7)	0.421	51 (32.7)	42 (26.9)	0.322
COPD, n (%)	387 (18.2)	43 (17.1)	344 (18.3)	0.711	28 (17.9)	30 (19.2)	0.884
Cancer, n (%)	348 (16.3)	38 (15.1)	310 (16.5)	0.646	24 (15.4)	27 (17.3)	0.759
CAD, n (%)	581 (27.3)	48 (19.1)	533 (28.4)	0.003	34 (21.8)	35 (22.4)	0.999
Pre-HF, n (%)	75 (3.5)	3 (1.2)	72 (3.8)	0.052	3 (1.9)	4 (2.6)	0.999
CABG, n (%)[†]	34 (1.6)	4 (1.6)	30 (1.6)	0.999	4 (2.6)	5 (3.2)	0.999
Pre-MVR, n (%)[†]	28 (1.3)	6 (2.4)	22 (1.2)	0.132	3 (1.9)	1 (0.6)	0.623
GFR (ml/min)	61 ± 22.3	67.2 ± 19.2	58 ± 22.4	<0.001	67 ± 19	67.3 ± 20	0.907
ACE-I, n (%)	656 (30.8)	76 (30.3)	580 (30.9)	0.903	47 (30.1)	52 (33.3)	0.627
ARBs, n (%)	1022 (48)	122 (48.6)	900 (47.9)	0.892	76 (48.7)	86 (55.1)	0.308
MRAs, n (%)	810 (38)	88 (35.1)	722 (38.4)	0.333	69 (44.2)	66 (42.3)	0.819
Beta-blockers, n (%)	1211 (56.9)	149 (59.4)	1062 (56.5)	0.437	101 (64.7)	97 (62.2)	0.724
Statins, n (%)	1280 (60.1)	152 (60.6)	1128 (60.1)	0.935	109 (69.9)	112 (71.8)	0.803

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%). [†]Differences in categorical variables were analyzed using Fisher's Exact Test.

Abbreviations: BMI: body mass index; HBP: hypertension; T2DM: Type 2 Diabetes Mellitus; AF: atrial fibrillation; COPD: Chronic obstructive pulmonary disease; CAD: coronary artery disease; HF = heart failure; CABG = coronary artery bypass graft surgery; MVR = mitral valve repair; GFR = glomerular filtration rate; ACE-I = Angiotensin-converting enzyme inhibitors; ARBs = Angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists (aldosterone blockers).

Table 2. Baseline echocardiographic indices of matched and unmatched patients with moderate and asymptomatic severe AS, divided into Heart Valve Clinic versus Standard-of-Care.

	Unmatched				Matched		
	Total (N = 2129)	**Heart Valve Clinic (N = 251)**	**Standard of Care (N = 1878)**	**P value**	**Heart Valve Clinic (N = 156)**	**Standard of Care (N = 156)**	**P value**
LVMi, (g/m^2)	198 ± 66	200.2 ± 66.7	197.1 ± 65.6	0.512	203 ± 70	207 ± 67	0.622
BP LVEF, (%)	55 [51-60]	55 [55-61]	55 [50-60]	<0.001	55 [55-60]	57 [55-61]	0.510
Severe AS	919 (43.2)	146 (58.2)	773 (41.2)	<0.001	56 (35.9)	52 (33.3)	0.634
AVmax	3.5 [3.2-4.1]	3.7 [3.2-4.2]	3.5 [3.2-4.1]	0.009	3.7 [3.3-4.2]	3.5 [3.2-4.2]	0.153
AVA, cm2	1.01 [0.8-1.3]	1 [0.8-1.2]	1 [0.8-1.3]	0.088	1 [0.8-1.3]	1 [0.8-1.4]	0.572
TR Pmax	31 ± 12	29 ± 10	32 ± 12	0.005	30 ± 11	30 ± 14	0.782
Moderate MR, n (%)	102 (4.8)	10 (4)	92 (4.9)	0.523	4 (2.6)	7 (4.5)	0.357

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%). Abbreviations: LVMi = left ventricular mass indexed to BSA; BP LVEF: two-dimensional bi-plane left ventricular ejection fraction; AV max = aortic valve velocity max; AVA = aortic valve area; TR Pmax = tricuspid regurgitation gradient; MR = mitral regurgitation.

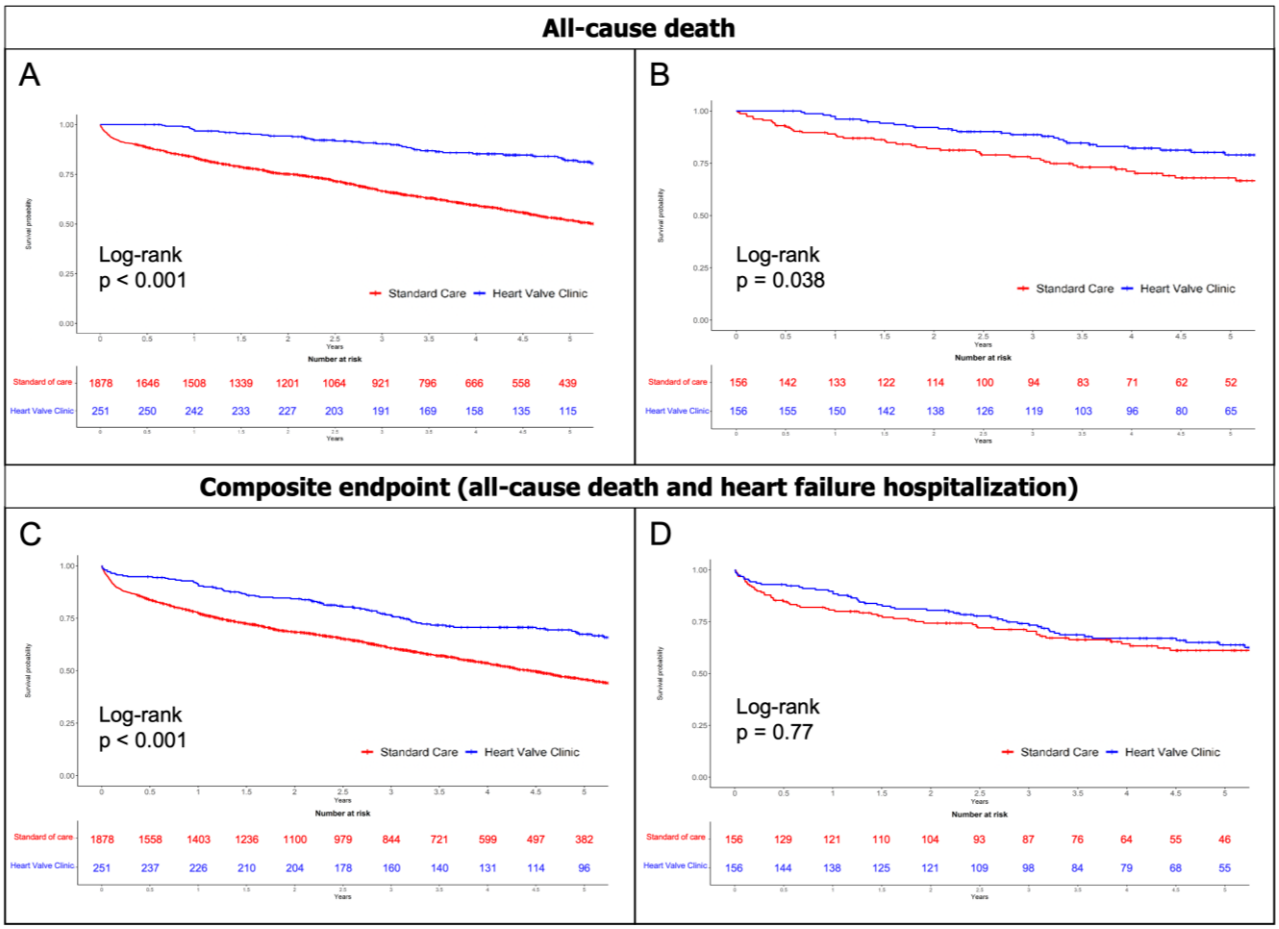

Figure 1. Kaplan-Meier survival curves for all-cause death and composite endpoint (all-cause death and heart failure hospitalization) in patients with moderate and asymptomatic severe aortic stenosis; *panel A*: all-cause death in unmatched population; *panel B*: all-cause death in matched cohorts; *panel C*: composite endpoint (all-cause death and heart failure hospitalization) in unmatched population; *panel D*: composite endpoint (all-cause death and heart failure hospitalization) in matched cohorts. *Blue curve*: Heart Valve Clinic (HVC)*; red line*: standard-of-care (SOC).

Findings and outcomes in the matched population

The number of cardiac consultations per year, exercise stress tests and BNP determinations was higher in the HVC cohort (p<0.001 for all). Moreover, a higher number of CTs was requested in the HVC group (p=0.002), with numerically higher values of calcium score, even though not statistically significant (**Table 3**). Significant correlations were observed between number of visits and outcomes in HVC patients (r= -0.283, p=0.021 and r= -0.263, p=0.004 for all-cause and cardiovascular death, respectively), but not in SOC group (r= -0.164, p=0.112 and r = -0.016, p=0.918 with for all-cause and cardiovascular death, respectively).

Similar incidences of asAS and referral to AVR were reported between the two cohorts, with a shorter time between indication to AVR and less advanced NYHA class in HVC (p<0.001 and p=0.032, respectively) (**Table 3**). Compared to SOC, a lower rate of all-cause death, but not of the composite endpoint, was observed in the HVC cohort (HR=0.63, 95%CI 0.40–0.98, p=0.038, **Figure 1**, ***panel B and D***). This benefit was also observed for cardiovascular death (52.9% versus 76.1%, p=0.030) and all ranges of age. Stratifying the population by LVEF (<or ≥50%), there was a significantly lower survival in SOC patients when LVEF was reduced (p=0.005). In the multivariable Cox regression model, after adjusting for confounding factors, the HVC was an independent predictor of reduced all-cause death (HR=0.54, 95%CI 0.34-0.85, p=0.007), together with younger age, absence of COPD and higher LVEF (**Table 4, matched columns**). In the competing risk regression analysis, stratifying the population by age (<70, 70-80, >80-year-old), the HVC approach was a significant predictor of all-cause mortality (p=0.011), but not of HF hospitalization (p=0.275) (**Figure 2**).

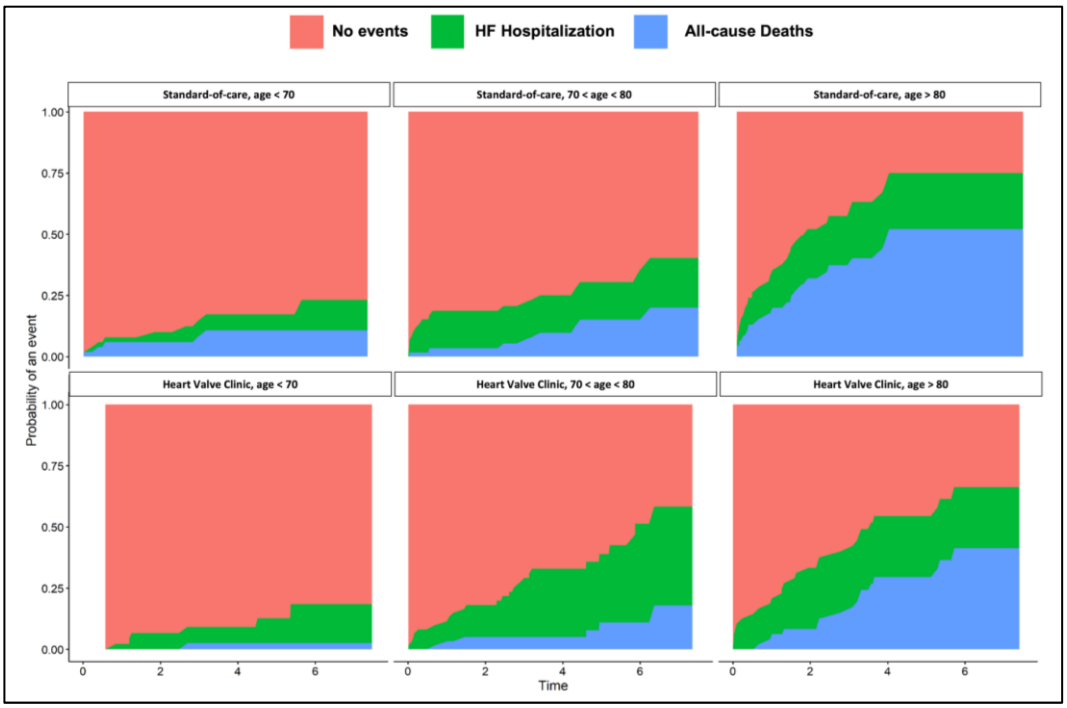

Figure 2. Competing risk analysis for all-cause death and HF hospitalization with cumulative incidence curves, stratified by age (<70, 70-80, >80-year-old). The cumulative incidence curves were not significantly different for HF hospitalization (p = 0.275) but were significantly different for all-cause death (p = 0.011). Abbreviation: HF = heart failure.

Table 3. Main findings and outcomes of matched patients with mAS and asAS, divided into HVC versus SOC.

	Heart Valve Clinic (N = 156)	Standard of care (N = 156)	P value
Total cardiac consultation/year, n	1.6 ± 1	0.8 ± 0.9	<0.001
Exercise stress/year, n	0.5 ± 0.3	0.2 ± 0.4	<0.001
BNP determinations, n	2.3 ± 0.7	1.3 ± 1.2	<0.001
Number of CCT, n (%)	41 (26.3)	20 (12.8)	0.002
Calcium Score, mean ± SD	2499 ± 1708	1812 ± 1232	0.413
Time Indication to AVR, months	1.9 ± 1	3.3 ± 1.3	<0.001
NYHA Class at AVR, n (%)			
I-II	38 (54.3)	20 (33.9)	0.032
III-IV	32 (45.7)	39 (66.1)	
AVR, n (%)	70 (44.9)	59 (37.8)	0.250
SAVR	63 (90)	54 (91.5)	0.994
TAVR	7 (10)	5 (8.5)	
HF readmission, n (%)	36 (23.1)	24 (15.4)	0.114
1-y all-cause death, n (%)†	4 (2.6)	17 (11.3)	0.003

Continuous variables are presented as mean (SD) or median [LQ-UQ], when indicated; categorical ones as n (%). †Differences in categorical variables were analyzed using Fisher's Exact Test. Abbreviations: AVR = aortic valve replacement; HF = heart failure; y = year.

Table 4. Predictors of all-cause death for patients with moderate and asymptomatic severe AS at univariable and multivariable analysis.

	Unmatched cohort						Matched cohort					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age, years	1.08	1.07 - 1.09	<0.001	1.06	1.05 - 1.07	<0.001	1.10	1.07 - 1.13	<0.001	1.10	1.07 - 1.14	<0.001
Gender, female	1.25	1.09 - 1.43	0.001	-	-	-	1.10	0.70 - 1.74	0.670	-	-	-
BMI	1.00	1.00 - 1.00	0.740	-	-	-	1.01	0.96 - 1.06	0.656	-	-	-
HBP	0.99	0.86 - 1.14	0.899	-	-	-	1.30	0.82 - 2.06	0.262	-	-	-
T2DM	1.20	1.03 - 1.39	0.016	1.22	1.03 - 1.46	0.023	1.47	0.92 - 2.35	0.106	-	-	-
AF	1.68	1.47 - 1.93	<0.001	-	-	-	1.81	1.16 - 2.83	0.009	-	-	-
COPD	1.57	1.34 - 1.83	<0.001	1.49	1.25 - 1.78	<0.001	1.97	1.22 - 3.19	0.005	2.08	1.28 - 3.37	0.002
Cancer	1.11	0.93 - 1.32	0.254	-	-	-	1.66	0.99 - 2.77	0.055	-	-	-
CAD	1.18	1.02 - 1.37	0.024	-	-	-	0.95	0.56 - 1.60	0.841	-	-	-
Pre-HF	2.06	1.49 - 2.86	<0.001	-	-	-	0.73	0.10 - 5.24	0.754	-	-	-
CABG	1.16	0.71 - 1.90	0.558	-	-	-	1.85	0.68 - 5.08	0.230	-	-	-
Pre-MVR	0.50	0.22 - 1.11	0.090	-	-	-	1.00	0.01 - 9.99	0.994	-	-	-
GFR	0.97	0.97 - 0.98	<0.001	0.98	0.98 - 0.99	<0.001	0.97	0.96 - 0.98	<0.001	-	-	-
ACE-I	0.89	0.76 - 1.03	0.108	-	-	-	0.70	0.42 - 1.16	0.165	-	-	-
ARBs	0.79	0.69 - 0.90	0.001	0.68	0.58 - 0.79	< 0.001	1.24	0.80 - 1.94	0.333	-	-	-
MRAs	0.75	0.72 - 0.97	0.001	0.84	0.72 - 0.99	0.036	2.19	1.40 - 3.43	0.001	-	-	-
Beta-blockers	0.70	0.61 - 0.80	0.001	0.64	0.55 - 0.75	<0.001	0.75	0.48 - 1.17	0.204	-	-	-
Statins	0.65	0.57 - 0.75	0.001	0.68	0.58 - 0.79	<0.001	0.88	0.55 - 1.41	0.584	-	-	-
AVmax	0.94	0.84 - 1.04	0.217	-	-	-	1.02	0.74 - 1.41	0.892	-	-	-
AVA	0.98	0.90 - 1.06	0.566	-	-	-	0.50	0.27 - 0.94	0.031	-	-	-
TR P max	1.03	1.03 - 1.04	<0.001	1.02	1.00 - 1.02	<0.001	1.03	1.02 - 1.05	<0.001	-	-	-
LV Mass	1.00	1.00 - 1.00	0.672	-	-	-	1.00	0.99 - 1.01	0.819	-	-	-
LVEF	0.96	0.95 - 0.97	<0.001	0.97	0.96 - 0.97	<0.001	0.97	0.95 - 0.99	0.003	0.97	0.94 - 0.99	0.007
Moderate MR	1.41	1.30 - 1.52	<0.001	-	-	-	1.49	1.33 - 1.54	0.010	-	-	-
HeartValveClinic	0.35	0.27 - 0.47	<0.001	0.50	0.36 - 0.70	<0.001	0.63	0.40 - 0.98	0.038	0.54	0.34 - 0.85	0.007

Abbreviations: BMI = body mass index; HBP = hypertensions; T2DM = type 2 diabetes mellitus; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HF = heart failure; CABG = coronary artery bypass graft surgery; MVR = mitral valve repair; GFR = glomerular filtration rate; ACE-I = ACE inhibitors; ARBs = angiotensin receptor blockers; MRAs = mineralocorticoid receptor antagonists (aldosterone blockers); AV Vmax = aortic valve velocity max; AVA = aortic valve area; TR = tricuspid regurgitation; LV = left ventricle; LVEF = left ventricular ejection fraction; MR: mitral regurgitation.

Impact of HVC in patients with mAS

Overall, 1210 (56.8%) patients had mAS (1105 [58.8%] in SOC and 105 [41.8%] in HVC, p<0.001). In patients with mAS, the HVC approach showed a higher survival rate (unadjusted p<0.001 versus adjusted p=0.003, **Figure 3, Panels *A* and *B***). In the multivariable analysis, the HVC strategy was an independent predictor of reduced all-cause of death, together with younger age, higher GFR and absence of COPD.

Impact of HVC in patients with asAS

Overall, 919 (43.2%) patients had asAS (773 [41.2%] in SOC and 146 [58.2%] in HVC, p<0.001). In the Kaplan–Meier curve analysis, the higher survival of the HVC approach, compared to SOC, turned out to be non-significant after PSM (unadjusted p<0.001 versus adjusted p=0.25, **Figure 3**, **Panels *C*-*D***). In the multivariable analysis, the HVC was not an independent predictor of reduced all-cause of death, unlike use of B-blockers, ACE-I, lower age, lower TR gradient and higher LVEF.

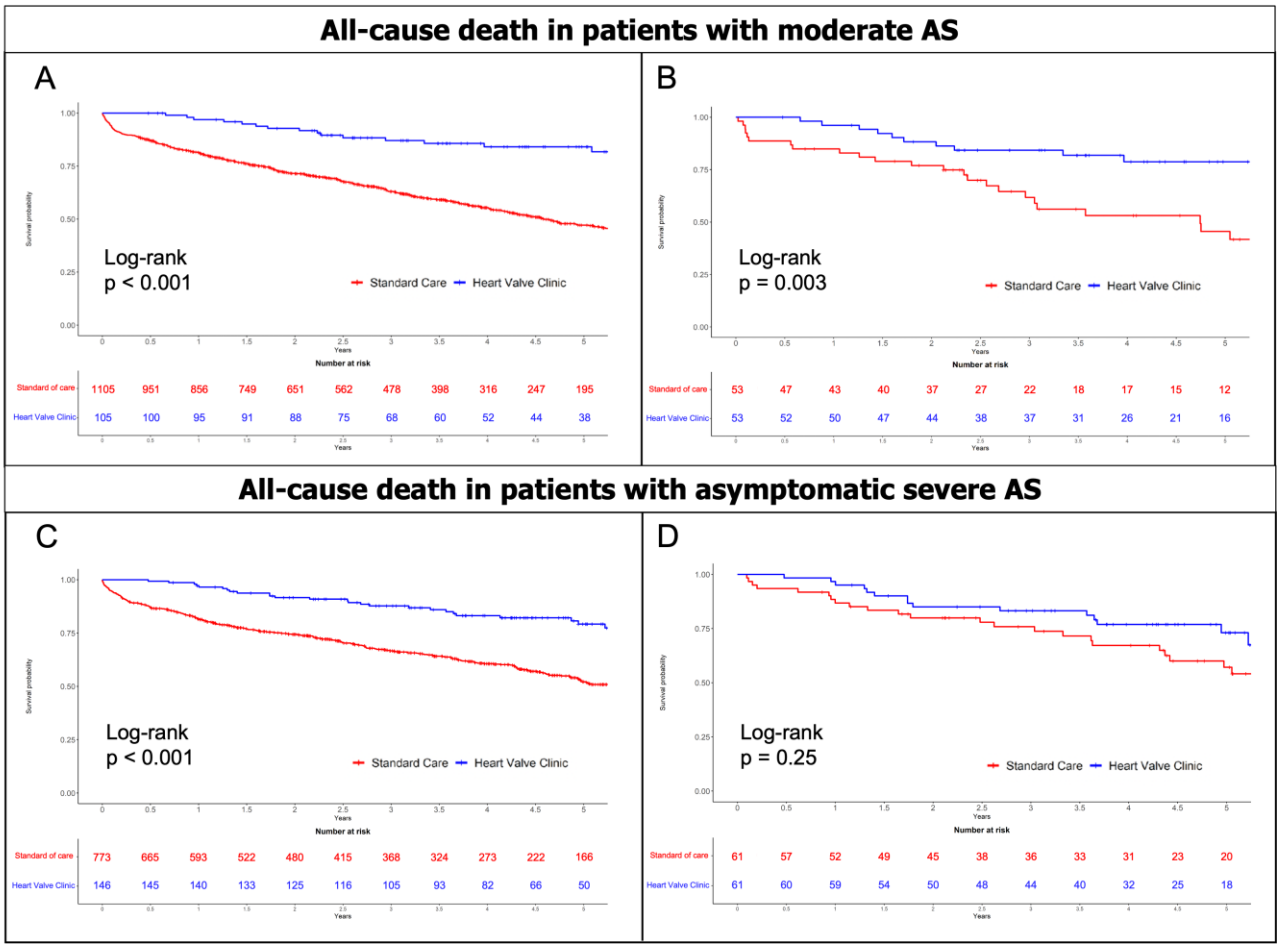

Figure 3. Kaplan-Meier survival curves for all-cause death in patients with moderate and asymptomatic severe aortic stenosis, separately. *Panel A*: all-cause death in patients with moderate aortic stenosis (AS) - unmatched population; *panel B*: all-cause death in patients with moderate AS - matched cohorts. *Panel C*: all-cause death in patients with asymptomatic severe AS - unmatched population; *panel D*: all-cause death in patients with asymptomatic severe AS - matched cohorts. *Blue curve*: Heart Valve Clinic (HVC)*; red line*: standard-of-care group (SOC).

Discussion

This is the first study investigating the outcome benefit of the HVC approach, compared to SOC, in patients with mAS and asAS. The main findings of our study include: i) lower rate of adjusted all-cause and cardiovascular death in HVC compared to SOC; ii) the HVC approach was an independent predictor of reduced all-cause death after adjusting for all confounding factors; iii) the same benefit was not observed for the composite endpoint (all-cause death and HF hospitalization); iv) the outcome benefit of HVC persisted in all groups of age; v) in the subgroup analysis, the HVC was associated with reduced all-cause death in patients with mAS but not in those with asAS.

Benefits of HVC for patients with clinically significant AS

Over the last years, a deeper understanding of pathophysiology of VHD, refinements in multimodality imaging and improvements in surgical techniques and technology have resulted in the development of HVCes (132). Several data have been published on the organization and requirements of HVC/HVCe (15,146-148). However, the outcome benefit of the HVC approach, compared to SOC, has never been investigated.

In the present study, we performed a direct comparison in the same institution between HVC and SOC for patients with mAS and asAS. This setting allowed a reduction of potential "environmental" biases (same hospital, healthcare providers, and period). Moreover, biases related to baseline patients' characteristics were reduced by PSM (149). Thus, for the first time, a benefit in outcome for HVC was demonstrated and confirmed for all age groups. These results could be explained by quantitative and qualitative differences in the health-care service provided in HVC versus SOC (**Figure 4**).

Quantitative benefits of HVC

In the present study, we observed a double number of consultations per year in HVC. Accordingly, HVC patients underwent a higher number (more than double) of exercise tests compared to SOC, allowing early identification of exercise-induced symptoms. Moreover, a higher number of CT scans

was requested in the HVC group, which provides further evidence of the closer follow-up and earlier detection of severe aortic valve calcification. The latter is one of the criteria considered to indicate AVR in asymptomatic patients with normal LVEF and exercise test (150-152). The same applies for BNP determinations, which were more frequent in HVC ($p<0.001$). Significant correlations were observed between number of visits and outcomes in HVC, but not in SOC. Although statistically significant, the correlation is not that "strong", suggesting an equal importance of qualitative aspects related to the HVC strategy.

Qualitative benefits of HVC

The strength of HVCs versus SOC does not lie in the merely higher number of consultations/medical services in the former, but in the delivery of high-quality medical care and patient education by a dedicated team of experts. Indeed, the greater amount of time-per-visit in HVC (40 versus 20 minutes) allows the involved cardiologist to thoroughly review the echocardiographic findings, complete the TTE examination with supplementary images and data measurements, if necessary, interpret them in the overall patient clinical context and, more importantly, to share and explain the information to each patient. This results in patients' education, a pivotal element of the HVC, which consists in: explaining the natural history of the disease, raising awareness on the signs and symptoms that could occur in follow-up, stressing the importance of prompt referral at their onset, providing means to inform the physician about changes in clinical status in the time between the scheduled consultations, and more generally the importance of controlling cardiovascular risk factors and adherence to medical indications/prescriptions. During consultations, the physician inquiries about the onset of AS-related symptoms and tries to determine their duration. The "educational strategy" leads to benefits for both the patient and the physician. Due to a deeper awareness of the disease, the patient feels more involved in the decision-making process and is more prone to follow the given medical indications/prescriptions. Closer medical contact allows better risk stratification, optimization of follow-up planning, and tailoring of comorbidities treatment, which could have prognostic

implications. Moreover, experience in VHD implies a deeper understanding of the echocardiographic exam, detection of details or unreported findings, which could be missed by other cardiologist specialists, allowing a "patient-tailored" follow-up planning.

Management of patients with clinically significant AS

The HVC approach might play a pivotal role in managing patients with mAS and asAS, optimizing the timing of indication to AVR (140,146). Indeed, symptoms could be recognized at an earlier and less severe stage before the occurrence of LV dysfunction (146). This evidence is further supported by the significantly lower survival of SOC patients with LVEF<50% and the shortened duration of symptoms before AVR in the HVC group (almost half-time than the SOC group, **Table 3**). Indeed, the severity of preoperative symptoms is a marker of increased operative risk, with worse survival rates for patients with severe symptoms (15,153). Patients managed in HVC underwent AVR in a less advanced stage, with less waiting time between indication to AVR. This is crucial considering a mortality risk on the waiting list for surgery of about 15% per year (154).

In the natural history of AS, HF occurrence adversely impacts prognosis. This is clearly shown in the competing risk analysis and supported by the similar rate of the composite endpoint, including HF hospitalization between the two groups. These results could be driven by the similar number of HF hospitalization and referral to AVR in patients with asAS included in both cohorts. Moreover, due to closer medical relationship with the referring physician, patients followed in HVC are more likely to undergo hospitalizations in case of clinical deterioration to optimize medical therapy and to reassess the progression and severity of AS. Therefore, comprehensive management would be beneficial, especially for patients with mAS, for whom the appropriate follow-up timing to prevent the onset of symptoms and HF occurrence might be challenging, compared to those with asAS, who are more directly referred to AVR. Accordingly, the outcome benefit of the HVC in the overall population is mainly driven by the outcome benefit of the sub-group of patients with mAS.

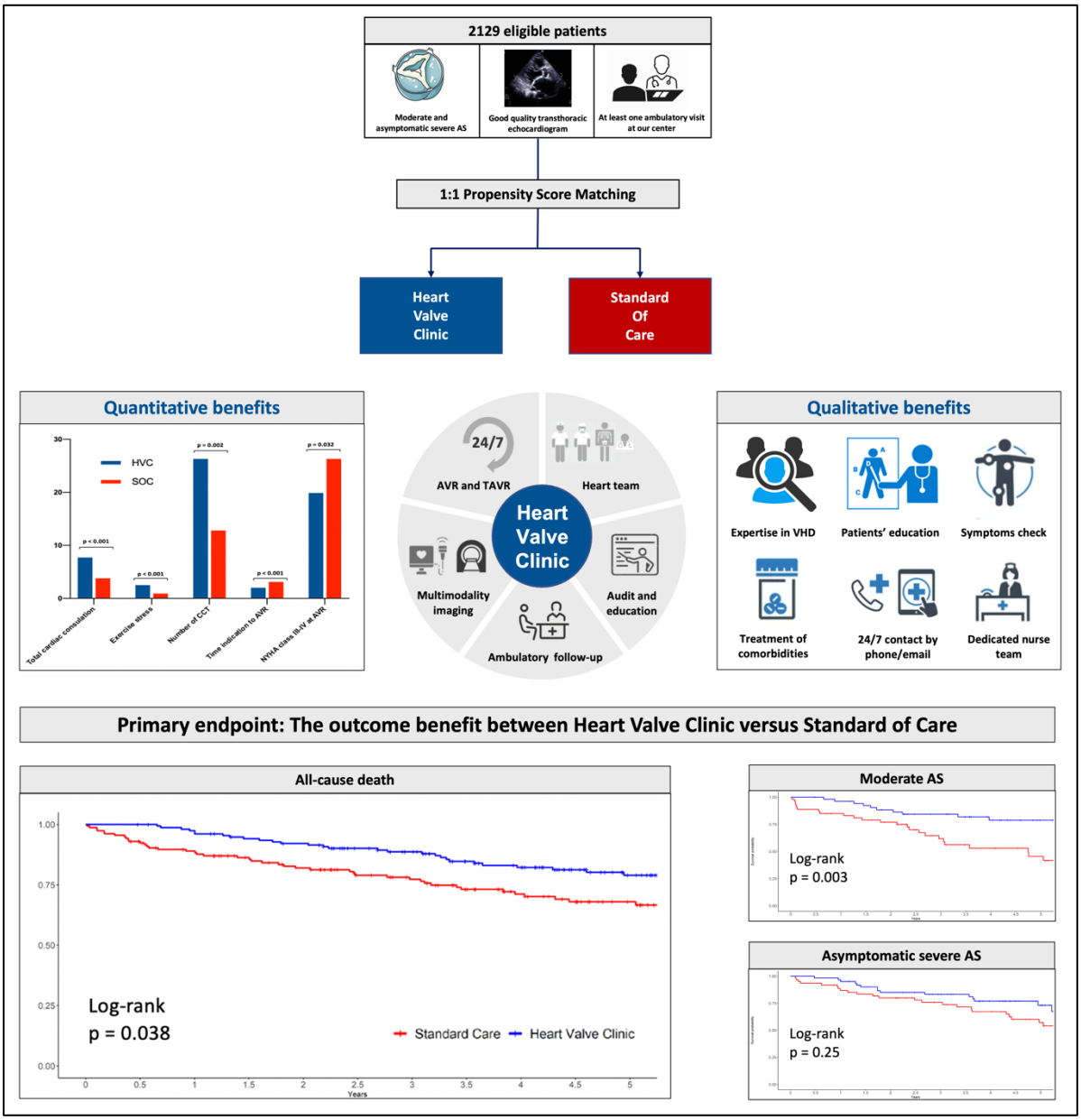

Figure 4. Summary of the main findings of the study. Abbreviations: HVC = Heart Valve Clinic; SOC = Standard-of-care group; AS = aortic stenosis; AVR = aortic valve replacement; TAVR = transcatheter aortic valve replacement.

PART IV

The role of coronary microvascular dysfunction in aortic stenosis.

CHAPTER 8

ABSOLUTE CORONARY FLOW AND MICROVASCULAR RESISTANCE RESERVE IN PATIENTS WITH SEVERE AORTIC STENOSIS: THE ABSOLUTE-AS STUDY

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Introduction

Severe AS is associated with variable impact on left ventricular remodeling and coronary flow regulation (18). Development of left ventricular hypertrophy (LVH) in patients with AS is an adaptive response aimed at increasing contractile forces and reducing wall stress in the left ventricle (LV) to eventually maintain a preserved stroke volume for many years despite an elevated LV afterload (19). In this setting, a series of unfavorable hemodynamic changes, including high LV cavity pressure, low coronary perfusion pressure and increased extravascular compressive forces lead to a flow shifts from the endocardium to the epicardium, resulting in subendocardial ischemia, despite the absence of significant obstructive coronary artery disease (20). In addition, the progression of LVH increases myocardial oxygen demand, resulting in a supply-demand mismatch, which requires an increase of the resting coronary flow due to the vasodilation of intramyocardial arterioles induced by the autoregulation phenomenon (20). On the clinical ground, as a result of the LV oxygen supply-demand mismatch, exercise/tachycardia-induced myocardial ischemia, and exertional angina might occur in patients with severe AS. However, the interplay among coronary flow, microvascular regulation, severity of AS, left ventricle hypertrophy, and hemodynamic overload remains complex, multifactorial, and poorly understood.

Invasive assessment of coronary microcirculation has been performed traditionally with bolus thermodilution and intracoronary Doppler (155,156). However, none of these methods provide a direct volumetric quantification of absolute coronary blood flow and resistance. Furthermore, both techniques present some limitations: Doppler tracings are sub-optimal in up to 30% of patients (157), whereas bolus thermodilution is associated with large variability both patient and operator-dependent (158). Intracoronary continuous thermodilution of saline is a novel invasive tool for the direct volumetric quantification of absolute coronary flow and microvascular resistance both at rest and during hyperemia (159-162). This methodology allows not only to calculate coronary flow reserve (CFR), but also the microvascular resistance reserve (MRR), which is a novel index specific for microcirculation, independent from the myocardial mass (163).

In the present study, we used for the first time intracoronary continuous thermodilution of saline to directly quantify absolute coronary flow and resistance, both at rest and during hyperemia, CFR and MRR, in order to assess in-vivo the pathophysiological mechanisms underlying the adaptive coronary flow regulation in patients with AS, comparing these hemodynamic findings with a propensity-score matched contemporary cohort of patients without AS.

Methods

In this observational prospective study, consecutive patients undergoing elective coronary angiography and right heart catheterization for symptomatic aortic stenosis (AS) from June to November 2021 were considered eligible. Inclusion criteria were: 1) presence of severe aortic stenosis in accordance with current ESC Guidelines (98); 2) absence of significant epicardial stenosis in the left anterior descending artery (LAD) (defined as diameter stenosis [DS] > 50% by visual estimation); 3) the assessment of both resting and hyperemic absolute flow and resistance in the LAD; 4) cardiac-CT (CCT) performed for TAVI procedural planning. Patients with previous myocardial infarction (MI) or coronary artery bypass graft (CABG) in the LAD territory, left ventricular ejection fraction < 50%, left bundle branch block, right ventricle pacing, acute coronary syndromes, or presence of a previous aortic-valve replacement (AVR) were excluded. A contemporary control group matched for age, gender, diabetes mellitus and functional severity of epicardial coronary lesions, without severe aortic stenosis, undergoing CCT and elective coronary angiography for suspected coronary artery disease with subsequent invasive functional assessment of microvascular function by intracoronary continuous thermodilution, was selected (164) (**Figure 1**). Aortic stenosis was defined according to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease (98).

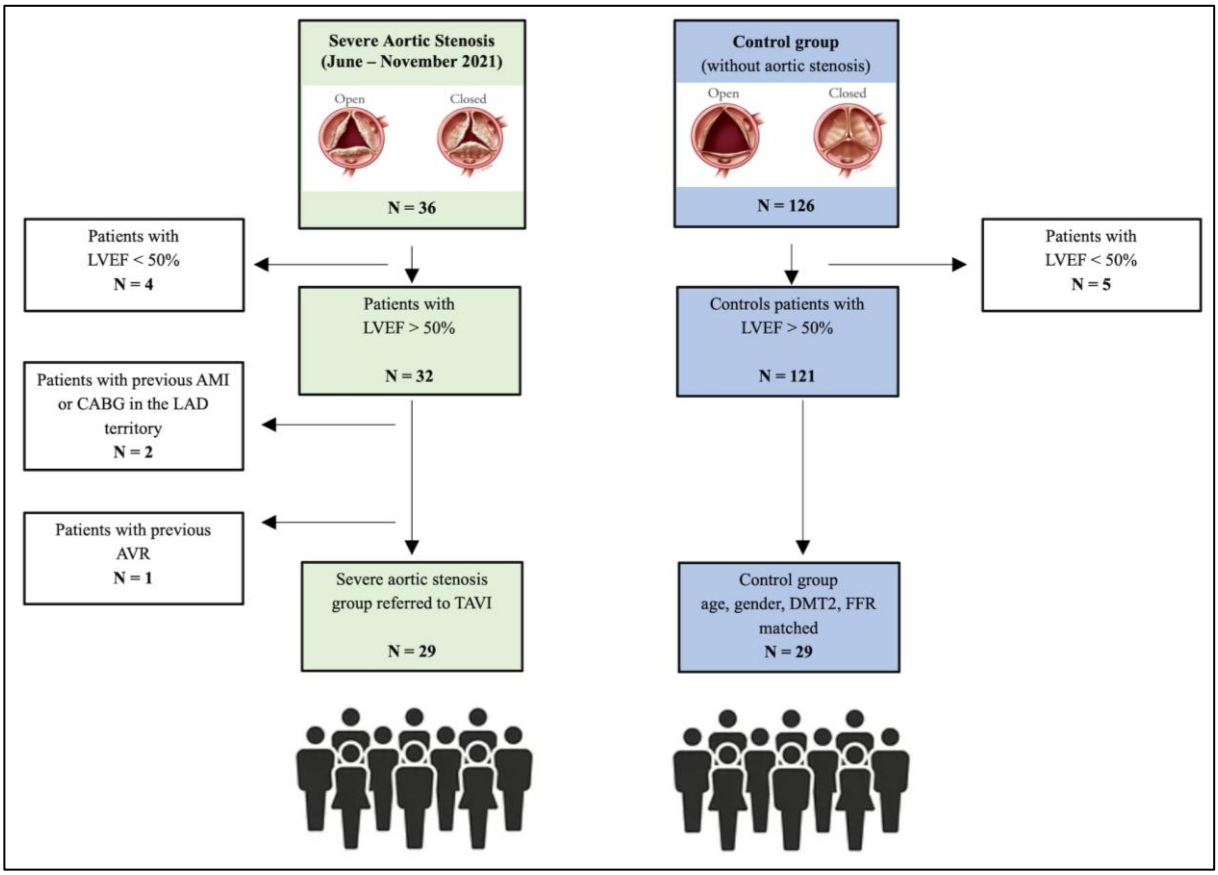

Figure 1. Study Flow chart.

Abbreviations: LVEF = left ventricular ejection fraction; AMI = acute myocardial infarction; CABG: coronary artery bypass graft surgery; LAD = left anterior descending artery; AVR = aortic valve replacement; TAVI = transcatheter aortic valve implantation; DMT2 = type 2 diabetes mellitus; FFR = fractional flow reserve.

Microcirculation assessment with intracoronary continuous thermodilution

Microvascular function was assessed with continuous intracoronary thermodilution of saline at room temperature in the LAD. Absolute coronary flow (Q, mL/min) as derived from continuous thermodilution was calculated by the previously validated equation (165):

$$Q = 1.08 \cdot \frac{T_i}{T} \cdot Q_i$$

Resting absolute coronary (Q_{rest}) flow was measured with saline infusion at 10 mL/min, whilst hyperemic flow (Q_{hyp}) was measured with saline infusion at 20 mL/min (162). An example of thermodilution tracings is given in **Figure 2, panel C and D**. Absolute resistance at rest ($R_{\mu\text{-rest}}$) and

during hyperemia ($R_{\mu\text{-}hyp}$) – in Woods Units (WU) – were calculated as the ratio between the distal coronary pressure during each infusion (P_d) and Q_{rest} or $Q_{hyp,}$ respectively. Myocardial perfusion (in mL/min/g of tissue) at rest and during hyperemia ($Q_{N\text{-}rest}$ and $Q_{N\text{-}Hyp}$, respectively) were calculated as the ratio between the absolute coronary flow in the LAD and the specific myocardial mass subtended to the LAD itself. Fractional Flow Reserve (FFR) was calculated as the ratio between distal coronary pressure and central aortic pressure (P_d and $P_{a,}$ respectively) during saline-induced hyperemia; Coronary Flow Reserve (CFR) was defined as the ratio between absolute hyperemic flow (Q_{hyp}) and absolute resting flow (Q_{rest})(166). Microvascular Resistance Reserve (MRR) was calculated with the previously validated formula (167):

$$MRR = \frac{CFR}{FFR} \cdot \frac{P_{a-rest}}{P_{a-hyp}}$$

Cardiac computed tomography and myocardial mass quantification

CCT were performed with a dual-source CT scanner (Somatotom Force 2 x 192-slice, Siemens, Germany) according to the protocol recommended by the Society of Cardiovascular Computed Tomography (67). Vessel-specific myocardial mass was quantified by the CCT images using the Voronoi's algorithm with a dedicated software (Synapse 3D, Fujifilm Healthcare Solutions, Holdings America Corporation) (168). A voxel in the LV myocardium was linked to the nearest voxel on the adjacent coronary artery. Subsequently the algorithm automatically calculates the territory by aggregating all myocardial voxels associated to the voxels of the coronary artery that are distal to the target point. The values of the total LV myocardial mass, the vessel-specific myocardial mass and the percentage of LAD mass on the total LV mass were exported. An example of this is given in **Figure 2, panel A**.

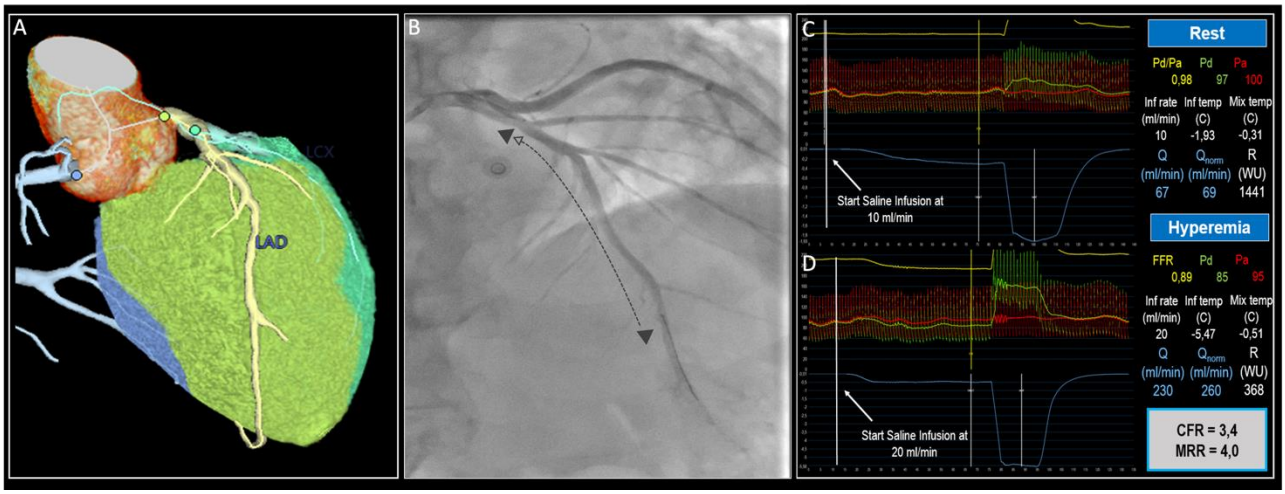

Figure 2. *Panel A.* Left-ventricular myocardial mass quantified by CCTA. *Panel B.* Coronary angiography - LAD. The heads of arrows indicate the position of the tip of the RayFlow™ catheter (the proximal one) and of the PressureWire (the distal one). The dashed arrow indicates the length of the pullback, a step needed for the measurement of absolute coronary flow by continuous thermodilution. *Panel C-D.* Example of thermodilution tracings of absolute coronary flow during the infusion of 10 mL/min (resting phase – *panel c)* and of 20 mL/min (hyperemic phase - *panel d*) in the LAD. During the infusion of saline at 10 mL/min through the RayFlow™ catheter located in the proximal LAD, no changes in Pd / Pa were observed. Resting flow was 67 mL/min and resting resistances were 1441 WU (*panel c*). Conversely, the infusion of saline at 20 mL/min was paralleled by a decrease in Pd and in Pd/Pa. Hyperemic flow was 230 mL/min and hyperemic resistance 368 WU (*panel d*).

Abbreviations: Q (ml/min) = Absolute Flow; Q norm = Normalized Absolute Flow (Q/FFR); R (mmHg) = Absolute Microvascular Resistance; CFR = Coronary Flow Reserve; MRR = Microvascular resistance Reserve.

Results

The final study population consisted of 58 patients, 29 patients with severe AS and 29 matched controls, selected from an initial cohort of 126 patients **(Figure 1)**. In the AS cohort, 2 patients were excluded because of a history of previous MI or CABG in the LAD territory and 4 because of a LVEF < 50%. One more patient was excluded because of previous aortic-valve replacement (AVR). AS patients were significantly older compared to the controls ($p < 0.001$). Cardiovascular risk factors and comorbidities were similarly distributed between the 2 study groups. Medical therapy at the admission was similar in both groups. Baseline and clinical characteristics are shown in **Table 1**.

Echocardiographic and CCT characteristics

LV volume and ejection fraction were similar between the 2 groups. In the AS cohort, the mean trans-aortic pressure gradient was 54 ± 16 mmHg with a mean peak aortic jet velocity of 4.6 ± 0.7 cm/sec and mean aortic valve area (AVA) of 0.64 ± 0.2 cm^2. Patients with AS presented thicker interventricular septum and grater relative wall thickness (RWT), showing positive remodeling of LV ($p < 0.001$ for both). In addition, these patients had also significantly greater left atrial volume index (LAVi) and prevalence of diastolic dysfunction (DDF), compared to control group ($p = 0.002$ and $p = 0.013$, respectively). Interestingly, analyzing baseline myocardial mechano-energetic parameters, patients with AS had a significantly lower global longitudinal strain (GLS) and higher global work efficacy (GWI) ($p < 0.05$ for both). The global work index (GWI) was higher, albeit not significantly different. Total LV myocardial mass and LAD-specific myocardial mass were significantly higher in patients with AS ($p = 0.001$ for both, **Table 2**).

Table 1. Clinical characteristics

	Total (N = 58)	Aortic Stenosis (N = 29)	Controls (N = 29)	P value
Age, years	80.6 ± 5.4	83.6 ± 4.4	78 ± 4.5	<0.001
Male Sex, n (%)	25 (43.1)	10 (34.5)	15 (51.7)	0.185
BMI, kg/m^2	27.2 ± 4.7	26.9 ± 6	27.6 ± 2.9	0.163
BSA, m^2	1.80 ± 0.18	1.77 ± 0.21	1.84 ± 0.14	0.261
Smoking, n (%)	8 (13.8)	2 (6.9)	6 (20.7)	0.219
Hypertension, n (%)	46 (79.3)	26 (89.7)	20 (69)	0.109
Diabetes Mellitus, n (%)	13 (22.4)	7 (24.1)	6 (20.7)	0.999
Dyslipidemia, n (%)	45 (77.6)	25 (86.2)	20 (69)	0.227
CKD, n (%)	16 (27.6)	11 (37.9)	5 (17.2)	0.070
CAD History, n (%)	16 (27.6)	10 (34.5)	6 (20.7)	0.454
Previous PCI, n (%)	11 (19)	7 (24.1)	4 (13.8)	0.549
AF, n (%)	4 (6.9)	1 (3.4)	3 (10.3)	0.125
Dyspnea, n (%)	32 (55.2)	24 (82.8)	8 (27.6)	<0.001
Angina, n (%)	24 (41.4)	2 (6.9)	22 (75.9)	<0.001
Syncope, n (%)	3 (5.2)	3 (10.3)	0 (0)	0.070
GFR	68.9 ± 18.1	63.4 ± 21.3	73 ± 16.1	0.151
ACEI/ARB, n (%)	26 (44.8)	12 (41.4)	14 (48.3)	0.791
CCB, n (%)	17 (29.3)	9 (31.0)	8 (27.6)	0.999
Statins, n (%)	41 (70.7)	23 (79.3)	18 (62.1)	0.302
BB, n (%)	28 (48.3)	18 (62.1)	10 (34.5)	0.058
Aldosterone blockers, n (%)	9 (15.5)	7 (24.1)	2 (6.9)	0.180
Diuretics, n (%)	19 (32.8)	15 (51.7)	4 (13.8)	0.003

Continuous variables are presented as mean±SD, while categorical variables as number (%). Abbreviations: BMI = Body Mass Index; BSA = Body Surface Area; CKD = Chronic kidney disease; CAD = Coronary Artery Disease; PCI = Percutaneous Coronary Intervention; AF = atrial fibrillation; ACEI= Angiotensin-converting enzyme; ARB = Angiotensin II Receptor Blockers; CCB = Calcium Channel Blockers; BB = B-blockers; GFR = Glomerular Filtration Rate.

Table 2. Total and LAD-specific myocardial mass assessed by CCTA and echo in patients with and without aortic stenosis**.**

	Total (N = 58)	Aortic Stenosis (N = 29)	Controls (N = 29)	P value
LV Mass (g)	195 ± 43	212.5 ± 44.8	177.8 ± 33.4	0.005
LV Mass index (g/m^2)	109 ± 24.5	121 ± 25.7	96.8 ± 16	< 0.001
LAD Mass (g)	90.5 ± 37.6	107 ± 46	74.4 ± 16.2	0.002
LAD Mass Index (g/m^2)	50.4 ± 20.7	60.3 ± 24.5	40.6 ± 8.4	0.001
(%) LAD/Total Mass	45.7 ± 11.7	49.5 ± 15	41.9 ± 5.2	0.039

Continuous variables are presented as mean±SD. Abbreviations: LV = left ventricle; LAD = left anterior descending artery.

Hemodynamics

Angiographic and hemodynamic characteristics of our study population are summarized in **Table 3**. The %DS among the two groups were similar (26 ± 10 % in the AS group vs 26 ± 15 % in the control group). The median FFR value was 0.81 ± 0.07 without any significant difference between the two groups. In the AS cohort, absolute resting flow was significantly higher (p = 0.009), while absolute resisting resistances was numerically, but not significantly lower (p = 0.082) as compared to controls (**Figure 3**). Absolute hyperemic flow and resistances in the LAD were similar between the 2 study cohorts (**Table 3**). Consistently, both CFR and MRR were significantly lower in the AS cohort compared to controls (p = 0.005 and p = 0.001, respectively) (**Figure 3**). Of note, hyperemic myocardial perfusion was significantly lower in the AS group, despite similar resting perfusion between the two cohorts (**Table 3 and Figure 4, panel B**). A multiple linear regression analysis was

used to estimate the association of AS with CFR, MRR, and myocardial perfusion (both at rest and during hyperemia), accounting for potential confounders (i.e., age, gender, and chronic kidney disease). Aortic stenosis turned out to be an independent predictor of CFR, MRR, and hyperemic myocardial perfusion (**Table 4**). In addition, hyperemic perfusion is modulated by both AVAi and LVMI, whereas resting myocardial perfusion is not (**Figure 5**). Similarly, CFR and MRR are influenced not only by the LVMi but also by the AVAi, an effect that might be related to the impact of the stenotic valve on the cardiac output. Thus, with the progression of myocardial hypertrophy, the compensatory mechanism of increased resting flow maintains an adequate perfusion at rest, but not during hyperemia (**Figure 4, panel B**).

Table 3. Angiographic and hemodynamic characteristics.

	Total (N = 58)	**Aortic Stenosis (N = 29)**	**Controls (N = 29)**	**P value**
DS (%)	26 ± 12	26 ± 10	26 ± 15	0.978
Rest Pd/Pa	0.91 [0.88 - 0.93]	0.91 [0.87 - 0.93]	0.92 [0.88 - 0.93]	0.642
Q_{rest} (mL/min)	71 [56 – 93]	86 [65 – 107]	67 [52 – 75]	0.009
$R_{\mu\text{-}rest}$ (WU)	1235 [943 – 1380]	1067 [720 – 1334]	1282 [1133 – 1381]	0.082
FFR	0.81 ± 0.07	0.81 ± 0.06	0.81 ± 0.08	0.991
Q_{hyp} (mL/min)	190 [142 – 224]	200 [144 – 225]	186 [13 – 226]	0.787
$R_{\mu\text{-}hyp}$ (WU)	398 [345 – 505]	405 [332 – 534]	395 [354 – 500]	0.524
CFR	2.60 ± 0.77	2.30 ± 0.69	2.9 ± 0.73	0.005
MRR	3.1 ± 0.91	2.73 ± 0.74	3.55 ± 0.90	0.001
Resting perfusion (Q_{rest} N, mL/min/gr)	0.78 [0.68 - 1.14]	0.78 [0.66 - 1.10]	0.78 [0.71 - 1.1]	0.611
Hyperemic perfusion (Q_{hyp} N, mL/min/gr)	2.2 [1.6 – 2.7]	1.87 [1.4 – 2.5]	2.3 [1.9 – 3.2]	0.035

Continuous variables are presented as mean±SD or median [IQR]. Abbreviations: DS = Diameter Stenosis; FFR = Fractional Flow Reserve; Q_{rest} = Resting Flow; $R_{\mu\text{-}rest}$ = Absolute Microvascular Resistance at Rest; Q_{hyp} = Hyperemic Flow; $R_{\mu\text{-}hyp}$ = Absolute Microvascular Resistance; CFR = Coronary Flow Reserve; MRR = Microvascular resistance Reserve; Q_{rest}N = Normalized Resting Flow (Q_{rest}/LAD Mass); Q_{hyp}N = Normalized Hyperemic Flow.

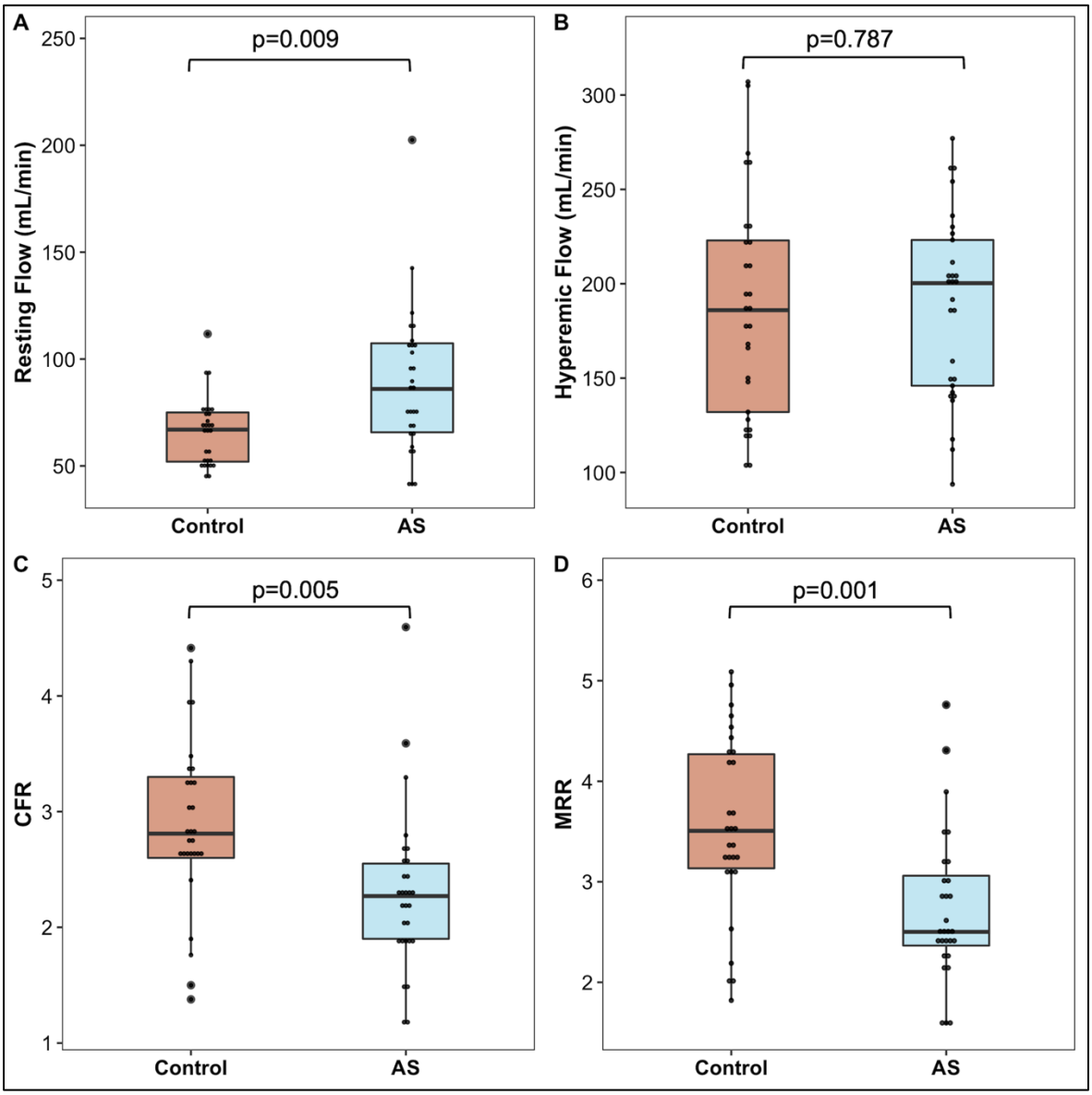

Figure 3. *Panel A and B*: comparison of the resting (rest Q) and hyperemic flow (hyp Q) in patients with and without aortic stenosis; in the AS cohort, absolute resting flow was significantly higher (p = 0.009) as compared to controls, while absolute hyperemic flow was similar between the 2 study cohorts. *Panel C and D* - comparison of CFR and MRR in patients with and without aortic stenosis; both CFR and MRR were significantly lower in the AS cohort compared to controls (p = 0.005 and p = 0.001, respectively). Differences between groups were analyzed using the paired Wilcoxon test for continuous variables. Abbreviations: Rest Q = resting flow; Hyp Q = hyperemic flow; CFR = Coronary Flow Reserve; MRR = Microvascular resistance Reserve.

Table 4. Multiple linear regression analysis to test the association between CFR, MRR and myocardial perfusion (both at rest and during hyperemia) and potential confounders between groups after the matching.

	Std Error	Beta	T value	P value	95%CI
CFR					
Severe Aortic stenosis	0.233	-0.432	-2.825	**0.007**	-1.128 – -10.191
Gender	0.195	-0.087	-0.685	0.496	-0.527 – 0.257
Age	0.022	0.151	0.994	0.325	-0.022 – 0.065
Chronic Kidney Disease	0.219	-0.132	-1.032	0.307	-0.665 – 0.213
MRR					
Severe Aortic stenosis	0.257	-0.432	-3.037	**0.004**	-1.298 – -0.266
Gender	0.215	-0.291	-2.474	0.067	-1.298 – 0.266
Age	0.024	0.110	0.781	0.438	-0.029 – 0.067
Chronic Kidney Disease	0.241	-0.130	-1.090	0.280	-0.747 – 0.221
Resting myocardial perfusion					
Severe Aortic stenosis	0.120	-0.070	-0.420	0.676	-0.291 – 0.190
Gender	0.100	-0.032	-0.232	0.818	-0.224 – 0.178
Age	0.011	0.146	0.872	0.387	-0.013 – 0.032
Chronic Kidney Disease	0.113	-0.106	-0.754	0.454	-0.311 – 0.141
Hyperemic myocardial perfusion					
Severe Aortic stenosis	0.288	-0.379	-2.452	**0.018**	-1.282 – -0.128
Gender	0.240	-0.131	-1.028	0.309	-0.729 – 0.235
Age	0.027	0.224	1.455	0.152	-0.015 – 0.093
Chronic Kidney Disease	0.270	-0.180	-1.387	0.171	-0.916 – 0.167

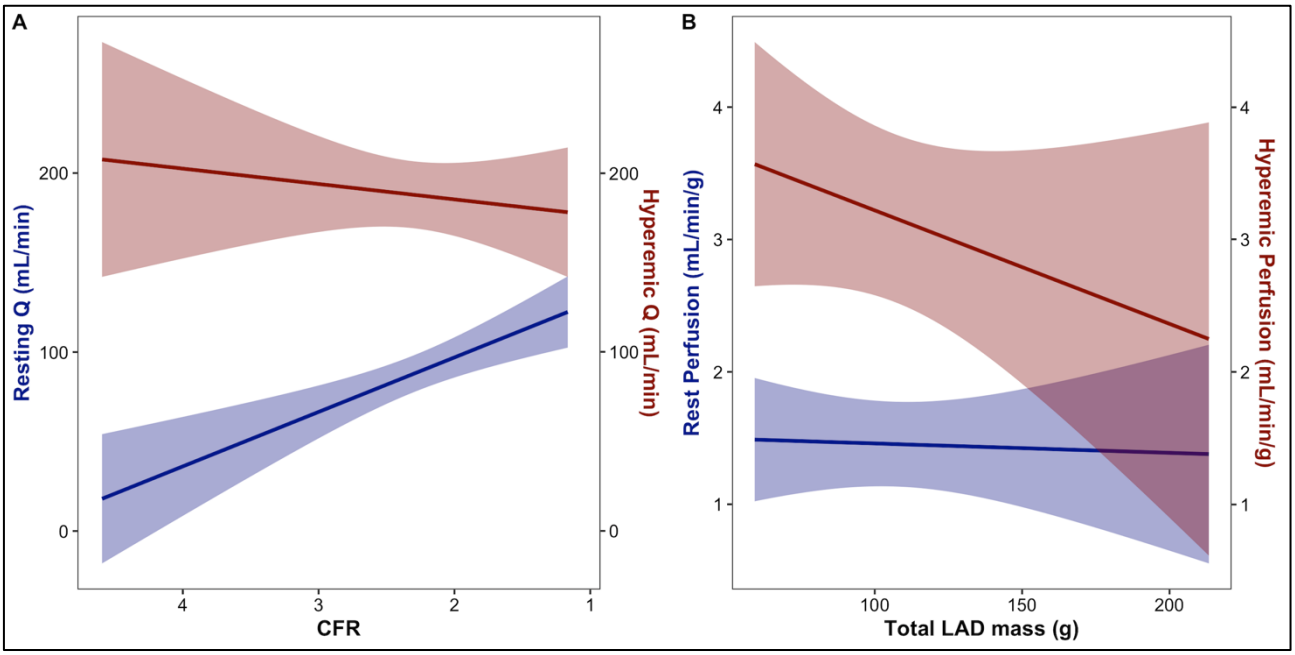

Figure 4. *Panel A.* Absolute flow variation in function of CFR in patients with AS. The hyperemic flow, represented by the red line, remains relatively constant despite the reduction in CFR whereas the resting flow (blue line) tends to increase as the CFR tends to lower values. Therefore, in patients with AS, the reduction in CFR is mainly the consequence of an increased resting flow. *Panel B.* Myocardial resting (blue line) and hyperemic (red line) perfusion expressed in flow per gram of tissue in the LAD. With the progression of LVH, the compensatory mechanism of increased resting flow maintains an adequate perfusion at rest, but not during hyperemia.

Abbreviations: CFR = Coronary Flow Reserve; LAD = left anterior descending artery; LVH = left ventricle hypertrophy.

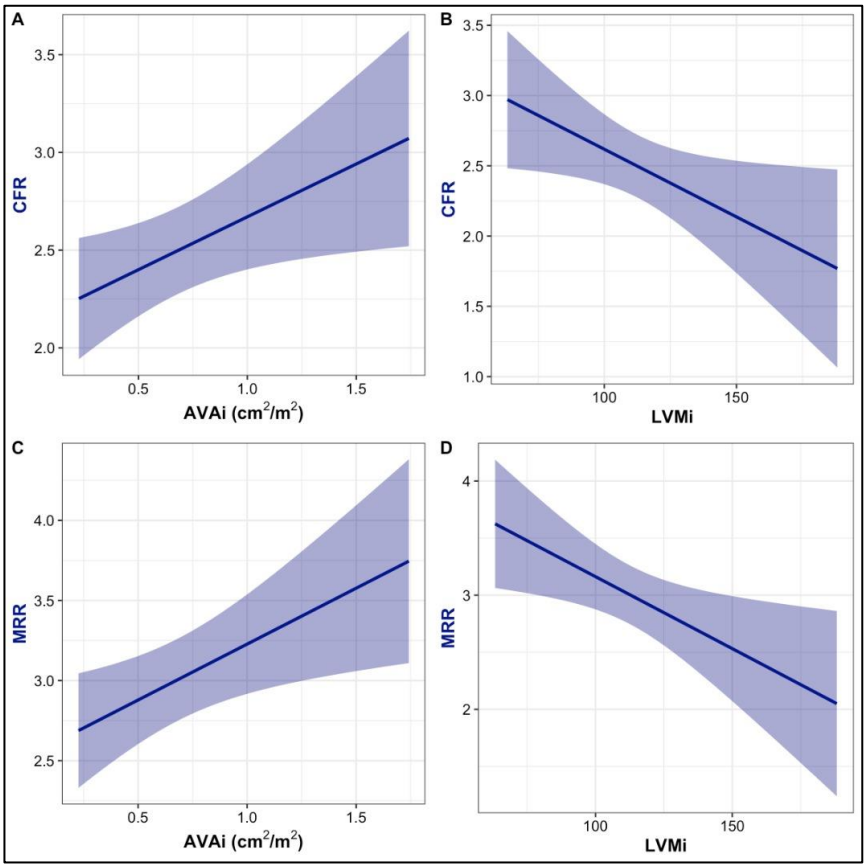

Figure 5. Impact of LVMi and AVAi on coronary circulation. *Panel A* and *B*. Correlation between CFR, AVAi, and LVMi. *Panel C* and *D*. Correlation between MRR, AVAi, and LVMi. *Panel E*. Correlation between LVMi and AVAi. Hyperemic perfusion is modulated by both AVAi and LVMI, whereas resting myocardial perfusion is not. Similarly, CFR and MRR are influenced not only by the LVMi but also by the AVAi, an effect that might be related to the impact of the stenotic valve on the cardiac output. Moreover, AVAi and LVMi are inversely correlated each other meaning that there is a complex pathophysiological interconnection between AS, LV remodeling and flow dysregulation.

Abbreviations: LVMi = left ventricle mass indexed; AVAi = aortic valve area indexed; CFR = Coronary Flow Reserve; MRR = microvascular resistance reserve.

Discussion

The present study is the first to evaluate absolute coronary flow, microvascular resistance, and myocardial perfusion at rest and during hyperemia in patients with severe degenerative AS.

Main findings of our study are: 1) compared to matched controls, absolute resting flow in the LAD was significantly higher while resting resistances numerically lower in the AS cohort, without any differences in absolute hyperemic flow and resistances; 2) hyperemic perfusion (mL/min/g of tissue subtended to LAD) - but not resting - was significantly lower in the AS group; 3) patients with severe AS had a lower CFR and MRR as compared to matched controls; 4) patients with AS had a significantly positive LV remodeling with lower global longitudinal strain and global work efficacy, compared to the controls.

Compared to the previously published data, we used intracoronary continuous thermodilution of saline to directly quantify absolute coronary flow and resistance, both at rest and during hyperemia, in order to assess in-vivo the pathophysiological mechanisms underlying the adaptive coronary flow regulation in patients with AS (169). In addition, for the first time, the MRR was assessed in AS patients and compared to a control group of patients without severe AS. Moreover, the assessment of myocardial perfusion was performed, by considering the relative CT-derived myocardial mass subtended by the LAD, thus providing high-quality data with the highest spatial resolution for the measurement of myocardial perfusion.

A proper understanding of the microcirculation in AS could improve clinical care by predicting left ventricular remodeling and the interplay between coronary flow and myocardial mass.

Coronary flow autoregulation in aortic stenosis

In our study we showed that the resting absolute flow - but not the hyperemic - is significantly increased in patients with AS, explaining the significant reduction of both CFR and MRR in this population.

The rising in intraventricular pressures induced by the AS leads to LV hypertrophy to lower wall stress with the disadvantage to further increase myocardial oxygen demand. In addition, the coronary flow shifts from endocardium to epicardium, as a consequence of both the increased intracavitary-pressure and the reduced coronary perfusion pressure. To balance these hemodynamic changes, coronary flow autoregulation induces vasodilation and minimize coronary microvascular resistance in order to maintain a constant resting perfusion (170). These phenomena result in a reduced coronary flow reserve (CFR) and microvascular resistance reserve (MRR) leading to subendocardial ischemia, apoptosis and fibrosis. Since the hyperemic flow cannot further increase, the progressive reduction in CFR appears to be related to a proportional increase in resting coronary flow (**Figure 4, panel A**). Myocardial perfusion (assessed as blood flow per g of tissue subtended to the LAD - Q_N expressed in ml/min/g) during hyperemia was significantly lower in patients with AS (**Table 3, Figure 4 panel B**). Thus, with the progression of myocardial hypertrophy, the compensatory mechanism of increased resting flow maintains an adequate perfusion at rest, but not during hyperemia. This reduced hyperemic capacity might also be related to capillary density rarefaction, as already demonstrated in animal models (171).

Clinical implications on functional evaluation of CAD

The functional evaluation of epicardial coronary stenosis in patients with severe AS remains challenging due to the hemodynamic changes occurring in these patients (172-174). Yet, the reliability of functional indexes and the best timing for their assessment (whether pre-TAVI or post-TAVI) is still controversial. Scarsini et al. evaluated in 23 patients with AS and coronary artery disease FFR and iFR before and after TAVI procedure and at follow-up and they found no significant changes in both resting and hyperemic indices (173,175). Conversely, Ahmad et al, evaluated iFR and FFR in 30 patients before and after TAVI showing that FFR, but not iFR significantly decreased after TAVI (174). Our findings raise significant concern over the reliability of invasive functional assessment of CAD in patients with significant AS, at least in the absence of a thorough investigation

of the coronary microvascular status. At rest, coronary autoregulation maintains myocardial perfusion relatively constant at the cost of increased flow, questioning whether resting indexes are truly measured in resting conditions, as they might be polluted already by some degree of microvascular dilatation (176). Likewise, hyperemic perfusion decreases significantly with LVH, questioning whether hyperemic indexes might by subject to significant changes after surgical or percutaneous aortic valve replacement, with pressure afterload relief and consequent LV remodeling.

The availability of tools informing the physician about the status of the microcirculation might significantly impact the overall management of these patients. For example, the knowledge of a preserved microvascular function leaves the door open to the functional assessment of the epicardial coronary disease that could therefore indicate possible need to coronary revascularization. In addition, in the presence of impaired microvascular function, CFR and MRR might inform on the severity of the microvascular disease and serve as reliable prognostic marker possibly predicting the clinical outcome of these patients after TAVR. In summary, our findings might represent a real paradigm shift in the functional assessment of the coronary circulation as we've known till today; Microcirculation should come first, and only if preserved could then allow further investigation of the functional impact of epicardial disease.

Conclusions

In patients with severe aortic stenosis and non-obstructive coronary artery disease, with the progression of LVH, the compensatory mechanism of increased resting flow maintains an adequate perfusion at rest, but not during hyperemia. As consequence, both CFR and MRR are significantly impaired.

CHAPTER 9

ABSOLUTE CORONARY FLOW AND MICROVASCULAR RESISTANCE BEFORE AND AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION: THE ABSOLUTE-TAVI STUDY

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Introduction

Severe aortic stenosis (AS) is associated with left ventricular (LV) remodeling and adaptive mechanisms in coronary flow regulation. Transcatheter aortic valve implantation (TAVI) has changed significantly the natural history of AS; however, the impact of this treatment on coronary flow and microvascular resistance remains unclear.

The aim of the present study is to explore the physiological changes in the microcirculatory function by using continuous intracoronary thermodilution to assess both resting and hyperemic absolute coronary flow and microvascular resistance, performed at 3 different times: i) before TAVI, ii) immediately after TAVI; iii) at 6 months follow-up.

Methods

Consecutive patients with AS undergoing TAVI procedure were included if they had no obstructive coronary disease (DS>50%) in the left anterior descending artery (LAD). Absolute coronary flow and microvascular resistance were measured in the LAD by continuous intracoronary thermodilution at rest (Q_{rest} and $R_{\mu\text{-}rest}$) and during hyperemia (Q_{hyp} and $R_{\mu\text{-}hyp}$) before, after TAVI and at 6 months follow up. Total myocardial mass and LAD-specific mass were quantified by echocardiography and cardiac-CT. Regional myocardial perfusion (Q_N) was calculated by dividing absolute flow for the subtended myocardial mass.

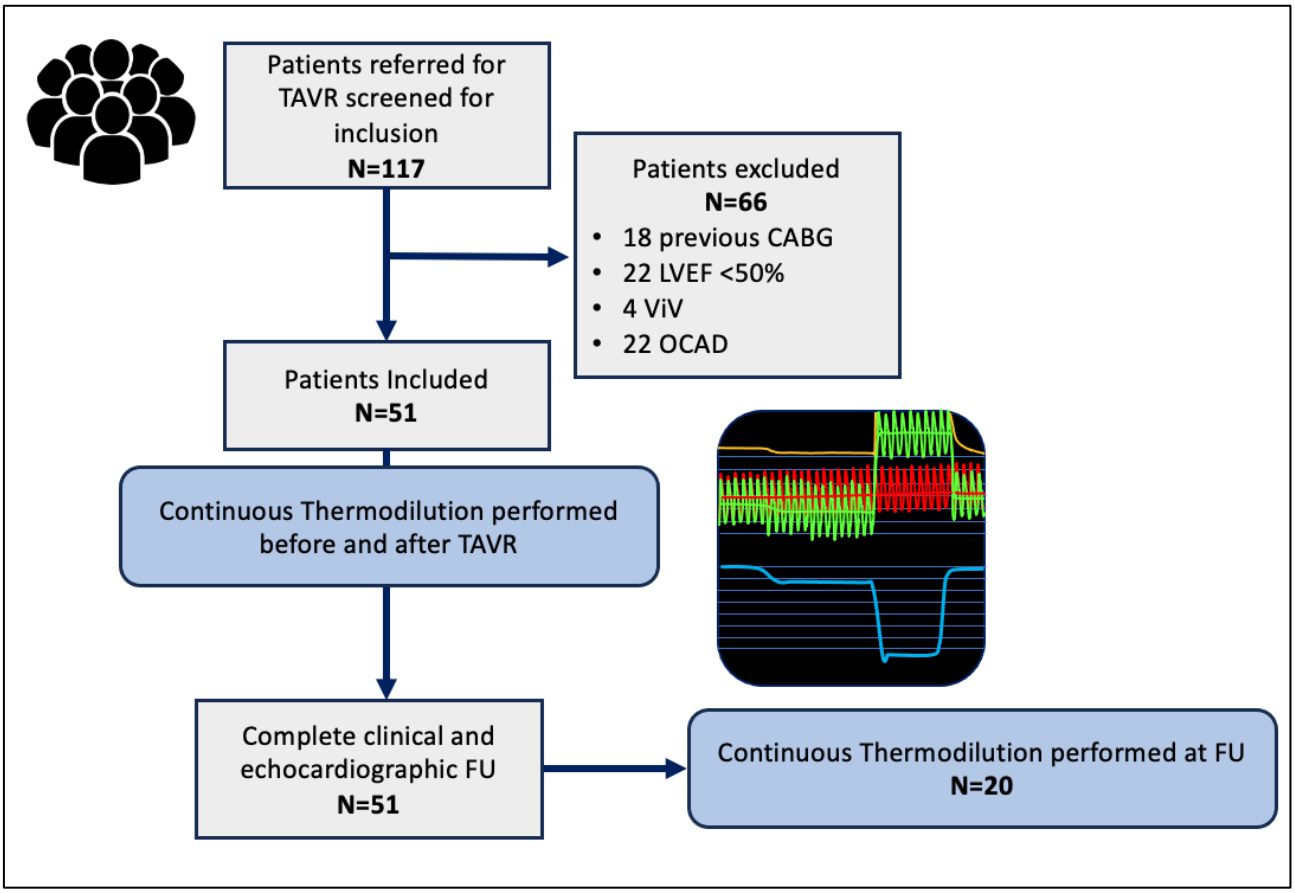

Figure 1: Study flow chart. Abbreviations: TAVR: transcatheter aortic valve replacement; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; VIV: valve-in-valve procedure; OCAD: obstructive coronary artery disease; FU: follow-up.

Results

In 51 patients absolute flow and microvascular resistance were measured at rest and during hyperemia before and after TAVI (**Figure 1**). Mean age was 83.7 years and 68% of patients were female. In 20 (39%) patients, measurements were also obtained 6 months after TAVI. There were no changes in flow and resistance both at rest and during hyperemia before and after TAVI. At follow-up a significant remodeling of the left ventricle was accompanied by an increase in coronary flow reserve (CFR) and microvascular resistance reserve (MRR) as well as an increase in hyperemic perfusion.

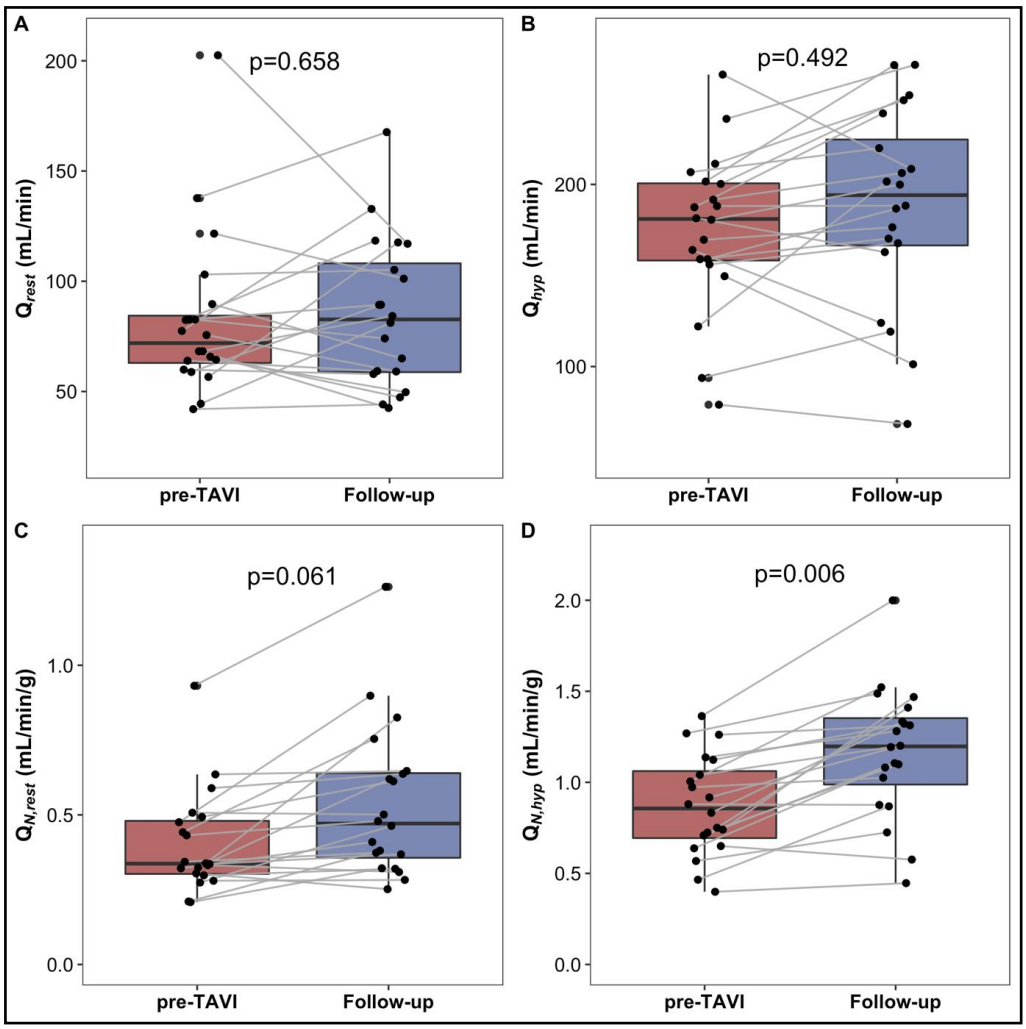

Figure 2. Absolute flow and myocardial perfusion at baseline and at 6 months follow-up (N=20).

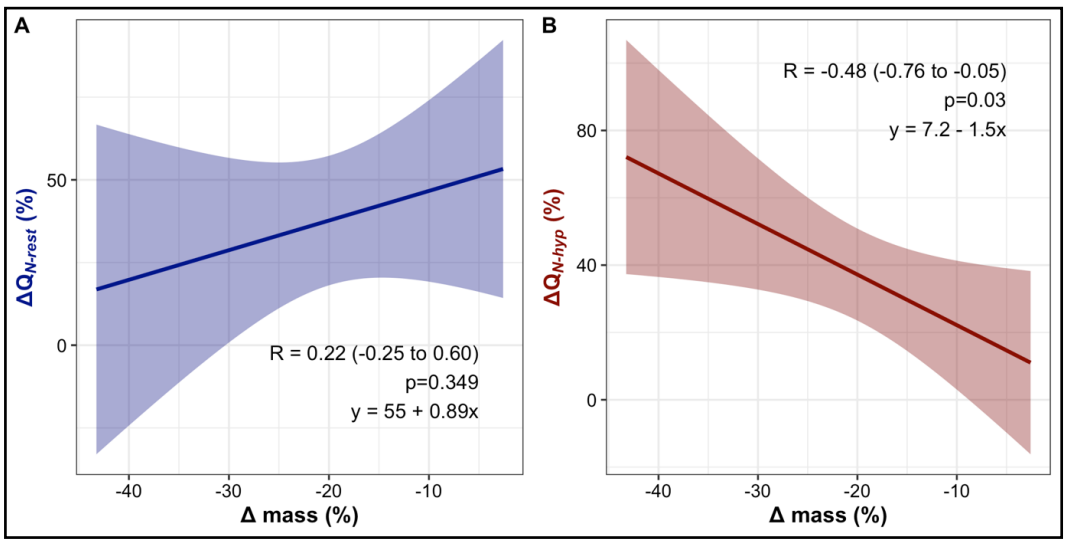

Figure 3. Correlation between the relative changes in myocardial mass and myocardial perfusion between baseline and follow-up measurements.

Discussion and Conclusion

To the best of our knowledge, our study is the first to directly quantify absolute coronary flow and microvascular resistance at rest and during hyperemia in patients with AS before and after TAVI and at 6 months follow-up. The findings of our study can be summarized as following: 1) no immediate changes occur in terms of absolute coronary flow and flow reserve after TAVI and this remained consistent at 6-month follow-up; 2) TAVI induces a significant reverse remodeling of the left ventricle with a significant reduction in the global myocardial mass; 3) consequently this reverse remodeling results in a significant improvement of hyperemic perfusion at follow-up, accompanied by an increase in CFR and MRR.

CHAPTER 10

CHARACTERIZATION OF CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH SEVERE AORTIC STENOSIS UNDERGOING TAVI

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Introduction

Microvascular resistance reserve (MRR) is a validated quantitative measure of coronary microvascular function independent of epicardial resistances.

In this study, we sought to assess the clinical features associated with impaired MRR in a prospective multicenter international cohort of patients with AS undergoing TAVI. In particular, we aimed to assess if low MRR was associated with low-flow phenotype and advanced extravalvular cardiac damage (EVCD).

Methods

This is a patient-pooled analysis of 3 prospective observational studies conducted in 3 European interventional centers (Verona University Hospital, Italy; Aalst OLV Cardiovascular Center, Belgium; Milan San Raffaele Hospital, Italy) between January 2021 and May 2023 on coronary microvascular function in AS. Patients with severe AS with a clinical indication for TAVI underwent thermodilution-based assessment of coronary microvascular function in the left anterior descending artery. The exclusion criteria were: significant angiographic epicardial stenosis in the LAD, previous coronary artery bypass graft surgery, previous anterior myocardial infarction, evidence of chronic total occlusion, hemodynamic instability, and severe chronic kidney disease. Patients in the lowest tertile of MRR were classified as low MRR. Hemodynamic measurements were repeated immediately after TAVI. EVCD and markers of low flow phenotype were assessed with echocardiography.

Coronary microcirculatory assessment

The intracoronary microcirculatory assessment was performed using a pressure/temperature-sensor wire (PressureWire X Guidewire, Abbott) connected to a dedicated software (Coroflow, Coroventis Research AB). Steady-state hyperemia was induced by continuous intracoronary infusion of saline at 20 mL/min through a dedicated catheter (RayFlow, Hexacath) or with intravenous adenosine infusion (140 mcg/kg/min).

Microvascular resistive reserve (MRR) was derived based on intracoronary continuous or bolus thermodilution using a previously validated formula:

$$\text{MRR} = \frac{CFR}{FFR} \cdot \frac{Pa\ rest}{Pa\ hyp}$$

Where CFR is coronary flow reserve, FFR is fractional flow reserve, and Pa is the aortic pressure invasively measured at rest or during steady-state hyperemia.

Evaluation of extravalvular cardiac damage

The extent of extravalvular cardiac damage (EVCD) was categorized into 5 stages according to a model described by Genereux et al. (11). To evaluate the interaction between measures of coronary microvascular function and EVCD and increase the statistical power, cardiac damage was dichotomized into stages 0-2 (group 1), corresponding to isolated left heart dysfunction, compared with stages 3 and 4 (group 2, damage extending to the pulmonary circulation and right heart; advanced cardiac damage) (177) (**Figure 1**).

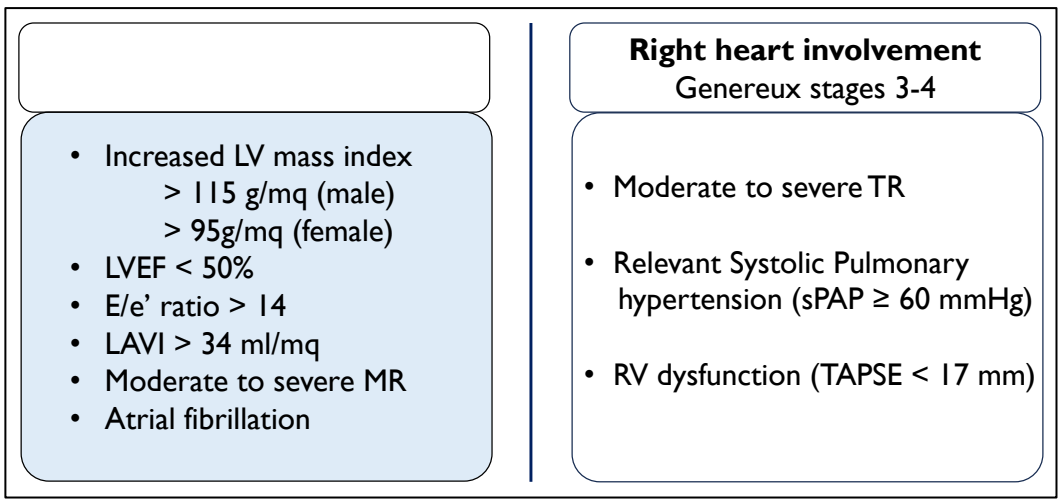

Figure 1. Definition of extravalvular cardiac damage staging. Genereux extravalvular cardiac damage (EVCD) classification was dichotomized in stages 0-2 (isolated left heart dysfunction) and stages 3-4 (advanced extravalvular cardiac damage with right heart involvement).

Abbreviations: LAVI: left atrial volume index; LV: left ventricular; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; RV: right ventricular; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspidalic anulus plane systolic excursion; TR: tricuspidalic regurgitation.

Results

One-hundred-thirty-four patients were included in this study. Patients with low MRR were more frequently females, with a lower estimated glomerular filtration rate (eGFR) and a higher rate of atrial fibrillation. MRR was significantly lower in patients with advanced EVCD (1.80 [1.26-3.30] vs 2.50 [1.87-3.41], p=0.038) and in low-flow low-gradient AS (LFLGAS) (1.85 [1.20-3.04] vs 2.50 [1.87-3.40], p=0.008) (**Figure 2**). Overall, coronary microvascular function tended to improve significantly after TAVI as an effect of the LV unloading induced by TAVI, and, in particular, MRR increased significantly after TAVI in the subgroup with low MRR at baseline. However, MRR did not significantly change in 38 (28.4%) patients immediately after TAVI. Advanced EVCD (odds ratio 3.08 [1.22-7.76], p=0.017) and low-flow state (odds ratio 3.36 [1.08-10.47], p=0.036) were significant predictors of impaired microvascular function.

Conclusions

Coronary microvascular dysfunction, defined by thermodilution-derived MRR, is associated with extravalvular cardiac damage and low-flow phenotype in patients with severe AS undergoing TAVI.

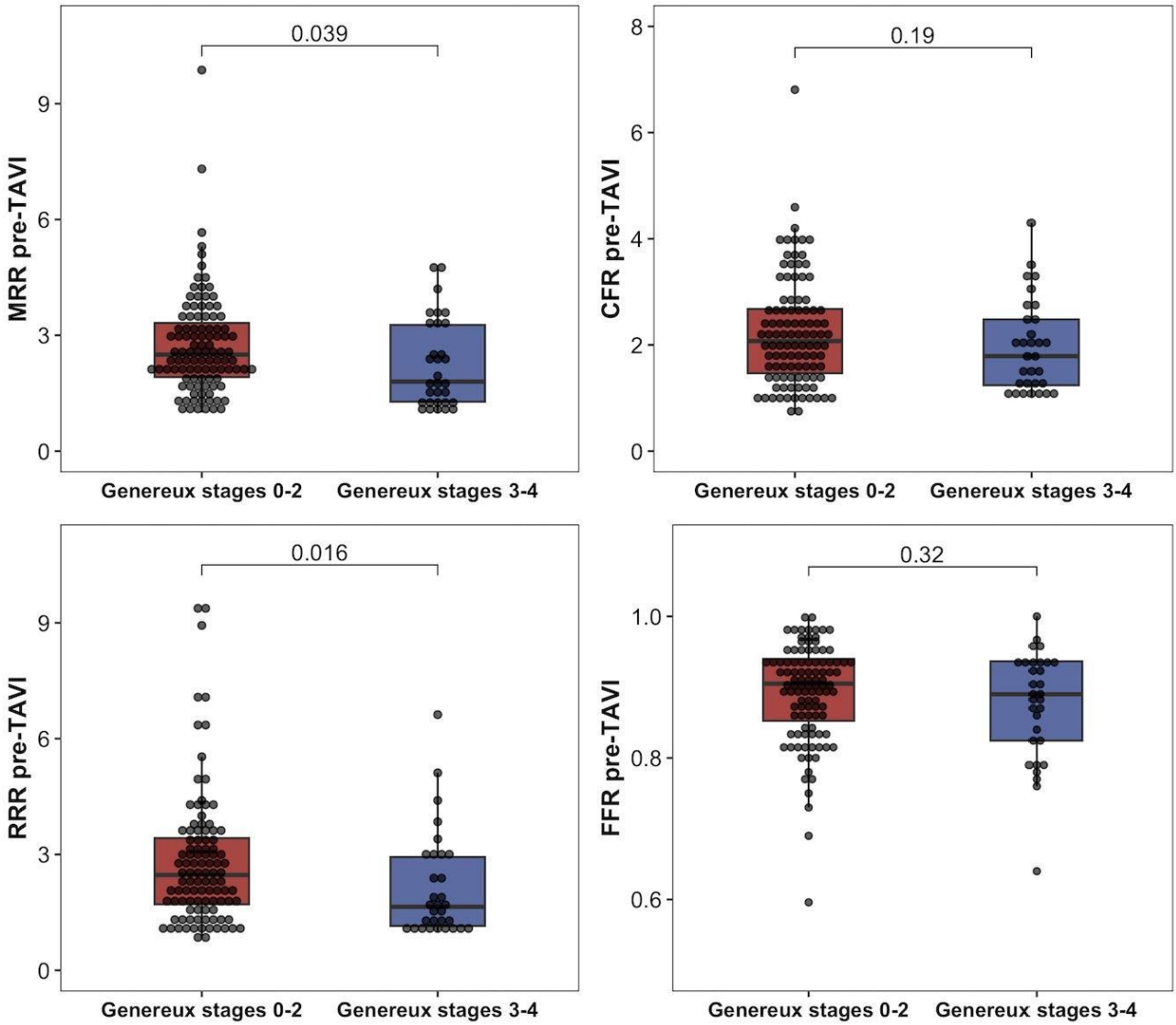

Figure 2. Coronary physiology data stratified according to the extravalvular cardiac damage. Coronary microvascular function expressed by MRR (upper left panel) and RRR (lower left panel) was significantly impaired in patients with advanced extravalvular cardiac damage.

CONCLUSIONS

In this long-lasting research journey, we investigated the complex field of aortic valve disease, starting from genetic and molecular expression to patient management and outcomes, aiming at improving patient care. Overall, we provided robust evidence contributing to the major paradigm shifts that we are facing in this field over the last decades. In details: i) we showed differential pattern and expression level in blood and tissue biomarkers according to AS phenotype (HG versus LF-LG), with the detection - for the first time - of SGLT2 hyper-expression in patients with LF-LG AS, which may retain a pathophysiological role in cardiac remodeling and metabolism (*Part I*); ii) we stressed the importance of considering AS as a pathology of both the valve and myocardium rather than an isolated pathology of the aortic valvular apparatus, by demonstrating how both non-invasive (echocardiography and computed tomography) and invasive (cardiac catheterization) techniques might assess and grade AS-related cardiac damage, and the related prognostic implications; remarkably, we were pleased to actively contributing to the consensus document of the European Society of Cardiovascular Imaging (EACVI) about the role of multi-modality imaging in AS, based on our experience and the latest available evidence (*Part II*); iii) we proved the outcome benefit of the Heart Valve Clinics, dedicated healthcare systems recently introduced for patients with valvular heart disease, thus encouraging their widespread (*Part III*); iv) we described and characterized coronary microvascular dysfunction in patients with aortic stenosis, also using the accurate and reproducible invasive technique of continuous intracoronary thermodilution, suggesting a possible pathophysiological role of coronary microvascular dysfunction in the outcomes after aortic valve replacement (*Part IV*).

LIST OF ABBREVIATIONS

AS: aortic stenosis

AVA: aortic valve area

AVR: aortic valve replacement

BMI: body mass index

CABG: coronary artery bypass graft

CAD: coronary artery disease

CFR: coronary flow reserve

CMD: coronary microvascular dysfunction

CMR: cardiac magnetic resonance

CT: computed tomography

DDF: diastolic dysfunction

DM: diabetes mellitus

eGFR: estimated glomerular filtration rate

EVCD: extra-valvular cardiac damage

FFR: fractional flow reserve

GLS: global longitudinal strain

GWI: global work index

HF: heart failure

HG AS: high gradient aortic stenosis

HVC: Heart Valve Clinics

LAD: left anterior descending artery

LF-LG AS: low-flow low-gradient aortic stenosis

LV: left ventricle

LVEF: left ventricle ejection fraction

LVH: left ventricle hypertrophy

LVM: left ventricle mass

LVOT: left ventricular outflow tract

MG: mean gradient

MW: non-invasive myocardial work

MRR: microvascular resistance reserve

Q_{rest}: Resting absolute coronary

Q_{hyp}: Hyperemic absolute flow

$R_{\mu\text{-}rest}$: Absolute resistance at rest

$R_{\mu\text{-}hyp}$: Absolute resistance during hyperemia

RWT: relative wall thickness

RHC: right heart catheterization

SAVR: surgical aortic valve replacement

SGLT2: Sodium–glucose cotransporter 2

SV: stroke volume

TAVR: transcatheter aortic valve replacement

TAVI: transcatheter aortic valve implantation

TTE: transthoracic echocardiogram

VHD: valvular heart disease

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34. Mileva N, **Paolisso P,** Gallinoro E, Fabbricatore D, Munhoz D, Bergamaschi L, Belmonte M, Panayotov P, Pizzi C, Barbato E, Penicka M, Andreini D, Vassilev D. Diagnostic and Prognostic Role of Cardiac Magnetic Resonance in MINOCA: Systematic Review and Meta-Analysis. JACC Cardiovasc Imaging. 2023 Mar;16(3):376-389. doi: 10.1016/j.jcmg.2022.12.029. PMID: 36889851.

35. Mileva N, Ohashi H, **Paolisso P**, Leipsic J, Mizukami T, Sonck J, Norgaard BL, Otake H, Ko B, Maeng M, Munhoz D, Nagumo S, Belmonte M, Vassilev D, Andreini D, Barbato E, Koo BK, De Bruyne B, Collet C. Relationship between coronary volume, myocardial mass, and post-PCI fractional flow reserve. Catheter Cardiovasc Interv. 2023 Jun;101(7):1182-1192. doi: 10.1002/ccd.30664. Epub 2023 Apr 27. PMID: 37102381.

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Rakisheva A, Ahrens I, Mortara A, Janowska EA, Almaghraby A, Damman K, Miro O, Huber K, Ristic A, Hill L, Mullens W, Chieffo A, Bartunek J, **Paolisso P**, Bayes-Genis A, Anker SD, Price S, Filippatos G, Ruschitzka F, Seferovic P, Vidal-Perez R, Vahanian A, Metra M, McDonagh TA, Barbato E, Coats AJS, Rosano GMC. Acute heart failure and valvular heart disease: A scientific statement of the Heart Failure Association, the Association for Acute CardioVascular Care and the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. Eur J Heart Fail. 2023 Jul;25(7):1025-1048. doi: 10.1002/ejhf.2918. Epub 2023 Jun 13. PMID: 37312239.

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MM, Botti G, Verstreken S, Morisco C, Barbato E, Bartunek J, Vanderheyden M. Innovative Device-Based Strategies for Managing Acute Decompensated Heart Failure. Curr Probl Cardiol. 2023 Aug 7;48(12):102023. doi: 10.1016/j.cpcardiol.2023.102023. Epub ahead of print. PMID: 37553060.

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48. Silverio A, Zilio F, Ciliberti G, **Paolisso P**, Barbato E. Definizione, classificazione e diagnosi di infarto miocardico in assenza di coronaropatia ostruttiva: a che punto siamo? [Definition, classification and diagnosis of myocardial infarction with non-obstructive coronary artery disease: where do we stand?]. G Ital Cardiol (Rome). 2023 Oct;24(10):29-36. Italian. doi: 10.1714/4101.40992. PMID: 37767845.

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50. Belmonte M, Gallinoro E, Bermpeis K, Bertolone DT, **Paolisso P**, Viscusi MM, Botti G, Bartunek J, Barbato E, Vanderheyden M. Comprehensive invasive evaluation of coronary microcirculation in patients with Takotsubo syndrome. Atherosclerosis. 2023 Oct 9;385:117332. doi: 10.1016/j.atherosclerosis.2023.117332. Epub ahead of print. PMID: 37866008.

51. Belmonte M, De Colle C, **Paolisso P**, Danino A, Pichersky Y, Lereya C, Kislev E, Planer D, Viscusi MM, Botti G, Bertolone DT, Gallinoro E, Shumkova M, Ratti A, Barbato E, Penicka M, Vanderheyden M, Bartunek J. Implantation of a Stent Graft System for Torrential Tricuspid Regurgitation: A First-in-Human Experience. JACC Cardiovasc Interv. 2023 Aug 22:S1936-8798(23)01152-4. doi: 10.1016/j.jcin.2023.08.008. Epub ahead of print. PMID: 37804288.

Manuscripts Under review

1. **Paolisso P**, Gallinoro E, Belmonte M, Bertolone DT, Bermpeis K, De Colle C, Shumkova M, Leone A, Caglioni S, Esposito G, Fabbricatore D, Moya A, Delrue L, Penicka M, De Bruyne B, Barbato E, Bartunek J, Vanderheyden M. Coronary microvascular dysfunction in patients with Heart Failure: characterization of patterns in HFrEF versus HFpEF – *Circulation Heart Failure*.

2. Belmonte M, **Paolisso P**, Gallinoro E, Bertolone DT, Caglioni S, Leone A, De Colle C, Viscusi MM, Bermpeis K, Storozhenko T, Mileva N, Sonck J, Wyffels E, Vanderheyden M, Collet C, De Bruyne B, Andreini D, Penicka M, Barbato E. Predictors of Percutaneous Coronary Intervention derived From CCTA in Patients with Chronic Coronary Syndrome – *JCCT*.

3. Belmonte M*, **Paolisso P***, Bertolone DT, Viscusi MM, Gallinoro E, De Oliveira EK, Shumkova M, Beles M, Esposito G, Addeo L, Botti G, Moya A, Leone A, Wyffels E, De Bruyne B, Van Camp G, Bartunek J, Barbato E, Penicka M and Vanderheyden M. Combined Cardiac damage staging in patients with clinically significant aortic stenosis – *Canadian Journal of Cardiology*

4. Scisciola L*, **Paolisso P***, Belmonte M, Gallinoro E, Delrue L, Taktaz T, Fontanella RA, Degrieck I, Pesapane A, Casselman F, Puocci A, Franzese M, Van Praet F, Torella M, Marfella R, De Feo MD Bartunek J, Paolisso G, Barbato E, Barbieri M, Vanderheyden MD2°. Myocardial SGLT2 expression in cardiac remodeling of patients with severe aortic stenosis: the BIO-AS Study – *European Journal of Heart Failure*

5. Gallinoro E, Bertolone DT, Mizukami T, **Paolisso P**, Bermpeis K, Munhoz D, Sakai K, Seki R, Ohashi O, Esposito G, Caglioni S, Mileva N, Leone A, Candreva A, Belmonte M, Storozhenko T, Viscusi MM, Vanderheyden M, Wyffels E, Bartunek J, Sonck J, Barbato E, Collet C, De Bruyne B. Continuous Versus Bolus Thermodilution to Assess Microvascular Resistance Reserve – *JACC Cardiovascular Interventions*

6. Scarsini R, Gallinoro E, Ancona M, Portolan L, **Paolisso P**, Springhetti P, Della Mora F, Belmonte M, Bertolone DT, Pesarini G, Benfari G, Chieffo A, Vanderheyden M, Montorfano M, De Bruyne B, Barbato E, Ribichini F. Microvascular resistance reserve is associated with

extravalvular cardiac damage and low flow phenotype in patients with severe aortic stenosis undergoing TAVI – *EuroIntervention*

CURRICULUM VITAE – DR. PASQUALE PAOLISSO

europass

Pasquale Paolisso

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Twitter: https://twitter.com/P_Paolisso

Gender: Male **Date of birth:** 16/03/1990 **Nationality:** Italian

WORK EXPERIENCE

[01/11/2022 – Current]

Cardiac Imager and Clinical Cardiologist

Galeazzi-Sant'Ambrogio Hospital - Gruppo San Donato

City: Milan
Country: Italy

EDUCATION AND TRAINING

[30/09/2012 – 30/07/2015]

Predoctoral intern in Department of Cardiology

University of Rome, Tor Vergata

City: Roma
Country: Italy
Supervisor: Prof. F. Romeo

[31/10/2014 – 29/11/2015]

Predoctoral intern in Department of Internal Medicine

University of Rome - Tor Vergata

City: Roma
Country: Italy
Supervisor: Prof. P. Sbraccia

[30/09/2009 – 30/07/2015]

Medical Degree (summa cum laude)

University of Rome - Tor Vergata

City: Roma
Country: Italy
Thesis title: "Additive role of MultiPoint Pacing in Cardiac Resynchronization Therapy"

[31/10/2016 – 29/10/2020]

Cardiology Residency

University Alma Mater Studiorum of Bologna- Policlinico Sant'Orsola-Malipighi - Dept. of Cardiology

City: Bologna
Country: Italy
Director of Cardiology: Prof. N. Galiè

[28/06/2019 – 29/06/2019]

ACLS - Provider Course - AHA

BIOS, Azienda Ospedaliera Universitaria di Parma

City: Parma
Country: Italy

[31/10/2020 – Current]

International PhD - CardioPaTh

Università Federico II - Napoli, Italy and Cardiovascolar Center OLV- Aalst, Belgium http://www.cardiopath.eu

Coordinator Prof. E. Barbato

[01/11/2020 – 30/10/2022]

Research and Non-Invasive Cardiac Imaging Fellowship

Cardiovascular Center, OLV-Clinic, Aalst, Belgium

Address: Moorselbaan 164, 9300, Aalst, Belgium
Supervisor:

- Prof. Martin Penicka
- Prof. Emanuele Barbato

[16/08/2021 – Current]

MitraClip Training Certification

Abbott Cardiovascular Education - Training Department Structural Heart Mitraclip

[21/09/2022 – Current]

TriClip Training Certification

Abbott Cardiovascular Education - Training Department Structural Heart Mitraclip

[01/11/2022 – Current]

Cardiac Imager and Clinical Cardiologist

Galeazzi-Sant'Ambrogio Hospital - Gruppo San Donato

City: Milan
Country: Italy

[22/02/2023 – Current]

National Scientific Qualification as Associate in the Italian Higher Education System (call 2021/2023) - Abilitazione Scientifica Nazionale di Professore Universitario di Seconda Fascia nel Settore Concorsuale 06/D1

Ministerial Decree n. 553/2021 and 589/2021

Country: Italy

LANGUAGE SKILLS

Mother tongue(s): Italian

Other language(s):

English

LISTENING C1 **READING** C1 **WRITING** C1

SPOKEN PRODUCTION C1 **SPOKEN INTERACTION** C1

Levels: A1 and A2: Basic user; B1 and B2: Independent user; C1 and C2: Proficient user

DIGITAL SKILLS

Microsoft Word | Microsoft Excel | Microsoft Powerpoint | Microsoft Office | Google Drive | Skype | Zoom | Microsoft Teams | Twitter | Outlook | GraphPad Statistics | Analyze Data Using SPSS

PUBLICATIONS

Publications

H-Index Scopus: 26

Documents: 94

Citations Scopus: 1775

Citation Google Scholar: 2160

Links: https://pubmed.ncbi.nlm.nih.gov/?term=Paolisso+P. | https://www.scopus.com/authid/detail.uri?authorId=55331305300

NETWORKS AND MEMBERSHIPS

Memberships

1. Fellow of European Society of Cardiology (FESC) - ESC ID 747780
2. EACVI Silver Member
3. Society of Cardiovascular Computed Tomography (SCCT) - Regular Member
4. EAPCI Regular Member - EAPCI Young Committee Member 2022-2024
5. Fellow Società Italiana di Cardiologia - Fellow SIC (FISC)

[21/09/2023 – Current] **Associate Editor of Cardiovascular Diabetology (IF 9.3)**

[31/05/2020 – Current]

Member of Editorial Board and Referee for "Kidney and Blood Pressure Research" (IF = 2.68)

[01/08/2023 – Current]

Member of Editorial Board and Referee for "Journal of Clinical Medicine - Section Cardiovascular Medicine" (IF = 3.9)

Link: https://www.mdpi.com/journal/jcm/sectioneditors/Cardiovascular_Medicine?page_no=5

HONOURS AND AWARDS

Honours and awards

"Ogni soluzione genera nuovi problemi - Anything that can go wrong will go wrong"

Paolisso P, D'Angelo E.C.

Best Abstract Award "Conoscere e Curare il Cuore" - Firenze 2019

Is Echocardiogram alone sufficient for characterization of cardiac masses?

P. Paolisso, EC. D'angelo, L. Bergamaschi, A. Foa, M. Coriano, G. Vitale, G. Saturi, I. Magnani, O. Leone, F. Pasquale, E. Biagini, M. Ferlito, C. Pizzi, C. Rapezzi, N. Galie

Best Poster Award - EuroEcho, Vienna 2019

10 Years survival in patients with cardiac masses: are pseudotumours really benign masses?

P. Paolisso, C.E. D'Angelo, A. Foà, L. Bergamaschi, G. Saturi, I. Magnani, S. Toniolo, M. Corianò, A. Stefanizzi, A. Rinaldi, O. Leone, D. Pacini, C. Pizzi, N. Galiè

Best Abstract Award - 80th Congress of the Italian Society of Cardiology Rome, December 2019

Diagnostic accuracy of cardiac Computed Tomography and F-Fluorodeoxyglucose Positron Emission Tomography/

Computed Tomography in the identification of cardiac masses.

C.E. D'Angelo, P. Paolisso, G. Vitale, A. Fo , L. Bergamaschi, I. Magnani, S. Toniolo, G. Saturi, A. Rinaldi, O. Leone, A.M. Pantaleo, D. Pacini, C. Pizzi, N. Galiè

Best Abstract Award "Conoscere e Curare il Cuore" - Firenze 2020

Microvascular Dysfunction in Patients With Diabetes Mellitus: Invasive Assessment of Absolute Coronary Blood Flow and Microvascular Resistance Reserve

P. Paolisso, Gallinoro E, Candreva A, Bermpeis K, Fabbricatore D, Esposito G, Bertolone D, Peregrina E.F. Munhoz D, Mileva D, Penicka M, Bartunek J, Vanderheyden M, Wyffels E, Sonck J, Collet C, De Bruyne B and Barbato E.

Best Abstract Award - 82th Congress of the Italian Society of Cardiology Rome, December 2021

[02/10/2020] **Expert of Cardiology Awarding institution:** Saint Camillus International University of Health Sciences - UniCamillus

JOB-RELATED SKILLS

Job-related skills

Database compilation and analyses

CONFERENCES AND PRESENTATIONS

Conferences and Presentations

Abstract - 76th Congress of the Italian Society of Cardiology Rome, December 2015

Abstract - 77th Congress of the Italian Society of Cardiology Rome, December 2016

Abstract - Conoscere e Curare il Cuore – Firenze Marzo 2018

Abstract - ESC Congress Munich 2018

Abstract - 79th Congress of the Italian Society of Cardiology Rome, December 2018

Best Abstract "Conoscere e Curare il Cuore" - Firenze 2019

Best Clinical Case "Conoscere e Curare il Cuore" - Firenze 2019

Abstract - 16th Congresso Nazionale Associazione Italiana Aritmologia e Cardiostimolazione, Bologna, Aprile 2019

Abstract - EuroCMR, Venezia 2019

Abstract - ESC Congress Paris 2019

Abstract - EuroEcho, Vienna 2019

Abstract - 80th Congress of the Italian Society of Cardiology Rome, December 2019

Abstract - ESC Digital Congress 2020

Abstract - Associazione Nazionale Medici Cardiologi Ospedalieri – Rimini Agosto 2020

Abstract - Conoscere e Curare il Cuore – Firenze Ottobre 2020

Abstract - 81th Digital Congress of the Italian Society of Cardiology, December 2020

Abstract - Conoscere e Curare il Cuore – Firenze Ottobre 2021

Abstract - 82th Congress of the Italian Society of Cardiology Rome, December 2021

Abstract - EuroPCR - Paris 2022

Abstract - BSC Congress - Bruxelles 2022

Abstract SCCT Congress - Las Vegas 2022

Abstract ESMED Congress 2022

Abstract ESC Congress 2022 - Barcelona 2022

Abstract - Conoscere e Curare il Cuore – Firenze Ottobre 2022

Oral Presentation - 29° Congresso Nazionale Società Italiana di Diabetologia

Abstract - 83th Congress of the Italian Society of Cardiology Rome, December 2022

Abstract - EACVI, Barcelona 2023

Abstract and Chairman - ESC Congress, Amsterdam 2023

RESEARCH PROJECTS

Research Projects

No Profit Studies

Co-investigator in "**Diabetic cardiomyopathy and vascular complications**"

P.I. Prof. R. Marfella, Università degli Studi della Campania L. Vanvitelli, Napoli, sulla

Co-investigator in "**Bologna Register of Cardiac Masses** "

P.I.: Prof. D. Pacini and Prof. N. Galiè - University Alma Mater Studiorum of Bologna

Co-investigator in "**Effect of SAcubitril/Valsartan on left VentricularEjection fraction and their potential impact on Implantable CardioverterDefibrillator implant rates for primary prevention of sudden cardiac death: the SAVE-ICD study**".

Local P.I.: Dott. M. Ziacchi - University Alma Mater Studiorum of Bologna

Co-investigator in **AMIPE Register**: "Acute Myocardial Infarction, Prognostic and Therapeutic Evaluation"

(ClinicalTrials.gov Identifier: NCT03883711)

P.I. Prof. Carmine Pizzi - University Alma Mater Studiorum of Bologna

Co-investigator in **SGLT2-I AMI PROTECT Study: "Cardioprotective Effect of SGLT2-I in Diabetic Patients With Acute Myocardial Infarction".**

(ClinicalTrials.gov Identifier: NCT05261867)

P.I. Prof. Emanuele Barbato - Cardiovascular Center, OLV-Clinic, Aalst, Belgium and Prof. Carmine Pizzi - University Alma Mater Studiorum of Bologna