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UNIVERSITY OF ATHENS
Medical School

In collaboration with

Doctor of Philosophy Dissertation

Effect of Diastolic Dysfunction on Outcomes of Patients with Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement

<u>Title in Greek:</u> Επίδραση προυπάρχουσας διαστολικής δυσλειτουργίας στην βραχυπρόθεσμη και μακροπρόθεσμη έκβαση ασθενών με στένωση αορτικής που υπέκεινται σε διακαθετηριακή αντικατάσταση αορτικής βαλβίδας

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ABSTRACT

Background and goals: Prior studies have shown that left ventricular diastolic dysfunction (DD) may be associated with worse outcomes after aortic valve replacement. Studies on transcatheter aortic valve replacement (TAVR) were limited, have not taken into account mitral annular calcification (MAC), which limits the use of mitral valve annular Tissue Doppler imaging, and have not shown the predictive value of DD beyond pulmonary hypertension. We performed a single-center retrospective analysis to better evaluate the role of baseline DD on outcomes after TAVR.

Methods: After excluding patients with atrial fibrillation, mitral valve prostheses and significant mitral stenosis, 359 consecutive TAVR patients were included. Moderate-to-severe MAC was present in 58% of the patients. We classified patients into severe vs. non-severe DD based on the evaluation of elevated left ventricular filling pressures. The outcome measure was all-cause mortality or heart failure hospitalization. Secondary, subgroup analyses were performed to investigate the role of DD in patients that develop paravalvular leak (PVL).

Results: Over a mean follow-up time of 13 months, severe DD was associated with an increased risk for the outcome measure (HR 2.02 (1.23-3.30), p=0.005). However, this association was lost in a propensity-matched cohort that took into account pulmonary hypertension. In multivariate analysis, STS score was the only independent predictor of all cause mortality of heart failure hospitalization (HR 1.1 (1.05-1.15), p<0.001). Patients with severe DD that develop even mild PVL after TAVR had an independent risk for increased mortality (HR 3.89, CI 1.76–8.6, p=0.001)

Conclusions: Severe DD was associated with increased all-cause mortality or heart failure hospitalization after TAVR but not independently of pulmonary hypertension and other known predictors of mortality. Severe DD may be particularly detrimental in patients who develop PVL via acute volume overload of a stiff left ventricle.

ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
AI	Aortic insufficiency
AS	Aortic stenosis
ASE	American Society of Echocardiography
AV	Aortic valve
AVR	Aortic valve replacement
CMR	Cardiac magnetic resonance
DD	Diastolic dysfunction
E/A	Early to late peak transmitral flow velocity ratio
EACVI	European Association of Cardiovascular Imaging
GLS	Global longitudinal strain
HF	Heart failure
IVRT	Isovolumic relaxation time
LA	Left atrium
LF	Low flow
LFLG AS	Low flow, low gradient AS
LGE	Lade gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVEDP	Left ventricular end diastolic pressure
LVSP	Left ventricular systolic pressure
LVH	Left ventricular hypetrophy
MAC	Mitral annular calcification
MF	Myocardial fibrosis
MR	Mitral regurgitation
PCWP	Pulmonary capillary wedge pressure
PVL	Paravalvular leak
SAVR	Surgical aortic valve replacement
STS	Society of Thoracic Surgeons
TAVR	Transcatheter aortic valve replacement
TR	Tricuspid regurgitation

1. GENERAL PART / INTRODUCTION

1.1 Aortic stenosis overview

Valvular aortic stenosis (AS), the predominant type of AS, is a progressive disease that is characterized by calcific degeneration of the aortic valve that eventually results in symptoms of decreased cardiac output, heart failure and death from cardiovascular causes (1, 2). AS and mitral regurgitation (MR) represent the most common valvular diseases with a prevalence that increases substantially with age (3); In the US, moderate or severe AS is present in <2% of the population before the age of 65, and prevalence increases to 8.5% in those aged 65-74 and 13.2% after 75 (4). Currently, there are no medical therapies to prevent or slow the progression of AS (2), and the disease has a mortality of around 50% at 2-years once it becomes symptomatic (5). The only treatment for severe, symptomatic AS has been aortic valve replacement (AVR), which dramatically decreases mortality. AVR had only been performed surgically (SAVR) prior to the establishment of transcatheter aortic valve replacement (TAVR). In 2019, following the FDA approval of TAVR for low-risk patients with severe AS, the volume of annually performed TAVRs in the US surpassed that of SAVRs (approximately 72,000 vs. 57,000 respectively) (6).

1.2 Study rationale and related challenges

Despite the profound increase in survival after AVR, long-term mortality remains increased compared to the general population, regardless of transcatheter or surgical approach (7, 8). From a pathophysiology standpoint, AS leads to increased left ventricular (LV) afterload, which in turn promotes left ventricular hypertrophy (LVH) and myocardial fibrosis (MF), both of which result in LV diastolic dysfunction (DD) and heart failure (1, 9). There is evidence to suggest that LVH and MF resolve long after AVR or may potentially not completely resolve (10, 11). More importantly, both processes have been associated with worse survival after AVR: Profound LVH in AS can result in restrictive LV physiology and paradoxical low-flow (LF) AS, an entity that is now very well known to be associated with increased mortality and worse outcomes (12, 13). On

the other hand, a number of prospective studies have associated the presence of MF, as evaluated by cardiac magnetic resonance (CMR), with worse outcomes in patients with AS (14, 15). A recent meta-analysis showed a 2.5-fold increase in the risk for mortality in patients with AS that developed MF (adjusted hazard ratio) (16). These findings may imply that certain patients could benefit from AVR earlier or even in the asymptomatic phase of the disease, beyond what is currently recommended by guidelines (17). In this framework, the individual role of DD in patients with AS had not been fully described despite the fact that both LVH and MF are functional mediators of DD. Previous retrospective studies on patients undergoing SAVR suggested that advanced degrees of DD are associated with worse outcomes (18-21). In the TAVR population and at the time of the inception of this doctoral study (2016), there were only a limited number of studies evaluating the impact of baseline DD in these patients (22, 23). Of note, different diagnostic and grading schemes of DD were used in all studies.

The TAVR population by definition includes patients with a large burden of comorbidities that are inoperable and therefore may have more advanced degrees of DD (24). In addition, TAVR is significantly different from SAVR not only because it is a non-surgical or minimally invasive surgical procedure with a particular complication that could be strongly associated with pre-existing DD: Paravalvular leak (PVL) remains an important complication after TAVR despite its decreasing frequency with newer generation transcatheter valves as it has been recognized as a mortality after TAVR (25, 26). The mechanism of increased mortality in PVL is thought to be secondary to acute volume overload of an LV with pre-existing DD (27) but this concept has not been validated. At the time of the conception and initiation of the current doctoral thesis in 2016, there were only a very limited number of studies examining the clinical role of DD in patients undergoing TAVR and none examining its relation to paravalvular leak (23).

Although it may appear intuitive from a pathophysiologic perspective, the true impact of DD on the outcomes

of these patients is challenging to prove due to a number of reasons: lack of an easily applicable and universal algorithm to evaluate DD; it is influenced by LV loading conditions; it is difficult to evaluate in the presence of structural parameters such as MR and mitral annular calcification (MAC), and finally it maybe the result of entities that coexist with AS such as amyloidosis or HTN.

1.3 Doctoral study goals

The primary goal of the current doctoral study was therefore to study the potential clinical role of DD in patients that undergo TAVR for severe AS. More specifically we sough to 1) perform a review of the existing literature on the prognostic role of DD in patients that undergo AVR as well as to review DD changes after AVR 2) study the association of advanced DD with mortality in a TAVR population from the Weill Cornell Heart Valve Center and establish whether DD is an independent predictor of mortality 3) evaluate whether worse baseline DD in patients who develop PVL after TAVR is associated with increased mortality in the same population, and investigate potential mechanism to explain this association

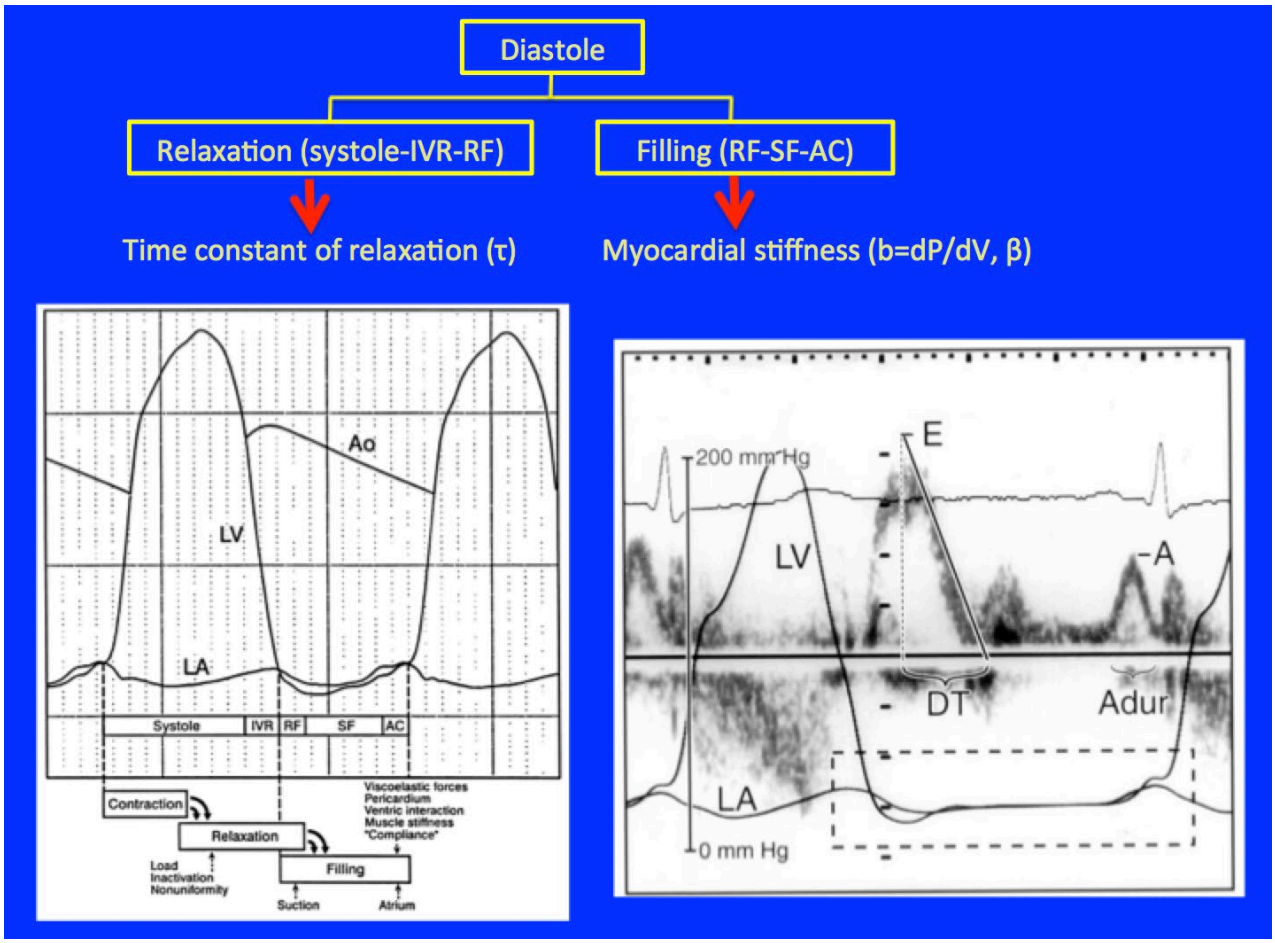
Two particular challenges of the current study were how to evaluate DD in these patients via non-invasive means and how to verify whether DD is an independent risk factor for mortality.

2. GENERAL PART / REVIEW OF DIASTOLIC DYSFUNCTION IN AORTIC STENOSIS

2.1 Pathophysiology

LV diastole is a complex sequence of events can be broken down in two phases, LV relaxation and filling.

The end result of normal diastole is the filling of the LV with normal left ventricular end diastolic pressure



(LVEDP) (28) (**Figure 1**).

Figure 1. Normal diastole results in normal LVEDP and can be divided into 2 phases, relaxation and filling, each comprising of different, overlapping sub-phases. Relaxation is characterized by the time constant of relaxation (τ) and filling by myocardial stiffness i.e. the derivate of pressure over volume (top). Bottom left, LV, LAD and Ao pressures measured invasively over time during over the cardiac cycle along with sub-phases of relaxation and filling. Bottom right, overlap of pressures and Doppler signals of diastole.

A=peak late filling velocity, Ao=aorta, AC=atrial contraction, DT=deceleration time, E=peak early filling velocity, IVR=isovolumic relaxation, LA=left atrium, LV=left ventricle, RF=rapid filling, SF=slow filling
(Permission from Nishimura et al. J Am Coll Cardiol 1997; 30:8-18)

Changes in either relaxation (increased time constant of relaxation, τ) or filling (increased stiffness) result in DD, the hallmark of which is elevated LVEDP in the absence of other obvious (29). Classic changes in the early to late peak transmitral velocities (E/A) have been noted in DD and have been used for its diagnosis and grading (**Figure 2**).

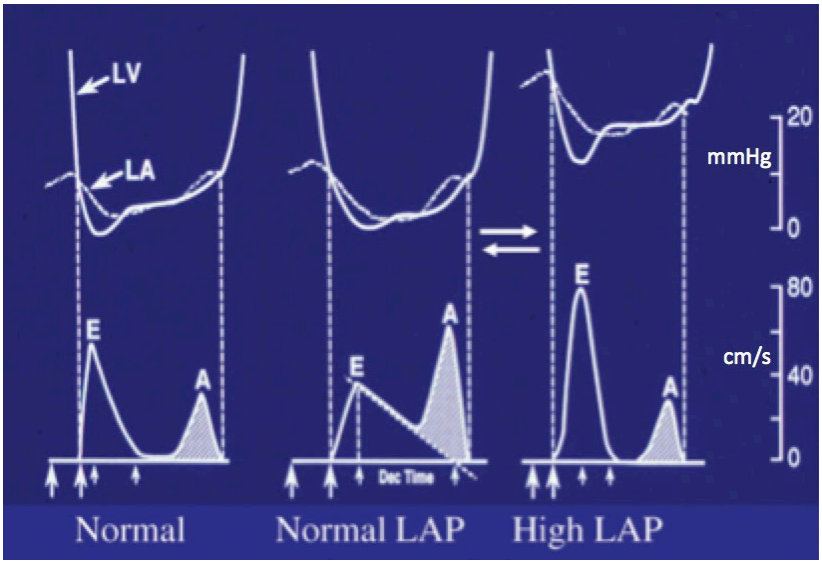


Figure 2. Abnormalities in either LV relaxation or stiffness result in diastolic dysfunction, the hallmark of which is elevated LVEDP and subsequently LA pressures. Top, invasive LV and LA pressures. Bottom, transmitral flow patters using Doppler echocardiography

LA=left atrium, LV=left ventricle, LVEDP=left ventricular end diastolic pressure
(Permission from Nagueh et al. Eur J Echocardiogr. 2009 Mar;10(2):165-93)

In AS, LV systolic pressure (LVSP) increases as a result of the progressive narrowing of the aortic valve orifice. Increased LVSP leads to compensatory concentric LVH, which maintains normal afterload (wall stress) and normal systolic function according to the Laplace equation (**Figure 3**) (1).

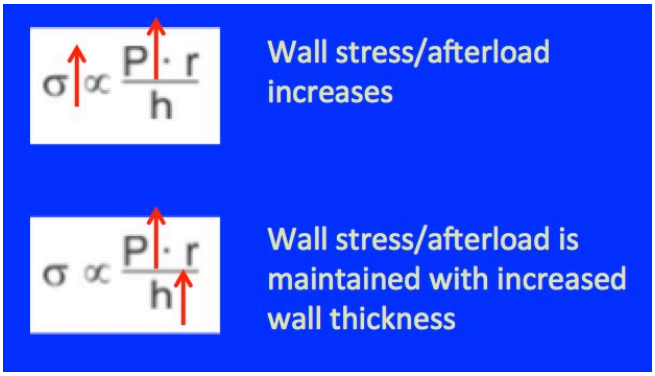


Figure 3. Laplace equation results in increased afterload/wall stress in the presence of high LV systolic pressure (top). Afterload/wall stress is maintained with compensatory LV hypertrophy and increased wall thickness (bottom).

σ=afterload/wall stress, P=pressure, r=radius, h=thickness

However, concentric LVH also results in impaired LV diastolic function as increased wall thickness prolongs relaxation, increases stiffness and eventually requires amplified filling pressure to achieve a normal diastolic volume (30). In addition to LVH, increased LVSP leads to progressive MF (31), which increases LV stiffness, thus contributing to impaired diastolic function. In summary, concentric LVH and MF are the 2 key pathophysiologic mechanisms of DD in patients with AS and are both a result of increased LVSP. With the progression of AS, filling of the LV is maintained only through increased LVEDP, thus DD ensues. This augmented diastolic pressure leads to pulmonary congestion, which manifests clinically as heart failure, one of the three classical symptoms of severe AS.

2.2 Non-invasive evaluation of diastolic dysfunction and associated challenges

The most accurate method of diagnosing DD is through direct measurement of LVEDP and the time constant of LV relaxation (τ) using high fidelity pressure transducers but this is limited by the need for cardiac catheterization (32, 33). In clinical practice, echocardiography or cardiac magnetic resonance (CMR) are the usual means of evaluating DD (15). In contrast to the evaluation of LV systolic function, where ejection fraction can be used as a single variable to approximate systolic function, echocardiographic evaluation of DD cannot be based simply on the calculation of E/A ratio; multiple 2D and Doppler variables that correlate with measurements derived by cardiac catheterization have to be measured (28, 34, 35): LA volume, transmitral and pulmonary venous flow velocities and time intervals, tissue Doppler of the mitral valve annulus all reflect DD and can be used to estimate LVEDP. However, DD evaluation is complicated by the fact that all of these variables also depend on additional factors such as LV ejection fraction, presence of other valvular disease including MAC, age, gender and the of course, the clinical setting. For example, MR and MAC are common in patients with severe AS and result in alterations in the transmitral flow patterns and tissue Doppler. As a

result, diastolic echocardiographic variables are often non-concurrent and can be interpreted differently by different imaging specialists (36). To complicate matters even more, there is no universally accepted way of evaluating DD. The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) have recently updated a combined guideline statement in an attempt to simplify the evaluation of DD, overcome some of the challenges and recommend a practical, standardized scheme for the diagnosis and grading of DD (**Figure 4)** (37). Our approach in the current doctoral study is based on these recommendations will be discussed in detail in the Methods Section (Section 3). Lastly, CMR has emerged as an alternative modality to echocardiography for the evaluation of DD (38). Apart from assessing the parameters derived by echocardiography, it has the additional benefit of quantifying MF.

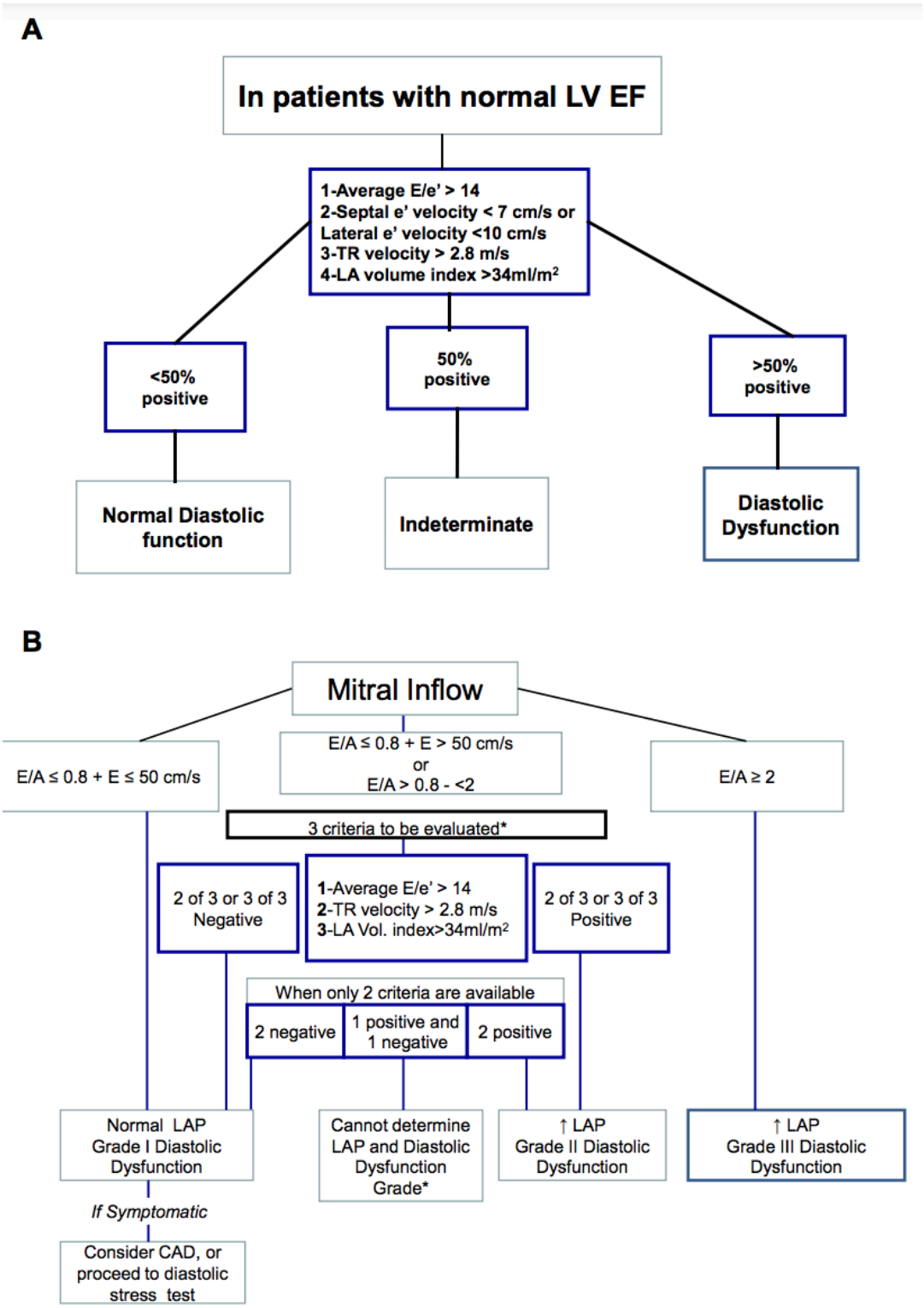


Figure 4. ASE/EACVI echo-based algorithm for (A) diagnosis and (B) grading of diastolic dysfunction in the general population.

LA=left atrium, LAP=left atrial pressure, TR=tricuspid regurgitation, e'=early peak mitral annular velocity, E=early peak transmitral flow velocity, E/A=early to late peak transmitral flow velocity ratio. (Permission from Nagueh et. al, J Am Soc Echocardiogr 2016;29:277-314)

2.3 Diastolic function after aortic valve replacement

In patients with AS, replacement of the diseased valve results in normalization of the main upstream pathophysiologic events of DD, i.e. afterload and LVSP. However, resolution of LVH and MF, which are the downstream mechanisms that sustain DD, requires a process of LV remodeling that lags behind AVR and may even be irreversible (10, 11). Improvement in DD after AVR seems to accompany this slow LV remodeling. Most of our knowledge on this topic comes from earlier studies on patients that underwent SAVR. We performed a systematic review (**Supplemental Figure 1)** to identify and summarize previous studies on LV remodeling after AVR **(Supplemental Table 1)** (9).

The main results of this review can be summarized as follows: Invasive evaluation of diastolic function with high-fidelity pressure transducers and concurrent endomyocardial biopsy of these patients has revealed that DD normalizes late (81 months) but not early (22 months) after AVR. These changes parallel changes in MF (39, 40). Interestingly, LV stiffness and MF increased early after AVR, a finding that has been attributed to a relative increase of MF in the setting of earlier LVH regression (i.e. there is more fibrosis in a given volume of myocardium) (30). Non-invasive studies of diastolic function have shown similar gradual improvement in DD late after AVR that follows LV remodeling (41-44) (25–28). Some studies have shown residual and even worse DD up to 10 years after AVR (45, 46).

Diastolic function after TAVR

Studies on DD after TAVR were extremely limited at the time of conception of the current doctoral study (2016) (23). Only recently, and after the publication of our published review (9), more studies on this topic were released. Improvement in DD early after TAVR has been shown in several studies, but remains incomplete as expected due to incomplete LV remodeling (47-50). **Figure 5** shows incomplete DD improvement at 30-days post-TAVR, a very recently published analysis from the PARTNER 2 trial (left) (50) and 6-months and 1-year after TAVR in a single study by Muratori et al (23).

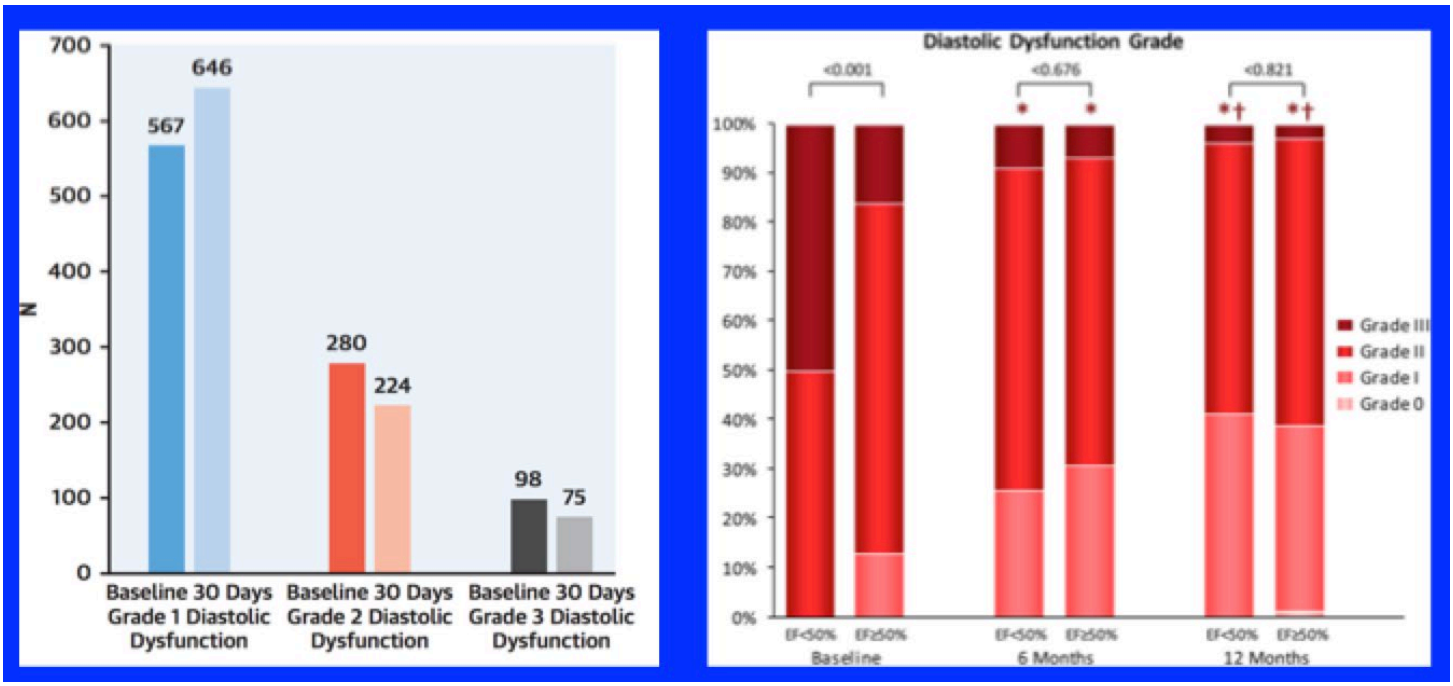


Figure 5. Change in diastolic dysfunction grade between baseline and (left) 30-days after TAVR in the PARTNER 2 trial (Permission from Ong et al. (J Am Coll Cardiol 2020;76:2940–51), (right) 6-months and 1-year after TAVR (N=242) (Permission from Muratori et al. Eur Heart J Cardiovasc Imaging 2016;11:1269-78)

However, we have to note that TAVR patients have a few distinct characteristics compared to SAVR patients that can potentially affect the LV remodeling and diastolic function after TAVR. For one, there is no prior literature on inoperable patients with AS. In addition, TAVR patients are more elderly, have more comorbidities, worse baseline functional status, more advanced myocardial fibrosis and possible worse LVH (24) As a result they may have worse DD at baseline with possibly more incomplete improvement compared to SAVR. Furthermore PVL is more common after TAVR and may increase DD as well as its impact on outcomes, as we will discuss further.

LV remodeling, improvement in DD and their relation to post-TAVR PVL will be discussed in the Discussion Section (Section 5), following the results of the present doctoral study.

Factors affecting DD and remodeling after AVR

It is not clear which factors may be hindering LV remodeling after AVR (51). Known factors that seem to prevent DD improvement include patient prosthesis mismatch, uncontrolled hypertension, extensive MF or

profound baseline LVH similar to LF-LG AS (10, 52). Patient-prosthesis mismatch, defined as effective orifice area that is too small in relation to body size, is essentially a marker of incomplete relief of pressure overload after AVR (53). It has been associated with slower rates of LV mass regression, LV remodeling and worse outcomes (51, 54).

2.3 Impact of baseline diastolic dysfunction on outcomes

The fact that DD parallels LV remodeling after AVR and resolves slowly or incompletely could mean that worse DD at baseline predicts worse clinical outcomes. Potential mechanisms for that are residual heart failure and ventricular arrhythmias from persistent MF. To that matter, the presence of both LVH and dilated LA after AVR have been associated with increased mortality (10). As already mentioned, paradoxical LF AS and MF are associated with worse baseline DD and have been linked to increased mortality. Paradoxical LF AS and MF will be discussed separately.

As an initial step, we performed a systematic search of studies on the impact of DD after AVR, either TAVR or SAVR. At the time of the review, the majority of these studies were on patients undergoing SAVR and they demonstrated increased mortality and morbidity ranging from the peri-operative setting to long term follow up, thus supporting the abovementioned hypothesis (9) (**Table 1**).

Table 1: Studies on the impact of diastolic dysfunction on clinical outcomes after AVR

1st author, year (n)	AVR	DD evaluation	DD variables	DD grading	Measured outcome	Results
Lund, 1997 (91)	SAVR	TTE	LV fast filling fraction, LV late filling fraction	No	Short and long-term mortality	LV fast filling fraction <45% had a regression coefficient = 0.98 (p=0.03) for crude mortality and 1.07 (p=0.03) for aortic stenosis specific deaths
Bernard, 2001 (66)	SAVR	TTE	E/A, DT, S/D	None, Grade I, Grade II, Grade III	Need for inotropic support 0-12 hours after surgery	DD OR: 6.17; 95% CI: (1.9–19.8), P= 0.002
Gjertsson, 2005 (399)	SAVR	TTE	E/A, S/D	None, Grade I, Grade II, Grade III	Long-term mortality	Grade II-III vs. Grade I-normal: HR 1.72; p=0.005 for mortality risk Patients with mild DD did not have decreased survival compared to the general population
Denault, 2006 (54)	SAVR	TTE	e'	None, Grade I, Grade II, Grade III	Separation from cardiopulmonary bypass	65.5% of the patients with moderate to severe DD had a difficulty in the separation from the cardiopulmonary bypass vs. 40.9% for patients with no or mild DD, P = 0.017
Ding, 2010 (112)	SAVR	TTE	E/A	No	Short and long-term mortality	HR 1.85; 95% CI: (1.06–3.22),P= 0.03 for short term mortality HR 2.09; 95% CI: (1.24–3.12) p<0.01 for long-term mortality HR 3.35; 95% CI: (1.23–9.17); p<0.01 for long-term mortality (elderly only)
Linker, 2010 (108)	SAVR	TEE	E/A, DT, S/D	None, Grade I, Grade II, Grade III	Weaning off ventilator	DD was a risk factor for post-CPB LV dysfunction. Multivariate logistic regression for Vp<40cm/s effect in weaning off ventilator: OR = 0.65; 95% CI: 0.52-0.81
Chang,2010 (248)	SAVR	TTE	E/e'	No	In-hospital and Long-term CV Events	E/e' >12 was associated with increased in- hospital (P=0.04) and long-term CV events (10.1% vs. 2.8%, P=0.03)
Rassi, 2013 (1267)	SAVR	Exercise TTE	E/A, S/D, LA size	Normal, stage I, stage II	Long term Mortality or AVR (combined)	Baseline stage II DD was an independent predictor of the composite endpoint of death and AVR, HR; 1.75; 95% CI: 1.13-2.71, P= 0.012. Mild DD had not a significant association with the endpoint

Timothy Tann, 2015 (432)	SAVR	TTE	E/e'	No	Combined Endpoint*, Long-term mortality	Combined Endpoint adjusted OR:1.40; 95% CI: 1.03-1.78 Long-term mortality adjusted OR:1.51; 95% CI: 1.18-1.92
Muratori, 2015 (358)	TAVR	TTE	E/A, DT, e', E/e'	None, Grade I, Grade II, Grade III	1 year mortality	Similar mortality among patients with advanced vs. mild DD Patients with baseline severe DD who showed an improvement in their DD after TAVR had better1 year survival (compared to those who did not show an improvement)
Kampaktsis, 2016 (195)	TAVR	TTE	e', LAVI, E/A, DT	None, Grade I, Grade II, Grade III	Long-term mortality	Severe DD was not independently associated with mortality Severe DD with Post-TAVR AI was associated with increased mortality (HR: 3.89; 95% CI: 1.76–8.6; P=0.001)

*combined endpoint: in-hospital mortality or major morbidity defined as all-cause death, stroke, renal failure (Risk, Injury, Failure, Loss of kidney function or End-stage kidney disease [RIFLE] classification ≥3)

DD=Diastolic Dysfunction, AS=Aortic Stenosis, AVR=Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement, TAVR=Transcatheter Aortic Valve Replacement, TEE=Transesophageal echocardiogram, TTE=Transthoracic echocardiogram, LAVI=Left Atrium Index Volume, LA=Left Atrial, LV=Left Ventricle, DT= deceleration time, Vp=transmitral flow propagation velocity. E=peak early transmitral velocity, A= peak late transmitral velocity, e'= peak early mitral annular velocity Doppler, S= peak systolic pulmonary vein flow velocity, D= peak diastolic pulmonary vein velocity, CV=Cardiovascular, HR= Hazard Ratio, OR=Odds Ratio, CI=Confidence Interval
(Permission from Heart. 2017 Oct;103(19):1481-1487)

SAVR

The following summarizes the findings in the SAVR population: In the peri-operative setting, worse baseline DD was associated with difficulty to wean off cardiopulmonary bypass and increased rates of complications during hospitalization (20, 55, 56). Moderate-to-severe DD was associated with increased rates of AVR or mortality in the first 2 years (21). Another study by Gjertsson et al. associated moderate-severe baseline DD in 399 patients with increased long term mortality up to 12 years after AVR (45). E/e', a non-invasive estimation of LVEDP that has been widely associated with worse outcomes in several cardiac diseases (57-60), has also been associated with increased in-hospital mortality and cardiovascular events (61). E/A, E wave deceleration time (DT) have also been associated with early and long term mortality after AVR (62). Lastly, LV fast filling fraction (percent of total filling volume in first half of diastole defined by LV ventriculography) is an uncommon DD variable that has been associated with increased mortality after AVR (63).

TAVR

In the TAVR setting, there were only 2 published studies evaluating the impact of DD on outcomes at the time of our review (2017). A study on 350 patients reported no difference in mortality among patients with different degrees of DD (23). Interestingly though, significantly increased mortality was noted in the subgroup of patients with severe DD that did not improve at 1-year post-TAVR compared to patients with severe DD that improved. A preliminary smaller study from our group on 190 patients showed a trend towards increased mortality in patients with severe DD vs. less than severe DD at baseline (22). Six more studies were published until, one of which was from our group in the setting of the current doctoral thesis, and are summarized in **Table 2** (64). All these studies consistently showed increased mortality with worse degrees of DD. Finally, results from the PARTNER 2 trial were recently published and showed a significant association of worse DD grades with the composite outcome of cardiovascular death or rehospitalization (50).

Table 2. Recent key studies on diastolic dysfunction and its association with outcomes after TAVR at the time of published results from the Partner 2 trial (12/2020) (Permission from Klein et al. J Am Coll Cardiol 2020 Dec 22;76(25):2952-2955)

First Author (Ref. #), Year	Number of Cases	Study Type	Results Summary
Blair et al. (4), 2017*	90	Retrospective, single-center	Baseline diastolic dysfunction grade, but not post-TAVR or changes in diastolic dysfunction grade, was associated with 1-yr death (HR: 1.163; 95% CI: 1.049 to 1.277) and combined death/cardiovascular hospitalization (HR: 1.174; 95% CI: 1.032 to 1.318).
Muratori et al. (5), 2015	358	Prospective, single-center	Survival was better in those with DD grade 3 with improvement in diastolic function grade vs. in those without improvement post TAVR (unadjusted).
Sato et al. (6), 2018*	237	Retrospective, single-center	Over a median follow-up of 1,320 days, neither pre- nor post-TAVR DD grade were associated with prognosis. In patients with grade III DD detected before TAVR and AR ≥2 after TAVR had poorer survival ($p < 0.008$). Patients with grade III DD detected after TAVR and AR ≥2 after TAVR had poorer prognosis ($p = 0.002$).
Thaden et al. (7), 2020*	1,383	Retrospective, single-center	Over a mean follow-up period of 7.3 yrs, increased left ventricular filling pressure (using ASE guidelines) remained an independent predictor of mortality after successful AVR (HR: 1.45; 95% CI 1.16 to 1.81).
Kampaktsis, et al. (8), 2020	359	Retrospective, single-center	Over a mean follow-up of 13 months, DD identified using an E/A ratio cut-off of 1.8 was associated with an increased risk for the outcome measure (HR: 2.02; 95% CI: 1.23 to 3.30). This association was lost in a propensity-matched cohort.
Anantha-Narayan et al. (9), 2020*	222	Prospective, single-center	Over a median follow-up of 385 days, advanced (Grades II–III) and indeterminate DD were associated with increased long-term mortality (25%–28% vs. 5%; $p = 0.02$).
Kampaktsis et al. (10), 2017	195	Retrospective, single-center	At mean follow-up of 14 months, patients with severe baseline DD (E/A >1.5) who developed ≥ mild post-TAVR AI was independently associated with increased mortality compared to all other patients (HR: 3.89; 95% CI: 1.76 to 8.60; $p = 0.001$).
Asami et al. (11), 2018*	777	Prospective, single-center	1-yr all-cause mortality was higher in patients with LVDD grades I (16.3%; HR: 2.32; 95% CI: 1.15 to 4.66), II (17.9%; HR: 2.58; 95% CI: 1.43 to 4.67), and III (27.6%; HR: 4.21; 95% CI: 2.25 to 7.86) than in those with normal diastolic function (6.9%).

Major limitations of the abovementioned studies include i) significant heterogeneity in the definition and classification of DD ii) the presence of parameters that limit DD evaluation such as MAC, severe MR or AI and atrial fibrillation was not taken into account iii) the independent impact of DD has not been well studied. In the analysis of the PARTNER 2 trial, multivariable analysis showed that severe vs. mild DD is a predictor of 1-year mortality independently of age, LVEF and STS score among other known predictors of mortality. However, pulmonary artery pressures, a known strong predictor of mortality in TAVR patients were not taken into account.

We will further discuss these findings in the Discussion Section (Section 5) after we present our findings in detail.

2.5 Association with paradoxical low-flow aortic stenosis and myocardial fibrosis

As already mentioned in the Introduction Section, DD is closely related with paradoxical LF AS and MF, both of which have been associated with worse survival after AVR. Here, we will discuss this in further detail.

Paradoxical low flow aortic stenosis and diastolic dysfunction

Paradoxical LF AS represents a condition of AS where disproportionate LVH and DD result in restrictive physiology, reduced filling of the LV and a low flow state (low stroke volume) despite a preserved ejection fraction (12). Classical LF AS is the condition where a low flow state exists in the setting of decreased ejection fraction. Paradoxical LF AS is an extreme type of AS in terms of pathophysiology, but not infrequent in terms of frequency. In a recent study, 33% of patients with severe AS and preserved ejection fraction had paradoxical LF AS. This entity represents a challenge for prompt diagnosis, particularly when accompanied by low transaortic gradient (65). However, the AV is always smaller than 1.0cm^2. The clinical importance of paradoxical LF AS lies on the fact that it has been associated with worse prognosis in several studies (66, 67), however these patients still benefit from AVR.

Both types of LF AS represent maladaptive LV responses to pressure overload, and have been associated with increased MF. In regards to the underlying pathophysiologic mechanism of the LF state, although a degree of systolic and diastolic dysfunction is present in both types, classical LF is associated more with systolic dysfunction and paradoxical with diastolic (12). Distinguishing paradoxical LF-LG from moderate AS in a symptomatic patient is crucial and challenging. A comprehensive clinical and echocardiographic approach has been proposed by experts on the field, and the entity has been incorporated in the ACC/AHA guidelines as D3 severe AS (17, 68). However, the importance of diastolic function evaluation in this clinical setting has not been emphasized or well studied. Identification of restrictive physiology or severe DD would help the physician diagnose severe symptomatic paradoxical LF AS. Additionally, severe DD could be associated with worse survival after AVR independently of LF AS, as studies mentioned earlier suggest.

Myocardial fibrosis and diastolic dysfunction in aortic stenosis

MF is a main pathophysiologic feature of advanced DD (69, 70), and in fact of all advanced cardiomyopathies (71, 72). CMR is the method of choice for detecting localized or diffuse MF via late gadolinium enhancement (LGE and post-contrast T1 mapping and extracellular volume. There is growing evidence from several prospective observational CMR studies and a meta-analysis that MF is an independent predictor of mortality in patients with AS after AVR, even when detected in the asymptomatic phase of the disease (16, 24, 73). Our group has also correlated the absence of LVH on surface ECG, a finding that may reflect underlying MF, with increased mortality after TAVR (74). Ventricular arrythmias caused by MF are the most likely pathophysiologic mechanism for these findings (75). Chin et al. used CMR to classify patients in 3 groups of MF severity regardless of AS severity (Figure 4). In their study, MF was associated with both DD grade and increased mortality regardless of AS severity (14) (**Figure 6**). These findings suggest that DD and may have additional prognostic significance compared to AS severity alone. Interesting questions therefore arise: Is the prognostic value of MF superior and/or independent of DD? are both DD and MF required for more accurate

prognostication. Nevertheless, MF has not been routinely incorporated in the management of patients with AS given the lack of any widely accepted clinical algorithms and the cost of CMR imaging.

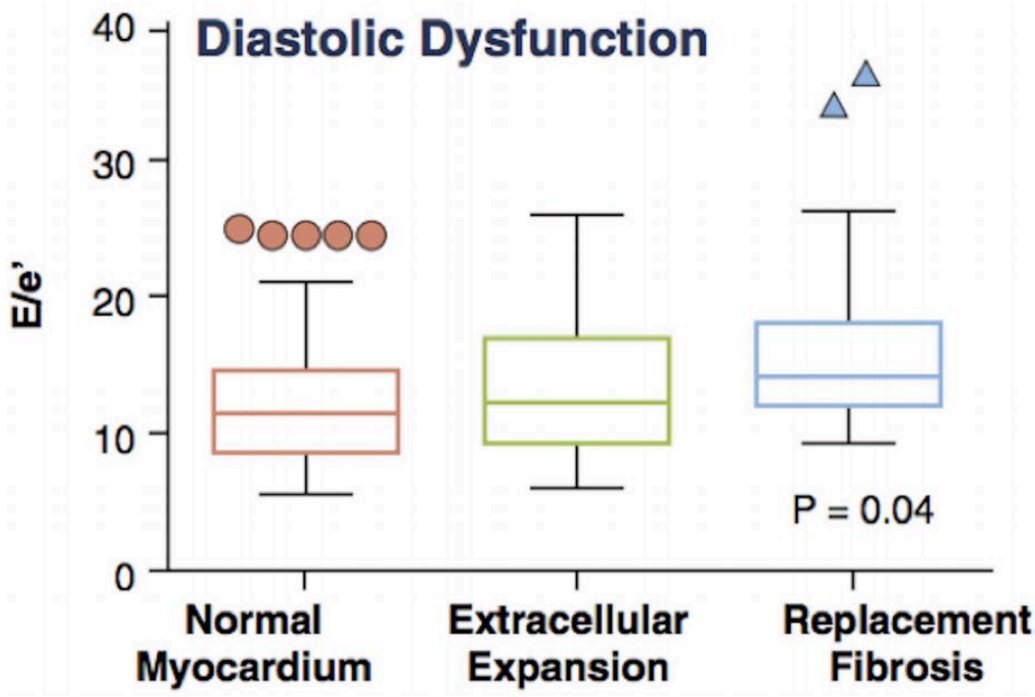


Figure 6. E/e' ratio increases with increased presence of myocardial fibrosis regardless of AS severity. In this prospective observational study, cardiac magnetic resonance imaging was used to evaluate myocardial fibrosis in patients with different degrees of AS and in controls (healthy volunteers). Patients were classified as having i) normal myocardium (n=80), ii) extracellular expansion, an early reversible form of myocardial fibrosis evaluated by extracellular volume expansion indexed above a cutoff in this study (n=38) and iii) replacement fibrosis, evaluated by presence of mid-wall late gadolinium enhancement (n=43). Echocardiography was used to measure E/e' ratios as a marker of diastolic dysfunction. E/e' ratio was significantly different among the groups with more advanced myocardial fibrosis correlating with higher E/e' and thus worse diastolic dysfunction.

AS=Aortic Stenosis (Adopted with permission and modified from Chin et al, JACC Cardiovasc Imaging 2016, doi: 10.1016/j.jcmg.2016.10.007. Open access under the CC BY license https://creativecommons.org/licenses/by/4.0/ and Kampaktsis et al. Heart. 2017 Oct;103(19):1481-1487).

3. STUDY SPECIFIC PART / METHODS

This section provides the detailed methodology of the current doctoral study's primary research analysis.

3.1 Population and exclusion criteria

Our initial study cohort comprised of 529 consecutive patients who underwent TAVR for severe symptomatic AS in New York Presbyterian Hospital / Weill Cornell Medicine from January 2010 to April 2016 using balloon or self-expandable prostheses (Edwards Sapien or Medtronic CoreValve). A retrospective analysis was performed. Patients with atrial fibrillation were excluded from this study, given the more complex evaluation of DD in these patients (76, 77). We also excluded patients with prior mitral valve replacement or at least moderate mitral stenosis given the effect of these conditions on transmitral flow waves. After exclusions, 359 patients were included in the study. Patients with baseline MR were not excluded regardless of severity, but results were adjusted for.

3.2 Data collection and ethics

Clinical and procedural data were gathered into an institutional TAVR database that has been used by our group in a previously published retrospective study (74). Briefly, study data were collected and managed using REDCap electronic data capture tools hosted at New York Presbyterian / Weill Cornell Medicine (78). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Per the doctoral study and institutional protocols, TAVR evaluation includes right heart catheterization in all patients. Thus, pulmonary capillary wedge pressure (PCWP) was collected for the majority of the patients. Clinical follow up was performed in clinical visits and/or phone contact at 1 month, 6 to 12 months after TAVR and yearly thereafter. The study was conducted with the approval of the local Institutional Review Board at Weill Cornell Medicine and written informed consent was obtained. The study was also approved by the Ethics board of the University of Athens Medical School.

3.3 Echocardiography

Transthoracic echocardiograms were performed pre-procedurally using commercial equipment (GE Vivid 7 [GE Healthcare, Madison, WI] and Phillips iE33 [Phillips Medical Systems, MA] and according to previously reported protocols for TAVR (79, 80). Echocardiograms were interpreted in a high-volume laboratory with which expertise and reproducibility in structural heart disease and TAVR in particular.

Pertinent echocardiographic variables were obtained as follows: E wave, DT and A wave were measured from transmitral flow patterns obtained between the mitral leaflets using pulsed-wave Doppler in the apical 4-chamber view. Early diastolic annular velocity (e') of the lateral and septal LV wall was measured by pulse-wave Tissue Doppler Imaging. LV ejection fraction was calculated by the Teichholz method, based on mid-cavity measurements in orthogonal antero-posterior and medio-lateral planes in the presence of regional wall motion abnormalities. LA volume was calculated using Simpson's rule, and LV mass was calculated using a necropsy-validated formula (81). Both variables were indexed to body surface area (LAVI and LVMI respectively). Relative wall thickness was also calculated. Continuous wave Doppler was used to calculate the mean AV gradient via the transaortic velocity waves in systole. The AV area was calculated by the continuity equation with measurements acquired in systole and was indexed to body surface (AVAI). MR was graded according to ASE recommendations (82). Continuous-wave Doppler was used to estimate the transmitral diastolic pressure gradient (MVG) from the transmitral velocity flow curve using the simplified Bernoulli equation. Post-TAVR, indices of AS severity were derived from transthoracic echocardiograms at the 30-day clinical follow-up visit.

Post-TAVR PVL was evaluated according to Valve Academic Research Consortum-2 criteria (83) and was defined as ≥ moderate paravalvular regurgitation.

MAC was evaluated based on parasternal short-axis views at the level of the mitral annulus according to the previously reported Cardiovascular Health Study and Northern Manhattan Study (84, 85). Severity was qualitatively determined as mild (focal, limited increase in echodensity of the mitral annulus), moderate (marked echodensity involving one-third to one-half of the ring circumference), or severe (marked echodensity involving more than one-half of the circumference of the ring or with intrusion into the left ventricular inflow tract). Maximal MAC thickness measured from the anterior to the posterior edge at its greatest width is also used to assess MAC severity, with a value >4 mm defining severe MAC.

Longitudinal strain (reported as absolute values) was retrospectively collected in subgroup of the study cohort with available baseline, 30-days and 1-year post-TAVR echocardiograms. We used quantified in (2-, 3-, 4-chamber) long axis orientations, for which images were acquired with frame rates> 50 Hz. Automated speckle tracking analysis was performed on a frame-by-frame basis using vendor independent software (Cardiac Performance Analysis, TomTec [Unterschleissheim, Germany]). Regional strain was determined using a 16-segment model. Global longitudinal strain (GLS) was calculated as a weighted average of all LV segments.

3.4 Assessment of diastolic dysfunction

We tested the applicability of the 2016 ASE/EACVI guidelines recommended algorithm for the diagnosis and grading of DD in the general population (**Figure 4**) (37) in our cohort. Our objective however was to use a simplified scheme for the diagnosis of DD that could be easily used in clinical practice and would also take into consideration the high incidence of MAC in this population. Towards that, the presence of DD can be safely assumed for patients with underlying structural abnormalities and also in the presence of heart failure symptoms. Therefore, for our study cohort of patients with symptomatic severe AS the 1st step of the ASE/EACVI algorithm to diagnose DD can be omitted. Following that, the key in detecting severe DD is the

presence of elevated filling pressures, particularly LA pressure and LVEDP. We therefore adopted a modified approach based on the ACC/EACVI recommendations to gain simplicity and adjust for the high prevalence of MAC (**Supplemental Figures 3-4**): Severe DD was defined as the presence of elevated LVEDP by echocardiography using the E/A ratio, which has been used in prior studies and has been shown to have prognostic significance (22, 86). A cutoff of 1.8 or higher has been shown to correlate with increased LVFP measured invasively in patients with MAC, and was therefore used in the current study (87). Patients who did not meet that criterion were classified as having non-severe DD.

3.5 Outcome measures

The primary outcome measure of the analysis was time to all-cause death or 1st hospitalization for heart failure exacerbation. Secondary clinical endpoints included all-cause death, cardiovascular death, myocardial infarction, disabling stroke and major adverse cardiac and cerebrovascular events (MACCE) at 1 year after TAVR. All suspected adverse events were independently adjudicated according to the criteria by the Valve Academic Research Consortium-2 (83).

We additionally performed 2 secondary, subgroup analyses to study: i) the impact of PVL on outcomes in patients with pre-existing DD ii) to compare LV remodeling and GLS changes in relation to PVL. Outcome measures were all-cause mortality and changes in LV structural variables 30-days and 1-year post-TAVR respectively.

3.6 Statistical analysis

Baseline clinical, procedural and echocardiographic characteristics were compared between patients with severe versus non-severe DD. Categorical variables are presented as absolute frequencies and were compared with the chi-square test or Fischer's exact test. Continuous variables are presented as mean ± standard deviation and were compared with the use of Student's t-test or Mann Whitney U test.

Cox regression was used to derive survival curves in regards to the outcome measure and to all-cause mortality. Univariate Cox regression models were used to detect predictors of the outcome measure among different groups, presented as hazard ratios (HR) with 95% confidence intervals (CI). Multivariate Cox-regression was used to adjust for structural variables and predictors of mortality. All reported probability values were two-sided and an alpha level of 0.05 was used for statistical significance.

Propensity score matching with replacement and predefined calipers (0.02) was performed and the matched groups were compared in terms of the primary outcome measure of the study to reduce covariate bias in the exposure group (severe DD).

Using data from the original PARTNER 1 trial (88) and preliminary results from the current doctoral thesis (22), the following assumptions were made: probability of death 20%, probability of heart failure exacerbation 20%, proportion of severe DD 0.2 and hazard rate 1.8; thus a sample size of 355 patients yielded a statistical power of 80%. Therefore our sample size of 359 patients was considered adequate to test the null hypothesis that severe DD is not associated with increased risk for the outcome measure. All statistical analyses were performed with the use of SPSS software (IBM, version 25.0, Chicago, Illinois, USA).

4. STUDY SPECIFIC PART / RESULTS

4.1 Incidence of diastolic dysfunction and baseline characteristics

Table 3 shows the results of applying the 2016 ASE/EACVI guidelines algorithm in our cohort. DD was diagnosed in 239 (66%) patients. Forty-six (12%) patients did not have DD, whereas in 87 (23%) patients DD could not be evaluated due to missing values or due to inability of the algorithm to classify.

Table 3. Diastolic dysfunction diagnosis and grading in our cohort per the ASE/EACVI guidelines algorithm (see Figure 4)

Group	N (%)
Overall cohort	359 (100%)
Diastolic dysfunction present	239 (66%)
Grade I	4 (1%)
Grade II	192 (52%)
Grade III	37 (10%)
Diastolic dysfunction absent	46 (12%)
Missing values/unable to determine	87 (23%)

When using our simplified, MAC-adjusted algorithm (**Supplemental Figures 3-4**), 56 (16%) and 303 (84%) patients were classified as having severe and less than severe DD respectively. Baseline clinical and procedural characteristics are presented in **Table 4**. Patients included were elderly (84 ± 7 years, 44% men) with mean STS score 6.9 ± 3.9. Transfemoral approach was used for the majority (70%) of patients. Either an Edwards Sapien XT or an Edwards Sapien 3 transcatheter heart valve were used for most cases (>80%). With the exception of higher pulmonary artery (PA) pressures (33 ±10 mmHg vs. 25 ± 9 mmHg, $p<0.001$) and beta-blockers (68% vs. 50%, $p=0.009$), patients with severe DD did not have significantly different clinical comorbidities, functional status or risk profile as assessed by STS score. PCWP was higher in the severe DD group (21 ± 8 mmHg vs. 15 ± 7 mmHg, $p<0.001$).

Table 5 summarizes pertinent echocardiographic characteristics at baseline. Moderate or severe MAC was present in 209 (58%) patients without significant difference between patients with versus without severe DD. Calculated mean AV gradient and LVEF were lower in patients with severe DD (47 ± 15 mmHg vs. 52 ± 17

mmHg, p=0.038 and 50 ± 15% vs. 55 ± 13% respectively). The frequency of low-flow, low-gradient AS (LF-LG AS) was not statistically different. Patients with severe DD had also more dilated LV (5.6 ± 0.8 cm vs. 5.3 ± 0.8 cm, p=0.028) and had eccentric LVH more frequently (64% vs. 49%, p=0.038). LA size, E/A, E wave, DT, E/e' were significantly worse in patients with severe DD (p value for all <0.05). Tissue Doppler of the mitral annulus (septal and lateral e') did not differ between the 2 groups. Patients with severe DD also had advanced tricuspid regurgitation (TR) and aortic insufficiency (AI) more frequently (23% vs. 7% and 14% vs. 5% respectively). Post-TAVR, there were no differences in mean AV gradient, AV area or PVL between the groups.

Table 4. Baseline and procedural characteristics

	Overall (n=359)	Non-severe DD (n=303)	Severe DD (n=56)	p
Age (years)	84 ± 7	85 ± 7	84 ± 7	0.869
Male gender	159 (44%)	129 (43%)	30 (53%)	0.167
Body Mass Index (kg/m^2)	27 ± 68	27 ± 6.0	27 ± 6	0.92
Atherosclerosis risk factors				
Diabetes mellitus	119 (33%)	99 (33%)	20 (35%)	0.734
Hypertension	307 (86%)	256 (85%)	51 (90%)	0.355
Tobacco use	200 (56%)	166 (55%)	34 (60%)	0.514
Hypercholesterolemia	287 (80%)	243 (81%)	44 (77%)	0.572
Coronary artery disease				
Prior MI	76 (21%)	59 (20%)	17 (30%)	0.203
Prior PCI	142 (40%)	121 (40%)	21 (37%)	0.888
Prior CABG	100 (28%)	78 (26%)	22 (39%)	0.143
History of stroke	27 (8%)	21 (7%)	6 (10.5%)	0.348
Chronic Lung Disease	111 (31%)	99 (33%)	12 (21%)	0.079
Hemodialysis	10 (3%)	8 (3%)	2 (4%)	0.707
Medications				
Aspirin	97 (27%)	75 (25%)	22 (39%)	0.096
Beta blocker	191 (53%)	152 (50%)	39 (68%)	**0.009**
ACE Inhibitor	57 (16%)	46 (15%)	11 (19%)	0.596
ARB Inhibitor	51 (14%)	45 (15%)	6 (11%)	0.639
Laboratory				
Creatinine (mg/dl)	1.32 ± 1.1	1.29 ± 1.1	1.47 ± 1.1	0.270
Hemoglobin (mg/dl)	11.3 ± 1.7	11.3 ± 1.7	11.1 ± 1.6	0.407
Invasive hemodynamics				
PA mean pressure (mmHg)	26 ± 10	25 ± 9	33 ±10	**<0.001**
PCWP (mmHg)	16 ± 8	15 ± 7	21 ± 8	**<0.001**
Pulmonary hypertension	159 (43%)	128 (40%)	42 (71%)	**<0.001**
NYHA III/IV	200 (56%)	166 (57%)	34 (62%)	0.477
STS score	6.9 ± 3.9	6.9 ± 3.9	7.7 ± 3.7	0.13
Procedural characteristics				
Transfemoral access	250 (70%)	214 (71%)	36 (63%)	0.456
Transapical access	97 (27%)	77 (26%)	20 (35%)	0.456
Edwards SAPIEN XT	218 (61%)	179 (59%)	39 (70%)	0.595
Edwards SAPIEN 3	82 (23%)	72 (24%)	10 (18%)	0.659
Medtronic CoreValve	38 (11%)	34 (11%)	4 (7%)	0.659

ACE=angiotensin converting enzyme, ARB=aldosterone receptor blocker, CABG=coronary artery bypass grafting, MI=myocardial infarction, PCI=percutaneous coronary intervention, PA=pulmonary artery, PCWP=pulmonary capillary wedge pressure, STS=Society of Thoracic Surgeons

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Table 5. Baseline and key post-TAVR (30-day) echocardiographic characteristics

	Overall (n=359)	Non-severe DD (n=303)	Severe DD (n=56)	p
Aortic stenosis severity				
Aortic valve area (cm^2)	0.75 ± 0.21	0.76 ± 0.21	0.75 ± 0.26	0.94
Mean aortic valve gradient (mmHg)	51 ± 16	52.3 ± 16.6	47.3 ± 14.7	**0.038**
LVEF (%)	54 ± 14	55 ± 13	50 ± 15	**0.025**
Stroke volume indexed (ml/m2)	42 ± 11	42 ± 115	42 ± 14	0.951
LF-LG AS (SVI<35 and MAG<40)	30 (8%)	22 (7%)	8 (14%)	0.091
LV dimensions				
LV end-systolic diameter (cm)	3.9 ± 0.9	3.8 ± 0.9	4.1 ± 1.0	**0.013**
LV end-diastolic diameter (cm)	5.4 ± 0.8	5.3 ± 0.8	5.6 ± 0.8	**0.028**
LV hypertrophy				
LV mass indexed (g/m^2)	113 ± 27.5	112 ± 28	118 ± 24	**0.006**
Relative wall thickness	0.35 ± 0.08	0.35 ± 0.08	0.34 ± 0.07	0.171
Concentric hypertrophy	30 (8%)	27 (9%)	3 (5%)	0.377
Eccentric hypertrophy	185 (52%)	149 (49%)	36 (64%)	**0.038**
LV diastolic function				
Left atrial volume indexed (cm^3/m^2)	48 ± 15	45 ± 16	52 ± 17	**0.006**
TR max velocity (cm/s)	2.98 ± 0.52	2.38 ± 1.39	3.18 ± 0.96	**<0.001**
E/A ratio	1.21 ± 0.82	0.93 ± 0.32	2.71 ± 1.02	**<0.001**
E wave (cm/s)	103 ± 33	98 ± 31	133 ± 29	**<0.001**
Septal e' (cm/s)	4.6 ± 1.4	4.5 ± 1.5	4.9 ± 1.8	0.075
Lateral e' (cm/s)	6.2 ± 2.3	5.9 ± 2.3	6.6 ± 3.0	0.06
E/e' ratio	24 ± 10	23 ± 10	28 ± 10	**0.002**
Deceleration time (ms)	252 ± 100	270 ± 101	170 ± 48	**<0.001**
Valvular				
Mitral annular calcification (≥ moderate)	209 (58%)	177 (60%)	32 (57%)	0.732
Mitral regurgitation (≥ moderate)	53 (15%)	40 (13%)	13 (23%)	0.058
Tricuspid regurgitation (≥moderate)	34 (9%)	21 (7%)	13 (23%)	**<0.001**
Aortic insufficiency (≥ moderate)	23 (6%)	15 (5%)	8 (14%)	**0.009**
Right ventricle				
TAPSE (cm)	1.9 ± 0.5	1.9 ± 0.5	1.8 ± 0.6	0.071
Post-TAVR				
Aortic valve area (cm^2)	1.75 ± 0.39	1.75 ± 0.39	1.68 ± 0.38	0.25
Mean aortic valve gradient (mmHg)	12 ± 6	12 ± 6	12 ± 5	0.74
Paravalvular leak (≥ moderate)	6 (2%)	4 (2%)	2 (4%)	0.19

LF-LG AS=low-flow, low-gradient aortic stenosis, LV=left ventricle, LVEF=LV ejection fraction, MAG=mean aortic gradient, SVI=stroke volume indexed, TAPSE=tricuspid annular plane systolic excursion
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4.2 Impact of diastolic dysfunction on outcomes

Over a mean follow up of 13.2 months, the primary outcome measure of all-cause death or 1st HF hospitalization occurred in 38% vs. 22% of patients with vs. without severe DD respectively (HR 2.0, CI 1.23-3.30, p=0.005, **Figure 7A**). This was driven by a difference in all-cause death, which occurred in 30% vs. 20% respectively (log rank p=0.01, **Figure 7B**). At 1-year follow up, cardiovascular death, myocardial infarction and cerebrovascular event rates were not statistically different between the 2 groups. MACCE however occurred more frequently among patients with severe DD (25% vs. 11%, p=0.005, **Table 6**). In univariate analysis, baseline predictors of the primary outcome measure besides severe DD were: MR (HR 1.16, CI 1.00-1.34, p=0.048), creatinine (1.31, CI 1.09-1.57, p=0.004) and STS score (HR 1.09, CI 1.06-1.13, p<0.001) (**Table 7**).

Table 6. One-year clinical outcomes after TAVR in the study's cohort

	Overall (n=359)	**Non-severe DD (n=303)**	**Severe DD (n=56)**	**p**
All-cause mortality	46 (13%)	34 (11%)	12 (21%)	**0.037**
Cardiovascular death	36 (10%)	27 (9%)	9 (16%)	0.10
Myocardial infarction	1 (0.3%)	0 (0%)	1 (2%)	0.34
Cerebrovascular event	1 (0.3%)	0 (0%)	0 (0%)	0.34
MACCE	48 (13%)	34 (11%)	14 (25%)	**0.005**

DD=diastolic dysfunction, MACCE=Major Adverse Cardiac and Cerebrovascular Events
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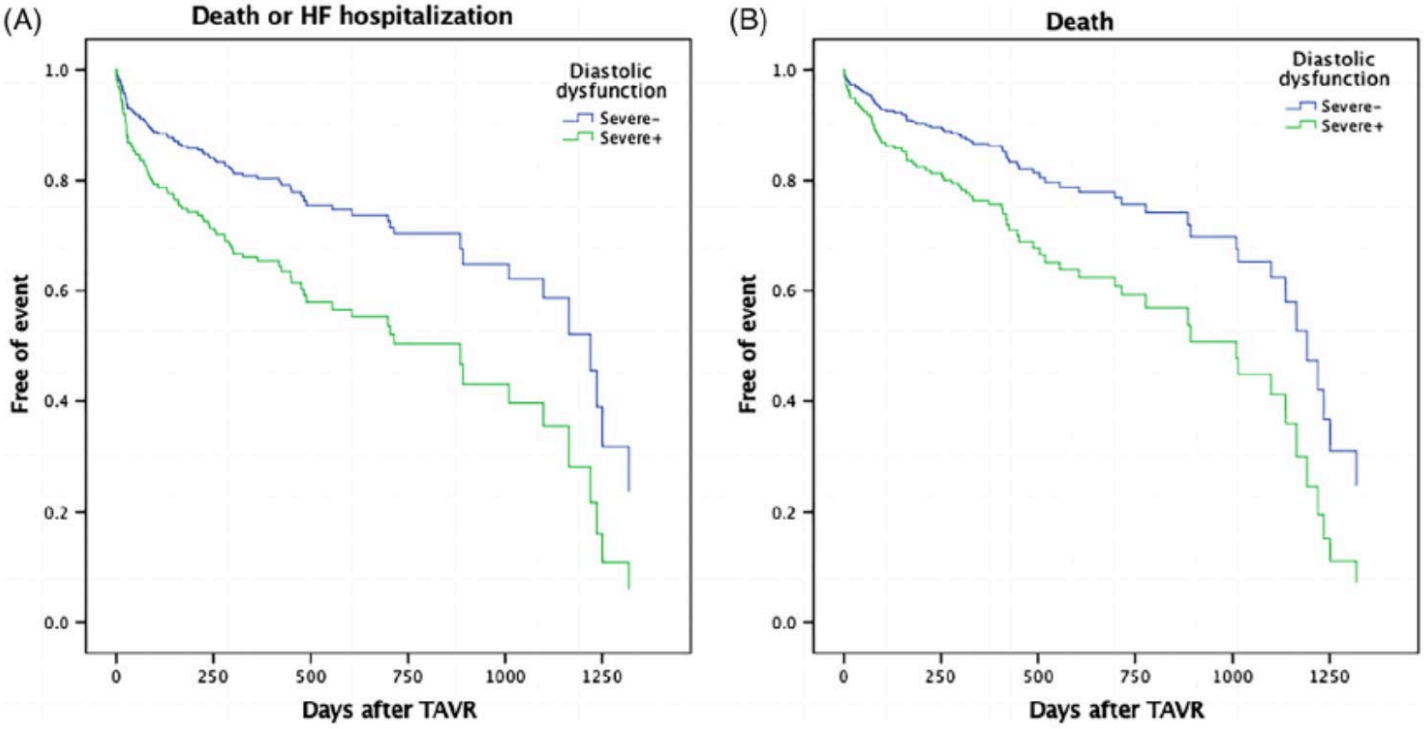

Figure 7. Cox regression curves comparing patients with severe vs. non-severe diastolic dysfunction for A) all-cause mortality or first heart failure hospitalization (log rank p-value=0.005) B) all-cause mortality (log rank p-value=0.01). TAVR=transcatheter aortic valve replacement
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4.3 Evaluation of diastolic dysfunction as an independent predictor of mortality

4.3.1 Multivariable analysis

In a multivariable analysis that included predictors of the primary outcome measure and pertinent structural variables (including pulmonary artery systolic pressure), only STS score remained as an independent predictor of the outcome measure (HR 1.1, CI 1.05-1.15, p<0.001) **(Table 7)**.

4.3.2 Propensity score matching

A separate propensity score matching analysis produced a cohort of 102 patients with a 1:1 ratio of severe to non-severe DD using clinical and echocardiographic covariates (age, gender, LVEF, LVIDs, transaortic mean gradient, LV mass, MR, TR, PASP). Severe DD was not associated with increased risk for the primary outcome measure in the matched analysis (HR 1.07 (0.55-2.08), p=0.85). Of note, the prognostic value of PVL (≥ moderate) was not assessed given the small number of available cases.

Table 7. Univariable and Multivariable Cox-Regression Models for baseline prediction of all-cause mortality or HF hospitalization

Baseline Variable	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Severe DD	2.02 (1.23-3.30)	**0.005**	NS	NS
EF	0.98 (0.97-1.00)	0.072	NS	NS
MR grade	1.16 (1.00-1.34)	**0.048**	NS	NS
TR grade	1.07 (0.88-1.30)	0.512	NS	NS
PA pressure *	1.01 (1.00-1.03)	0.058	NS	NS
LF-LG AS	1.55 (0.82-2.92)	0.18	N/A	N/A
Cr	1.31 (1.09-1.57)	**0.004**	NS	NS
COPD	1.00 (0.81-1.26)	0.94	N/A	N/A
Stroke	1.03 (0.70-1.52)	0.87	N/A	N/A
STS score	1.09 (1.06-1.13)	**<0.001**	1.1 (1.05-1.15)	**<0.001**

COPD=chronic obstructive pulmonary disease, Cr=creatinine, DD=diastolic dysfunction, HF=heart failure, LF-LG AS=low-flow, low-gradient aortic stenosis, LVEF=left ventricular ejection fraction, MR=mitral regurgitation, PASP=pulmonary artery systolic pressure, STS=Society of Thoracic Surgeons

* Derived from echocardiography

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4.4 Secondary analyses for paravalvular leak

4.4.1 Outcomes in the setting of paravalvular leak and diastolic dysfunction

In this secondary analysis (22), 146 patients were included and DD was evaluated using a modified ASE/EACVI algorithm. Forty patients (27%) had mild, 68 (47%) moderate and 38 (26%) severe DD. Post-TAVR AI was at least mild in 57 (39%) patients and more than mild AI in 16 (11%) (Main analysis PVL definition of at least moderate post-TAVR AI was not used here).

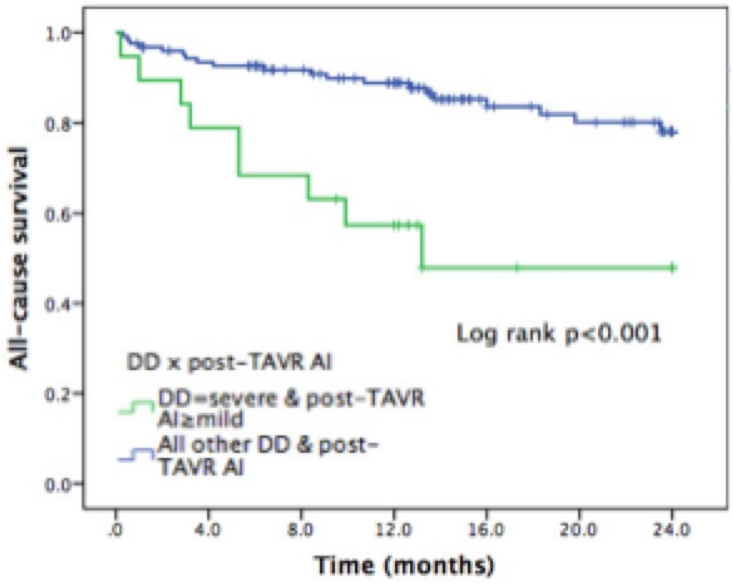
Patients with severe DD who developed post-TAVR AI ≥mild had increased mortality compared to all other patients (HR 3.89, CI 1.76–8.6, p=0.001, **Figure 8 top**) even after adjusting for post-TAVR AI, baseline AI, grade of DD, MR, LVEF, mean PA pressure, renal function, history of stroke, age and gender. Even baseline moderate-to-severe DD with post-TAVR AI ≥mild was also associated with increased all-cause mortality (HR 2.52, CI 1.22-5.23, p=0.013, **Figure 8 down**). However, this association did not remain significant after adjusting for post-TAVR AI.

Diastolic function changes and LV remodeling

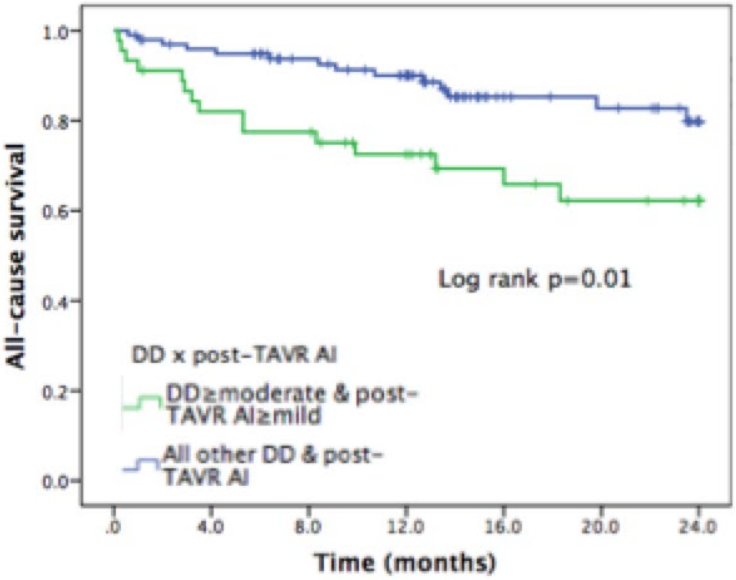
In another secondary analysis (89) 99 patients with available echocardiograms at baseline and 1-year after TAVR were analyzed to study the impact of PVL on LV remodeling and DD. PVL was defined as either new mild paravalvular regurgitation post-TAVR or moderate/severe paravalvular regurgitation post-TAVR regardless of whether preexisting or new. DD was not graded, and echocardiographic indices were used as continuous variables. Results are shown in **Table 8.**

When comparing diastolic function indices in terms of E/A and S/D, patients without PVL had more favorable diastolic function changes at 1-year (0.97 ± 0.50 vs. 1.35 ± 0.73, p=0.03 and 1.16 ± 0.37 vs. 0.81 ± 0.31, p=0.002 respectively). These patients also had more favorable LV remodeling compared to patients with PVL, as seen by the significant reduction in interventricular wall and posterior wall thickness, as well as LV mass (p<0.001 for both). LVEF and stroke volume index also improved significantly in patients without PVL (p<0.001 and p=0.046 respectively). Right ventricular systolic function also significantly improved in

patients without PVL (TAPSE from 14 ± 14 mm to 18 ± 8 mm, Δ= 4 ± 14 mm, p=0.018), whereas it remained unchanged in patients with PVL (TAPSE from 13 ± 12 mm to 11 ± 14 mm, Δ=-3 ± 2 mm, p=0.63). GLS improved significantly at 1-year regardless of PVL (p=0.016 and p=0.01 for patients without vs. with PVL respectively).



No at risk							
DD=severe& post-TAVR AI≥mild	19	15	13	8	4	3	2
All other DD&post-TAVR AI	123	107	95	72	51	40	17



No at risk							
DD≥moderate& post-TAVR AI≥mild	97	85	75	55	35	28	11
All other DD&post-TAVR AI	44	36	32	24	19	15	7

Figure 8. Survival curves for patients with severe baseline diastolic dysfunction (up) and mild or more post-TAVR AI and severe moderate or more diastolic dysfunction and mild or more post-TAVR AI (down). Results from a secondary analysis of the doctoral study. For the vast majority of patients, AI was synonymous to paravalvular leak. Diastolic dysfunction classified based on a modified ASE/EACVI algorithm.

AI=aortic insufficiency, DD=diastolic dysfunction, TAVR=transcatheter aortic valve replacement
(Permission from Kampaktsis et. al Catheter Cardiovasc Interv. 2017 Feb 15;89(3):445-451.

Table 8. LV remodeling and function 1-year post-TAVR stratified by paravalvular leak ^

	Paravalvular leak – N=84				Paravalvular leak + N=15				
	Baseline	1 year	Δ	p	Baseline	1 year	Δ	p	p *
Aortic valve mean gradient (mmHg)	51 ± 15	12 ± 4	-39 ± 14	<0.001	56 ± 17	11 ± 4	-44 ± 18	<0.001	0.48
Aortic valve peak velocity (m/s)	4.6 ± 0.7	2.4 ± 0.4	-2.3 ± 0.7	<0.001	4.9 ± 0.6	2.4 ± 0.3	-2.5 ± 0.7	<0.001	0.80
Aortic valve area (cm2)	0.72 ± 0.18	1.73 ± 0.38	1.0 ± 0.4	<0.001	0.72 ± 0.12	1.86 ± 0.39	1.1 ± 0.3	<0.001	024
LVEF (%)	54 ± 13	58 ± 10	4 ± 10	**<0.001**	55 ± 15	57 ± 12	2 ± 13	0.63	0.86
Stroke volume indexed (ml/m2)	42 ± 11	44 ± 10	3 ± 11	**0.046**	41 ± 9	46 ± 11	4 ± 8	0.06	0.34
LV end-diastolic diameter (cm)	5.3 ± 0.7	5.3 ± 0.7	-0.1 ± 0.7	0.36	5.4 ± 0.6	5.5 ± 0.8	0.1 ± 0.5	0.52	0.28
LV end-systolic diameter (cm)	3.8 ± 0.8	3.7 ± 0.8	-0.2 ± 0.7	0.12	3.8 ± 0.9	3.8 ± 1.0	0.01 ± 0.7	0.97	0.47
LV posterior wall thickness (cm)	0.9 ± 0.1	0.8 ± 0.1	-0.1 ± 0.1	**<0.001**	0.9 ± 0.1	0.9 ± 0.2	-0.03 ± 0.1	0.24	0.21
Interventricular septum thickness (cm)	1.0 ± 0.2	0.9 ± 0.1	-0.1 ± 0.1	**<0.001**	1.0 ± 0.3	0.9 ± 0.1	-0.1 ± 0.3	0.16	0.11
LV mass indexed (g/m2)	108 ± 27	95 ± 24	-13 ± 24	**<0.001**	113 ± 24	106 ± 22	-8 ± 27	0.32	0.08
Left atrial volume indexed (ml/m2)	47 ± 13	46 ± 14	-0.1 ± 1.5	0.93	53 ± 14	55 ± 18	3 ± 11	0.37	**0.04**
RVSP (mmHg)	44 ± 14	40 ± 13	-4.0 ± 12	0.12	52 ± 18	46 ± 11	-5 ± 12	0.15	0.10
GLS (%)	-12.9 ± 6.2	-14.7 ± 5.7	-1.8 ± 7	**0.016**	-9.9 ± 5.2	-14.1 ± 5.4	-4 ± 5	**0.01**	0.69
E/A	1.12 ± 0.76	0.97 ± 0.50	-0.2 ± 0.8	0.11	1.25 ± 0.72	1.35 ± 0.73	0.1 ± 0.6	0.55	**0.03**
E/e’	25 ± 15	25 ± 14	-1 ± 14	0.75	27 ± 13	27 ± 15	-0.3 ± 6	0.85	0.59
e’ lateral (cm/s)	6.4 ± 2.7	6.8 ± 2.4	0.4 ± 2.4	0.15	7.6 ± 3.5	7.5 ± 2.7	-0.1 ± 2	0.85	0.30
e’ medial (cm/s)	5.1 ± 2.0	5.0 ± 1.8	-0.1 ± 1.8	0.70	4.7 ± 1.6	5.2 ± 1.5	0.5 ± 1.8	0.34	0.88
S/D	0.97 ± 0.80	1.16 ± 0.37	0.2 ± 0.9	0.19	1.30 ± 0.69	0.81 ± 0.31	-0.5 ± 0.6	0.08	**0.002**
TAPSE (mm)	14 ± 12	18 ± 8	4 ± 14	**0.018**	13 ± 12	11 ± 14	-3 ± 2	0.63	0**.011**

GLS=global longitudinal strain, E/A=peak transmitral early to late velocity ratio, e’=peak tissue Doppler velocity at mitral annulus, LVEF=left ventricular ejection fraction, RVSP=right ventricular systolic pressure, S/D=peak systolic to diastolic pulmonary flow velocity ratio, TAPSE=tricuspid annular plane systolic excursion

^ Defined as either new mild paravalvular regurgitation post-TAVR or moderate/severe paravalvular regurgitation post-TAVR regardless of whether preexisting or new * Comparing patients with vs. without paravalvular leak at 1 year after TAVR
(Permission from Kampaktsis et al. Future Cardiol. 2021 Mar;17(2):337-345)

5. STUDY SPECIFIC PART / DISCUSSION

The key findings of this doctoral study can be summarized as follows: i) Non-invasive evaluation DD is not straightforward in the TAVR population and the application of the ASE/EACVI guidelines algorithm was not clinically meaningful in our cohort ii) DD is present in patients with symptomatic, severe AS undergoing TAVR and does not require a formal diagnostic step iii) The majority of TAVR patients in our cohort had moderate or severe MAC. DD evaluation has to be appropriately adjusted for as MAC excludes the use of Tissue Doppler imaging iv) By excluding patients with prosthetic mitral valves, moderate or more mitral stenosis and atrial fibrillation, we showed that severe DD, as defined by elevated LVEDP, is associated with a two-fold increase in mortality or HF hospitalization after TAVR v) In a multivariable analysis and a propensity score matching analysis, severe DD was not a predictor of the primary outcome independently of other predictors such as PA pressure and STS score vi) In secondary analyses, severe DD was an independent predictor of mortality in patients who developed even mild PVL after TAVR. Hindered LV remodeling and residual DD was noted 1-year after TAVR in these patients.

5.1 Evaluation of diastolic dysfunction in the TAVR population

As discussed in the Review Section (Section 2), DD undoubtedly develops in AS secondary to LVH and MF, both of which are the LV consequences of increased afterload (1). In addition, patients with valvular AS typically have advanced age, higher rates of hypertension, renal failure, coronary artery disease and diabetes, which can independently contribute to DD (88, 90, 91). Regardless of its etiology, our review revealed extensive evidence from retrospective studies that DD may be associated with worse outcomes after valve replacement (**Tables 1 and 2**). Of note, most of the evidence in the TAVR population was published when the current doctoral study was ongoing. The first step towards the evaluation of DD as predictor of worse outcomes however, is its proper echocardiographic evaluation, which remains challenging.

A recent study by Asami et al. (49) applied the latest (2016) ASE/EACVI guidelines algorithm to evaluate DD in patients undergoing TAVR. Two points can be made about this approach: First, MAC, a common finding in

patients with AS (92), was not taken into account. In the presence of moderate or severe MAC, the ASE/EACVI guidelines state that DD evaluation cannot rely on Tissue Doppler imaging, given that the calcified annular excursion that significantly affects tissue velocities (37, 93). This means that e' and E/e' cannot be used and therefore the ASE/EACVI algorithm is not applicable, as it is heavily based on these variables (**Figure 4**). This brings a second point: the ASE/EACVI algorithm for the diagnosis of DD was created for the general population with normal LVEF and suspected DD. Patients with severe AS that undergo TAVR are symptomatic, therefore DD is already present on clinical grounds and diagnosing it is redundant. A more direct and simplified approach would be to grade the severity of DD based on elevated LVEDP as suggested by the ASE/EACVI algorithm for patients with established DD or decreased LVEF. This one-step approach was also followed by Ong et al. in their very recent study on DD in the PARTNER 2 trial (50). Notably, the key variable for evaluating increased LVEDP in that algorithm is E/A, which is independent of Tissue Doppler imaging and therefore applicable to patients with moderate or severe MAC (87).

In this matter, we first verified the high frequency of moderate-to-severe MAC in our TAVR cohort (58%). This is not surprising because AS is a known a risk factor for degenerative calcification of the mitral annulus: the chronically elevated LV systolic pressure results in excess annular tension and subsequent annulus degeneration (94, 95). In addition, risk factors for MAC such as advanced age and atherosclerosis are highly prevalent in the TAVR populations. In contrast to the PARTNER 2 trial study where MAC was not taken into consideration for the evaluation of DD (50), we subsequently detected severe DD using an E/A cutoff that has been validated by Abudiab et al. to correlate well with increased LVEDP in patients with significant MAC (87). We note that in the study by Abudiab et al., isovolumic relaxation time (IVRT) was used as a secondary variable. Unfortunately, this variable was not available in a significant percentage of our cohort and therefore could not be used for classification. However, E/A ratio has been identified as an important predictor of worse outcomes even in different populations (86) and holds a central role in the grading of DD per the 2016 ASE/EACVI

guidelines. IVRT has the advantage of applicability in patients with atrial fibrillation (76) and mitral stenosis (96), conditions that were excluded in this study.

5.2 Diastolic dysfunction as a predictor of worse outcomes after TAVR

Our primary analysis used a simplified DD evaluation that took into account the presence of MAC and confirmed that baseline severe DD is associated with increased rates of mortality or HF hospitalization after TAVR. This parallels the results of other studies (**Table 2**) and in particular the studies by Asami et al. and Ong et al (49, 50). The issue, however, of whether severe DD is an independent predictor of outcomes is very important and requires attention. First, DD evaluation is dependent on loading conditions, particularly mitral valve disease (28, 58) and is associated with pulmonary hypertension (97). Pulmonary hypertension, in particular, is a known predictor of mortality in TAVR (98, 99) and was not adjusted for by Asami et al and Ong et al. We performed a multivariable (**Table 7**) as well as a propensity-matched cohort based on pertinent echocardiographic covariates that included pulmonary hypertension for the first time. Neither of these analyses revealed an association between severe DD and the outcome measure, suggesting that the impact of advanced DD is not independent of other comorbidities including pulmonary hypertension. Furthermore, patients undergoing TAVR tend to be elderly, often have poor baseline functional status, higher rates of comorbidities including renal failure, diabetes and more advanced MF (24), characteristics that are associated with both worse outcomes and more advanced degrees of DD (9, 14). Therefore, the true impact of DD has to be carefully examined independently of other comorbidities.

Whereas MF is not yet routinely evaluated in patients with aortic stenosis, well-established tools such as the STS score captures the clinical risk associated with TAVR and can easily be obtained from clinical variables. Our multivariable analysis showed severe baseline DD was not an independent predictor of increased rate of all-cause mortality or heart failure hospitalization. Instead, the STS score emerged as the only independent predictor of worse outcome measure after TAVR (**Table 7**). This is in contrast to the results of previously

published studies on outcomes of patients with AS and DD. However, we do note that all previous studies on the topic have been retrospective and thus prone to bias (**Table 2**). On the other hand, both the EuroSCORE (100) and the STS score have been extensively used to define clinical risk in TAVR patients. The STS score in particular, developed for the prediction of early (30-day) mortality after SAVR, was used with success in the early PARTNER trials (101) and is currently endorsed by ACC/STS as the preferred risk assessment tool prior to TAVR (102). Similar to the EuroSCORE, it integrates multiple cardiac (including history of prior cardiac surgeries) and systemic (including body size, functional status and medical comorbidities) parameters.

5.3 Impact of paravalvular leak on patients with pre-existing diastolic dysfunction

Although our results suggest that severe DD may not be an independent predictor of outcomes after TAVR, the results of our secondary analysis suggest that severe DD may have a particularly deleterious and independent effect on survival of patients who develop PVL (**Figure 8**). Despite its decreasing frequency with newer generation transcatheter heart valves, PVL remains an important complication after TAVR and our findings could have important clinical implications.

Previously, even mild PVL was associated with increased mortality (25, 103). Recent studies have shown that more than mild PVL, particularly when not previously present, is associated with higher short to medium-term mortality (104, 105). The finding that acute or persistent post-TAVR AI has a negative impact on outcomes suggests that acute or persistent volume overload of a LV with decreased compliance and DD from chronic pressure overload can have detrimental effects (27, 106). As the degree of LV non-compliance and DD varies in patients with severe AS, similar adverse hemodynamics could theoretically be caused by a smaller degree of acute AI in a LV with greater degree of DD. In our secondary analysis, PVL ≥mild was associated with increased mortality. Moreover, the interaction between severe baseline DD and PVL ≥mild was associated with increased mortality even after adjusting for baseline DD, AI, PVL, age, gender, LVEF, PA pressure and other predictors of mortality. In another secondary analysis (**Table 8**) (89) as well as in a preliminary analysis (107) we also showed that in patients with new or persistent PVL, LV remodeling is hindered and DD persists. These

findings support the hypothesis of increased mortality from adverse hemodynamics caused by the combination of baseline DD and PVL after TAVR.

These results could have significant clinical implications. The evaluation of baseline DD may prove to be a useful way of identifying patients who are at particularly high risk for worse outcomes if PVL develops. These patients could be treated with bioprosthetic valves that are associated with lesser degrees of PVL for primary prevention. If PVL ≥mild develops, the risk-benefit ratio may suggest that additional steps, such as post-deployment re-expansion of the bioprosthetic valve, are warranted to eliminate PVL.

5.4 Limitations

The current study has several limitations. First, our cohort comprised of a modest number of patients with a mean follow up time of 13 months. Resolution of LVH and MF, which are the downstream mechanisms that sustain DD, require a process of LV remodeling that lags years behind aortic valve replacement (10, 11) and thus the long-term affect of severe DD may not have been captured in our study. Secondly, as the majority of patients had significant MAC, we used the E/A ratio to classify patients with severe DD / increased LVEDP, a method that has not been extensively validated in other cohorts. However, to our knowledge, it represents the simplest and most validated method of assessing DD in the presence of MAC. Moreover, we did not evaluate DD in patients with atrial fibrillation, who were excluded from this study. Finally, interobserver or intraobserver error evaluation was not performed.

In regards to our secondary analyses, these are notably limited by the small study subgroups that lack statistical power, as well as by the different definitions of PVL that were used compared to our primary analysis. DD was not graded using the same scheme in the analysis that studied remodeling; instead, indices of DD were used as continuous variables.

6. CONCLUSIONS

DD represents a main underlying pathophysiologic mechanism for the development of symptoms in severe AS, which mark the onset of increased mortality in these patients. The current doctoral study is one of the recent studies that examined the value of DD as a predictor of worse outcomes in patients with severe AS undergoing TAVR. We applied a simplified algorithm to evaluate DD that takes into account for the first time the increased prevalence of MAC. Our results confirmed that severe AS is associated with increased mortality or HF hospitalization. However, severe DD failed to emerge as an independent risk factor when pulmonary hypertension, STS score and other known predictors of mortality were taken into account. We conclude that severe DD is associated with worse outcomes, however its importance as a predictor may lag behind pulmonary hypertension (a downstream pathophysiologic result of DD) and other comorbidities represented in the STS score. Severe DD may lead to increased mortality in patients who develop even mild PVL. Therefore, we recommend that DD be evaluated in all patients being considered for TAVR to assist with clinical decision making to reduce PVL, if such a complication occurs. Further well-designed studies are required to confirm the prognostic role of DD in this group of TAVR patients.

FIGURE LEGENDS

Figure 1. Normal diastole can be broken into 2 phases, relaxation and filling, each comprising of different, overlapping sub-phases, and results in normal LVEDP. Relaxation is characterized by the time constant of relaxation (τ) and myocardial stiffness by the stiffness constant, or the derivate of pressure over volume (top). Bottom left, LV, LAD and Ao pressures measured invasively over time during over the cardiac cycle along with sub-phases of relaxation and filling. Bottom right, overlap of pressures and Doppler signals of diastole.

Figure 2. Abnormalities in either LV relaxation or stiffness result in diastolic dysfunction, the hallmark of which is elevated LVEDP and subsequently LA pressures. Top, invasive LV and LA pressures. Bottom, transmitral flow patters using Doppler echocardiography.

Figure 3. Laplace equation results in increased afterload/wall stress in the presence of high LV systolic pressure (top). Afterload/wall stress is maintained with compensatory LV hypertrophy and increased wall thickness (bottom).

Figure 4. ASE/EACVI echo-based algorithm for (A) diagnosis and (B) grading of diastolic dysfunction in the general population.

Figure 5. Change in diastolic dysfunction grade between baseline and (left) 30-days after TAVR in the PARTNER 2 trial (Permission from Ong et al. (J Am Coll Cardiol 2020;76:2940–51), (right) 6-months and 1-year after TAVR (N=242) (Permission from Muratori et al. Eur Heart J Cardiovasc Imaging 2016;11:1269-78).

Figure 6. E/e' ratio increases with increased presence of myocardial fibrosis regardless of AS severity. In this prospective observational study, cardiac magnetic resonance imaging was used to evaluate myocardial fibrosis in patients with different degrees of AS and in controls (healthy volunteers). Patients were classified as having i) normal myocardium (n=80), ii) extracellular expansion, an early reversible form of myocardial fibrosis evaluated by extracellular volume expansion indexed above a cutoff in this study (n=38) and iii) replacement fibrosis, evaluated by presence of mid-wall late gadolinium enhancement (n=43). Echocardiography was used to measure E/e' ratios as a marker of diastolic dysfunction. E/e' ratio was significantly different among the groups with more advanced myocardial fibrosis correlating with higher E/e' and thus worse diastolic dysfunction.

Figure 7. Cox regression curves comparing patients with severe vs. non-severe diastolic dysfunction for A) all-cause mortality or first heart failure hospitalization (log rank p-value=0.005) B) all-cause mortality (log rank p-value=0.01). TAVR=transcatheter aortic valve replacement

Figure 8. Survival curves for patients with severe baseline diastolic dysfunction (up) and mild or more post-TAVR AI and severe moderate or more diastolic dysfunction and mild or more post-TAVR AI (down). Results from a secondary analysis of the doctoral study. For the vast majority of patients, AI was synonymous to paravalvular leak. Diastolic dysfunction classified based on a modified ASE/EACVI algorithm.

REFERENCES

1. Carabello BA, Paulus WJ. Aortic stenosis. Lancet. 2009;373(9667):956-66.
2. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. N Engl J Med. 2014;371(8):744-56.
3. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol. 2011;8(3):162-72.
4. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.
5. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012;366(18):1696-704.
6. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, Deeb GM, Thourani VH, Cohen DJ, Desai N, Kirtane AJ, Fitzgerald S, Michaels J, Krohn C, Masoudi FA, Brindis RG, Bavaria JE. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020;76(21):2492-516.
7. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG, investigators Pt. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet (London, England). 2015;385(9986):2477-84.
8. Brennan JM, Edwards FH, Zhao Y, O'Brien SM, Douglas PS, Peterson ED, Team DEtIDAEAVRDAR. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. Circulation. 2012;126(13):1621-9.
9. Kampaktsis PN, Kokkinidis DG, Wong S-C, Vavuranakis M, Skubas NJ, Devereux RB. The role and clinical implications of diastolic dysfunction in aortic stenosis. Heart (British Cardiac Society). 2017.
10. Beach JM, Mihaljevic T, Rajeswaran J, Marwick T, Edwards ST, Nowicki ER, Thomas J, Svensson LG, Griffin B, Gillinov AM, Blackstone EH. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. The Journal of thoracic and cardiovascular surgery. 2014;147(1):362-9.e8.
11. Yarbrough WM, Mukherjee R, Ikonomidis JS, Zile MR, Spinale FG. Myocardial remodeling with aortic stenosis and after aortic valve replacement: mechanisms and future prognostic implications. The Journal of thoracic and cardiovascular surgery. 2012;143(3):656-64.
12. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. Journal of the American College of Cardiology. 2012;60(19):1845-53.
13. Hirji S, Kaneko T, McGurk S, Cherkasky O, Ahmed H, Wong SC, Salemi A, Kampaktsis P, Kaple R, Forrest J, Kini AS, Malarczyk A, Kiehm S, Percy E, Harloff M,

Yazdchi F, Shah P, Tang G. MULTICENTER EVALUATION OF QUALITY OF LIFE IN PATIENTS WITH PARADOXICAL LOW-FLOW, LOW-GRADIENT UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT (PLO-FLOW TAVR STUDY). Journal of the American College of Cardiology. 2020;75(11_Supplement_1):1488-.
14. Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, Jenkins W, Koo M, Mirsadraee S, White AC, Japp AG, Prasad SK, Semple S, Newby DE, Dweck MR. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. JACC Cardiovascular imaging. 2016.
15. Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, Beer M, Gattenlohner S, Voelker W, Ertl G, Strotmann JM. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation. 2009;120(7):577-84.
16. Papanastasiou CA, Kokkinidis DG, Kampaktsis PN, Bikakis I, Cunha DK, Oikonomou EK, Greenwood JP, Garcia MJ, Karamitsos TD. The Prognostic Role of Late Gadolinium Enhancement in Aortic Stenosis: A Systematic Review and Meta-Analysis. JACC Cardiovascular imaging. 2020;13(2 Pt 1):385-92.
17. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77(4):450-500.
18. Tan TC, Flynn AW, Chen-Tournoux A, Rudski LG, Mehrotra P, Nunes MC, Rincon LM, Shahian DM, Picard MH, Afilalo J. Risk Prediction in Aortic Valve Replacement: Incremental Value of the Preoperative Echocardiogram. Journal of the American Heart Association. 2015;4(10):e002129.
19. Gjertsson P, Caidahl K, Bech-Hanssen O. Left ventricular diastolic dysfunction late after aortic valve replacement in patients with aortic stenosis. The American Journal of Cardiology. 2005;96(5):722-7.
20. Bernard F, Denault A, Babin D, Goyer C, Couture P, Couturier A, Buithieu J. Diastolic dysfunction is predictive of difficult weaning from cardiopulmonary bypass. Anesthesia and Analgesia. 2001;92(2):291-8.
21. Rassi AN, Aljaroudi W, Naderi S, Alraies MC, Menon V, Rodriguez L, Grimm R, Griffin B, Jaber WA. Exercise stress echocardiography in patients with aortic stenosis: impact of baseline diastolic dysfunction and functional capacity on mortality and aortic valve replacement. Cardiovascular diagnosis and therapy. 2013;3(4):205-15.
22. Kampaktsis PN, Bang CN, Chiu Wong S, Skubas NJ, Singh H, Voudris K, Baduashvili A, Pastella K, Swaminathan RV, Kaple RK, Minutello RM, Feldman DN, Kim L, Hriljac I, Lin F, Bergman GS, Salemi A, Devereux RB. Prognostic Importance of Diastolic Dysfunction in Relation to Post Procedural Aortic Insufficiency in Patients Undergoing Transcatheter Aortic Valve Replacement. Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions. 2016.
23. Muratori M, Fusini L, Tamborini G, Gripari P, Delgado V, Marsan NA, Ghulam Ali S, Barbier P, Bartorelli AL, Alamanni F, Pepi M. Sustained favourable haemodynamics 1 year after TAVI: improvement in NYHA functional class related to improvement of left ventricular diastolic function. European Heart Journal Cardiovascular Imaging. 2015.
24. Barone-Rochette G, Pierard S, Ravenstein CDMd, Seldrum S, Melchior J, Maes F, Pouleur AC, Vancraeynest D, Pasquet A, Vanoverschelde JL, Gerber BL. Prognostic

significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. Journal of the American College of Cardiology. 2014;64(2):144-54.
25. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB, Investigators PT. Two-year outcomes after transcatheter or surgical aortic-valve replacement. The New England journal of medicine. 2012;366(18):1686-95.
26. Hayashida K, Lefevre T, Chevalier B, Hovasse T, Romano M, Garot P, Bouvier E, Farge A, Donzeau-Gouge P, Cormier B, Morice MC. Impact of post-procedural aortic regurgitation on mortality after transcatheter aortic valve implantation. JACCCardiovascular interventions. 2012;5(12):1247-56.
27. Gotzmann M, Lindstaedt M, Mugge A. From pressure overload to volume overload: aortic regurgitation after transcatheter aortic valve implantation. American Heart Journal. 2012;163(6):903-11.
28. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. Journal of the American College of Cardiology. 1997;30(1):8-18.
29. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, Keulenaer GD, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. European heart journal. 2007;28(20):2539-50.
30. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. Circulation. 1984;69(5):855-65.
31. Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. Circulation. 1989;79(4):744-55.
32. Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. The Journal of clinical investigation. 1976;58(3):751-60.
33. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. American journal of physiologyHeart and circulatory physiology. 2005;289(2):H501-12.
34. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschope C. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007;116(6):637-47.
35. Kampaktsis PN, Vavuranakis M. Diastolic Function Evaluation: What Can We Learn From Machine Learning? JACC Cardiovasc Imaging. 2020;13(1 Pt 2):336-7.
36. Chapman CB, Ewer SM, Kelly AF, Jacobson KM, Leal MA, Rahko PS. Classification of left ventricular diastolic function using American Society of Echocardiography

Guidelines: agreement among echocardiographers. Echocardiography (Mount Kisco, NY). 2013;30(9):1022-31.
37. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2016;29(4):277-314.
38. Westenberg JJ. CMR for Assessment of Diastolic Function. Current cardiovascular imaging reports. 2011;4(2):149-58.
39. Villari B, Vassalli G, Betocchi S, Briguori C, Chiariello M, Hess OM. Normalization of left ventricular nonuniformity late after valve replacement for aortic stenosis. The American Journal of Cardiology. 1996;78(1):66-71.
40. Villari B, Vassalli G, Monrad ES, Chiariello M, Turina M, Hess OM. Normalization of diastolic dysfunction in aortic stenosis late after valve replacement. Circulation. 1995;91(9):2353-8.
41. Ikonomidis I, Tsoukas A, Parthenakis F, Gournizakis A, Kassimatis A, Rallidis L, Nihoyannopoulos P. Four year follow up of aortic valve replacement for isolated aortic stenosis: a link between reduction in pressure overload, regression of left ventricular hypertrophy, and diastolic function. Heart (British Cardiac Society). 2001;86(3):309-16.
42. Bech-Hanssen O, Caidahl K, Wall B, Myken P, Larsson S, Wallentin I. Influence of aortic valve replacement, prosthesis type, and size on functional outcome and ventricular mass in patients with aortic stenosis. The Journal of thoracic and cardiovascular surgery. 1999;118(1):57-65.
43. Ding W-h, Lam Y-y, Kaya MG, Li W, Chung R, Pepper JR, Henein MY. Echocardiographic predictors of left ventricular functional recovery following valve replacement surgery for severe aortic stenosis. International Journal of Cardiology. 2008;128(2):178-84.
44. Lamb HJ, Beyerbacht HP, de Roos A, van der Laarse A, Vliegen HW, Leujes F, Bax JJ, van der Wall EE. Left ventricular remodeling early after aortic valve replacement: differential effects on diastolic function in aortic valve stenosis and aortic regurgitation. Journal of the American College of Cardiology. 2002;40(12):2182-8.
45. Gjertsson P, Caidahl K, Farasati M, Oden A, Bech-Hanssen O. Preoperative moderate to severe diastolic dysfunction: a novel Doppler echocardiographic long-term prognostic factor in patients with severe aortic stenosis. The Journal of thoracic and cardiovascular surgery. 2005;129(4):890-6.
46. Seo J-S, Jang M-K, Lee E-Y, Yun S-C, Kim D-H, Song J-M, Kang D-H, Song J-K. Evaluation of left ventricular diastolic function after valve replacement in aortic stenosis using exercise Doppler echocardiography. Circulation Journal: Official Journal of the Japanese Circulation Society. 2012;76(12):2792-8.
47. Mehdipoor G, Chen S, Chatterjee S, Torkian P, Ben-Yehuda O, Leon MB, Stone GW, Prince MR. Cardiac structural changes after transcatheter aortic valve replacement: systematic review and meta-analysis of cardiovascular magnetic resonance studies. J Cardiovasc Magn Reson. 2020;22(1):41.
48. Sugiura A, Weber M, von Depka A, Tabata N, Shamekhi J, Al-Kassou B, Nickenig G, Werner N, Sinning JM, Sedaghat A. Outcomes of myocardial fibrosis in patients

undergoing transcatheter aortic valve replacement. EuroIntervention. 2020;15(16):1417-23.
49. Asami M, Lanz J, Stortecky S, Räber L, Franzone A, Heg D, Hunziker L, Roost E, Siontis GC, Valgimigli M, Windecker S, Pilgrim T. The Impact of Left Ventricular Diastolic Dysfunction on Clinical Outcomes After Transcatheter Aortic Valve Replacement. JACC Cardiovascular interventions. 2018;11(6):593-601.
50. Ong G, Pibarot P, Redfors B, Weissman NJ, Jaber WA, Makkar RR, Lerakis S, Gopal D, Khalique O, Kodali SK, Thourani VH, Anwaruddin S, McAndrew T, Zhang Y, Alu MC, Douglas PS, Hahn RT. Diastolic Function and Clinical Outcomes After Transcatheter Aortic Valve Replacement: PARTNER 2 SAPIEN 3 Registry. J Am Coll Cardiol. 2020;76(25):2940-51.
51. Villa E, Troise G, Cirillo M, Brunelli F, Tomba MD, Mhagna Z, Tasca G, Quaini E. Factors affecting left ventricular remodeling after valve replacement for aortic stenosis. An overview. Cardiovascular ultrasound. 2006;4:25.
52. Gavina C, Falcao-Pires I, Rodrigues J, Marinho B, Goncalves N, Lopes R, Amorim MJ, Almeida J, Pinho P, Goncalves A, Rocha-Goncalves F, Leite-Moreira A. Load independent impairment of reverse remodeling after valve replacement in hypertensive aortic stenosis patients. International journal of cardiology. 2014;170(3):324-30.
53. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart (British Cardiac Society). 2006;92(8):1022-9.
54. Rao V, Jamieson WR, Ivanov J, Armstrong S, David TE. Prosthesis-patient mismatch affects survival after aortic valve replacement. Circulation. 2000;102(19 Suppl 3):III5-9.
55. Licker M, Cikirikcioglu M, Inan C, Cartier V, Kalangos A, Theologou T, Cassina T, Diaper J. Preoperative diastolic function predicts the onset of left ventricular dysfunction following aortic valve replacement in high-risk patients with aortic stenosis. Critical Care (London, England). 2010;14(3):R101.
56. Denault AY, Couture P, Buithieu J, Haddad F, Carrier M, Babin D, Levesque S, Tardif J-C. Left and right ventricular diastolic dysfunction as predictors of difficult separation from cardiopulmonary bypass. Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie. 2006;53(10):1020-9.
57. Biner S, Rafique AM, Goykhman P, Morrissey RP, Naghi J, Siegel RJ. Prognostic value of E/E' ratio in patients with unoperated severe aortic stenosis. JACCCardiovascular imaging. 2010;3(9):899-907.
58. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. Journal of the American College of Cardiology. 1997;30(6):1527-33.
59. Okura H, Takada Y, Kubo T, Iwata K, Mizoguchi S, Taguchi H, Toda I, Yoshikawa J, Yoshida K. Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. Heart (British Cardiac Society). 2006;92(9):1248-52.
60. Hillis GS, Møller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK. Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. Journal of the American College of Cardiology. 2004;43(3):360-7.

61. Chang SA, Park PW, Sung K, Lee SC, Park SW, Lee YT, Oh JK. Noninvasive estimate of left ventricular filling pressure correlated with early and midterm postoperative cardiovascular events after isolated aortic valve replacement in patients with severe aortic stenosis. The Journal of thoracic and cardiovascular surgery. 2010;140(6):1361-6.
62. Ding W-h, Lam Y-y, Pepper JR, Kaya MG, Li W, Chung R, Henein MY. Early and long-term survival after aortic valve replacement in septuagenarians and octogenarians with severe aortic stenosis. International Journal of Cardiology. 2010;141(1):24-31.
63. Lund O, Flo C, Jensen FT, Emmertsen K, Nielsen TT, Rasmussen BS, Hansen OK, Pilegaard HK, Kristensen LH. Left ventricular systolic and diastolic function in aortic stenosis. Prognostic value after valve replacement and underlying mechanisms. European heart journal. 1997;18(12):1977-87.
64. Klein AL, Ramchand J, Nagueh SF. Aortic Stenosis and Diastolic Dysfunction: Partners in Crime. J Am Coll Cardiol. 2020;76(25):2952-5.
65. Pibarot P, Clavel MA. Management of paradoxical low-flow, low-gradient aortic stenosis: need for an integrated approach, including assessment of symptoms, hypertension, and stenosis severity. J Am Coll Cardiol. 2015;65(1):67-71.
66. Guzzetti E, Poulin A, Annabi M-S, Zhang B, Kalavrouziotis D, Couture C, Dagenais F, Pibarot P, Clavel M-A. Transvalvular Flow, Sex, and Survival After Valve Replacement Surgery in Patients With Severe Aortic Stenosis. Journal of the American College of Cardiology. 2020;75(16):1897-909.
67. Dayan V, Vignolo G, Magne J, Clavel M-A, Mohty D, Pibarot P. Outcome and Impact of Aortic Valve Replacement in Patients With Preserved LVEF and Low-Gradient Aortic Stenosis. Journal of the American College of Cardiology. 2015;66(23):2594-603.
68. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. European Heart Journal. 2010;31(3):281-9.
69. Ellims AH, Shaw JA, Stub D, Iles LM, Hare JL, Slavin GS, Kaye DM, Taylor AJ. Diffuse Myocardial Fibrosis Evaluated by Post-Contrast T1 Mapping Correlates With Left Ventricular Stiffness. Journal of the American College of Cardiology. 2014;63(11):1112-8.
70. Rommel K-P, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, Besler C, Sandri M, Lücke C, Gutberlet M, Linke A, Schuler G, Lurz P. Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology. 2016;67(15):1815-25.
71. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary Microvascular Rarefaction and Myocardial Fibrosis in Heart Failure With Preserved Ejection Fraction. Circulation. 2015;131(6):550-9.
72. Heling A, Zimmermann R, Kostin S, Maeno Y, Hein S, Devaux B, Bauer E, Klövekorn WP, Schlepper M, Schaper W, Schaper J. Increased expression of cytoskeletal, linkage, and extracellular proteins in failing human myocardium. Circulation Research. 2000;86(8):846-53.
73. Dweck MR, Joshi S, Murigu T, Alpendurada F, Jabbour A, Melina G, Banya W, Gulati A, Roussin I, Raza S, Prasad NA, Wage R, Quarto C, Angeloni E, Refice S, Sheppard M, Cook SA, Kilner PJ, Pennell DJ, Newby DE, Mohiaddin RH, Pepper J, Prasad SK. Midwall Fibrosis Is an Independent Predictor of Mortality in Patients With Aortic Stenosis. Journal of the American College of Cardiology. 2011;58(12):1271-9.

74. Kampaktsis PN, Ullal AV, Swaminathan RV, Minutello RM, Kim L, Bergman GS, Feldman DN, Singh H, Wong SC, Okin PM. Absence of electrocardiographic left ventricular hypertrophy is associated with increased mortality after transcatheter aortic valve replacement. Clinical Cardiology. 2018;41(9):1246-51.
75. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, Lucci D, Nollo G, Ravelli F. Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction: A Meta-Analysis. JACC Cardiovascular imaging. 2016.
76. Al-Omari MA, Finstuen J, Appleton CP, Barnes ME, Tsang TS. Echocardiographic assessment of left ventricular diastolic function and filling pressure in atrial fibrillation. The American Journal of Cardiology. 2008;101(12):1759-65.
77. JS eaD. Atrial fibrillation in severe aortic stenosis - association with left ventricular left atrial remodeling. IJC Heart & Vessels. 2014;http://dx.doi.org/10.1016/j.ijchv.2014.06.006.
78. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-81.
79. Douglas PS, Waugh RA, Bloomfield G, Dunn G, Davis L, Hahn RT, Pibarot P, Stewart WJ, Weissman NJ, Hueter I, Siegel R, Lerakis S, Miller DC, Smith CR, Leon MB. Implementation of echocardiography core laboratory best practices: a case study of the PARTNER I trial. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2013;26(4):348-58.e3.
80. Hahn RT, Nicoara A, Kapadia S, Svensson L, Martin R. Echocardiographic Imaging for Transcatheter Aortic Valve Replacement. Journal of the American Society of Echocardiography. 2018;31(4):405-33.
81. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. The American Journal of Cardiology. 1986;57(6):450-8.
82. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, Echocardiography ASo. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2003;16(7):777-802.
83. Kappetein AP, Head SJ, Genereux P, Piazza N, Mieghem NMv, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es GAv, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Journal of the American College of Cardiology. 2012;60(15):1438-54.
84. Kohsaka S, Jin Z, Rundek T, Boden-Albala B, Homma S, Sacco RL, Di Tullio MR. Impact of Mitral Annular Calcification on Cardiovascular Events in a Multiethnic Community. JACC: Cardiovascular Imaging. 2008;1(5):617-23.
85. Barasch E, Gottdiener JS, Larsen EKM, Chaves PHM, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and aortosclerosis

in community dwelling elderly. The Cardiovascular Health Study (CHS). American Heart Journal. 2006;151(1):39-47.
86. Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET, Fabsitz RR, Howard BV, Devereux RB. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation. 2002;105(16):1928-33.
87. Abudiab MM, Chebrolu LH, Schutt RC, Nagueh SF, Zoghbi WA. Doppler Echocardiography for the Estimation of LV Filling Pressure in Patients With Mitral Annular Calcification. JACC Cardiovascular imaging. 2017.
88. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England journal of medicine. 2010;363(17):1597-607.
89. Kampaktsis PN, Subramayam P, Sherifi I, Vavuranakis M, Siasos G, Tousoulis D, Worku B, Minutello RM, Wong SC, Devereux RB. Impact of paravalvular leak on left ventricular remodeling and global longitudinal strain 1 year after transcatheter aortic valve replacement. Future Cardiol. 2021;17(2):337-45.
90. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Bärwolf C, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjærpe T, Wachtell K, Willenheimer R. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. New England Journal of Medicine. 2008;359(13):1343-56.
91. Mottram PM, Haluska BA, Leano R, Carlier S, Case C, Marwick TH. Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease. Heart (British Cardiac Society). 2005;91(12):1551-6.
92. Kizer JR, Wiebers DO, Whisnant JP, Galloway JM, Welty TK, Lee ET, Best LG, Resnick HE, Roman MJ, Devereux RB. Mitral annular calcification, aortic valve sclerosis, and incident stroke in adults free of clinical cardiovascular disease: the Strong Heart Study. Stroke. 2005;36(12):2533-7.
93. Pellikka PA, Padang R. Diastolic Dysfunction Pre-Transcatheter Aortic Valve Replacement: Is it Too Late? JACC Cardiovascular interventions. 2018;11(6):602-4.
94. Silbiger JJ. Anatomy, mechanics, and pathophysiology of the mitral annulus. American Heart Journal. 2012;164(2):163-76.
95. Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral Annulus Calcification. Journal of the American College of Cardiology. 2015;66(17):1934-41.
96. Diwan A, Diwan A, McCulloch M, Lawrie GM, Reardon MJ, Nagueh SF. Doppler estimation of left ventricular filling pressures in patients with mitral valve disease. Circulation. 2005;111(24):3281-9.
97. Testa L, Latib A, De Marco F, De Carlo M, Fiorina C, Montone R, Agnifili M, Barbanti M, Petronio AS, Biondi Zoccai G, Ettori F, Klugmann S, Tamburino C, Brambilla N, Colombo A, Bedogni F. Persistence of Severe Pulmonary Hypertension After Transcatheter Aortic Valve Replacement: Incidence and Prognostic Impact. Circulation: Cardiovascular Interventions. 2016;9(6):e003563.
98. Alushi B, Beckhoff F, Leistner D, Franz M, Reinthaler M, Stähli BE, Morguet A, Figulla HR, Doenst T, Maisano F, Falk V, Landmesser U, Lauten A. Pulmonary Hypertension in Patients With Severe Aortic Stenosis: Prognostic Impact After

Transcatheter Aortic Valve Replacement: Pulmonary Hypertension in Patients Undergoing TAVR. JACC Cardiovascular imaging. 2018.
99. Kaple RK, Pawar S, Schoenfeld MS, Haider MA, Kampaktsis P, Baduashvili A, Wilson S, Kim L, Swaminathan R, Feldman D, Singh H, Bergman G, Minutello R, Devereux R, Salemi A, Krieger K, Horn E, Wong S-C, Lin F. IMPACT OF ETIOLOGY OF PULMONARY HYPERTENSION ON POST-PROCEDURAL MANAGEMENT AND OUTCOMES IN PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT. Journal of the American College of Cardiology. 2014;63(12):A1476.
100. Roques F. The logistic EuroSCORE. European Heart Journal. 2003;24(9):882.
101. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, Webb JG, Mack MJ, Douglas PS, Thourani VH, Babaliaros VC, Herrmann HC, Szeto WY, Pichard AD, Williams MR, Fontana GP, Miller DC, Anderson WN, Akin JJ, Davidson MJ, Smith CR, investigators Pt. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet (London, England). 2015;385(9986):2485-91.
102. Bavaria JE, Tommaso CL, Brindis RG, Carroll JD, Deeb GM, Feldman TE, Gleason TG, Horlick EM, Kavinsky CJ, Kumbhani DJ, Miller DC, Seals AA, Shahian DM, Shemin RJ, Sundt TM, Thourani VH. 2018 AATS/ACC/SCAI/STS Expert Consensus Systems of Care Document: Operator and Institutional Recommendations and Requirements for Transcatheter Aortic Valve Replacement: A Joint Report of the American Association for Thoracic Surgery, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2018.
103. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, Tarantini G, Sinning JM, Nickenig G, Capodanno D, Tamburino C, Latib A, Colombo A, Kapadia SR. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. Journal of the American College of Cardiology. 2013;61(15):1585-95.
104. Belle EV, Juthier F, Susen S, Vincentelli A, Iung B, Dallongeville J, Eltchaninoff H, Laskar M, Leprince P, Lievre M, Banfi C, Auffray JL, Delhaye C, Donzeau-Gouge P, Chevreul K, Fajadet J, Leguerrier A, Prat A, Gilard M, Teiger E, Investigators F. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation. 2014;129(13):1415-27.
105. Jerez-Valero M, Urena M, Webb JG, Tamburino C, Munoz-Garcia AJ, Cheema A, Dager AE, Serra V, Amat-Santos IJ, Barbanti M, Imme S, Briales JHA, Lawati HA, Benitez LM, Cucalon AM, Blanco BGd, Revilla A, Dumont E, Ribeiro HB, Nombela-Franco L, Bergeron S, Pibarot P, Rodes-Cabau J. Clinical impact of aortic regurgitation after transcatheter aortic valve replacement: insights into the degree and acuteness of presentation. JACCCardiovascular interventions. 2014;7(9):1022-32.
106. Carabello BA, Puskas JD. Transcatheter aortic valve replacement: the leak goes on. JACCCardiovascular interventions. 2014;7(9):1033-5.
107. Kampaktsis PN, Ullal AV, Minutello RM, Feldman DN, Swaminathan RV, Voudris K, Baduashvili A, Pastella K, Pawar S, Kaple RK, Vavuranakis M, Bergman GS, Skubas NJ, Lin F, Salemi A, Devereux RB, Chiu Wong S. Impact of Paravalvular Aortic Insufficiency on

Left Ventricular Remodeling and Mortality after Transcatheter Aortic Valve Replacement. The Journal of Heart Valve Disease. 2016;25(3):301-8.

Supplemental

Table of Contents

Supplemental Table 2: Change in DD in patients with AS after AVR

Author, Year (N)	AVR	DD evaluation	DD variables	Grading	Change in DD after AVR
Villari, 1995 (12)	SAVR	Cath	Peak filling rate early and late, and the myocardial stiffness constant (b)	No	**Baseline** / **Early (22m)** / **Late (81m)** PFR Early: 402±111 / 372±83 / 330 ±132 PFR Late: 370±107 / 332 ±121 / 276±123 b: 21±6 / 30±7 / 11 ±4
Villari, 1996 (10)	SAVR	Cath	Peak filling rate, myocardial stiffness constant (b)	No	**Baseline** / **Early (21m)** / **Late(89m)** PFR: 384 ±95 / 388±57 / 353 ±79 b: 19±5 / 28±7 / 10±3 * * P<0.001 early vs. late after AVR
Odd Bech Hanssen, 1999 (239)	SAVR	TTE	E/A, S/D, DT	None, mild to moderate, severe	**Baseline** / **2 years** **Mechanical Valves** E/A: 1.0 ± 0.74 / 1.02 ± 0.31 P=0.4 S/D: 1.41 ± 0.64 / 1.26 ± 0.33 P<0.01 DT: 239 ± 99.5 / 238 ± 72.5 P=0.21 **Biologic prosthetic valves** E/A: 1.0 ± 0.57 / 0.94 ± 0.3 P=0.4 S/D: 1.36 ± 0.58 / 1.29 ± 0.53 P=0.15 DT: 268 ± 120 / 241 ± 68 P=0.15
McKenney, 1999 (14)	SAVR	TTE	LVED area at similar pulmonary arterial wedge pressure, DT	No	**Baseline** / **Postprocedural** LVED area: 17.9 ±1.7 / 12.1 ±1.2 P< 0.0001 DT: 260 ±30 / 108 ±4 P<0.0001
Ikonomidis, 2001 (41)	SAVR	TTE	E/A, IVRT, DT	No	**Baseline** / **2w after SAVR** / **4y after SAVR** DT: 241 ±102 / 205 ±77 / 226 ±96 * IVRT: 93 ± 20 / 78 ±12 / 81 ±15 * E/A: 1.05 ±0.5 / 1.0 ±0.5 / 91 ±0.3 * P<0.05 baseline vs. 4y after SAVR
Lamb, 2002 (12)	SAVR	MRI	E/A peak	No	**Baseline** / **Postprocedural** E/A peak: 1.40 ±0.88 / 1.34 ±0.6 P=NS
Gjertsson,2005 (57)	SAVR	TTE	DT	None, Grade I, Grade II, Grade III	**Baseline** / **2y** / **10y** DT: 272±107 / 248 ±73 (P<0.05) / 236 ±88 (P<0.05) 10y follow-up: 61% decrease in patients with moderate to severe DD (P< 0.0001)
Ding, 2007 (66)	SAVR	TTE	E/A, IVRT	No	**Baseline** / **46 months** E/A: 2.6±0.2 / 1.9±0.1 P<0.05 IVRT: 57±4 / 69±3 P<0.01
Brown, 2009 (115)	SAVR	TTE	E/e', LA size, DT	None, delayed relaxation, increased LA pressure	DD persisted postoperatively in 84% of patients with baseline DD, while 46% of them (persisted DD) had P/PM
Guaraccino, 2010	SAVR & TAVR	TEE	Vp, e'	No	**Baseline** / **Postprocedural** **TAVR**

(30)					Vp 35 ± 6.4 43 ±7.5 * e' 4.0 ±0.5 5.0 ±0.7 * **SAVR** Vp 37 ±6.0 29 ±5.4 * e' 4.2 ±0.5 3.1 ±0.7 * * p <0.001 baseline vs. postprocedural
Jeong-Sook Seo, 2012 (38)	SAVR	TTE	e', E/A, E/e', DT	No	**Baseline** **25weeks** **50weeks** E/A 1.2±0.4 0.9±0.3 * 0.9±0.3 DT 237.8±54 177.8±30.6 * 162.7±35.6 E/e' 15.5±4.7 16.9±4.8 * 17.8±5 e' 6.3±1.8 7.8±2.0 * 9.2±3.3 * * P<0.05 baseline vs. 25w or 50w
Gotzmann, 2010 (39)	TAVR	TTE	e', E/e'	No	**Baseline** **30d** **6m** e' 5.19 ± 1.56 5.62 ± 1.54 (P=0.15) 5.8 ± 1.53 (P=0.004) E/e' 20 ± 6.7 18.1 ± 5.7 (P=0.153) 17.2 ± 5.4 (P=0.21)
Vizzardi, 2010 (135)	TAVR	TTE	E/A, E/e', DT	None, Grade I, Grade II, Grade III	**Baseline** **6 months** DT 210±48 230 ±71 P=0.08 e' 4.1 6 ±1.7 5.6±2.2 P<0.0001 E/e' 24 ±7 17±6 P<0.0001
Tzikas, 2011 (63)	TAVR	TTE	E/A, DT, e', E/e'	None, Grade I, Grade II, Grade III	**Baseline** **Discharge** **1y** Grade I 59% 51% 57% Grade II 23% 36% 33% Grade III 18% 13% 10% P=1.0
Gonzalvez, 2011 (61)	TAVR	TTE & TEE	E/A, IVRT, DT	None, Grade I, Grade II, Grade III	**Baseline** **Postprocedural** E/A 1.2 (0.9, 1.4) 1.5 (1.2, 1.8) P=0.002 DT 211.2 (191.7, 230.6) 252.7 (226.8, 278.7) P=0.001 IVRT 83.0 (73.8, 92.8) 97.1 (87.9, 106.4) P=0.003
Spethmann, 2013 (46)	TAVR	TTE	E/e'	None, Grade I, Grade II, Grade III	46.9% of the patients improved by at least one grade **Baseline** **8 days after TAVR** E/e' 18.7±8 17.6±7.3 P=NS
Spethmann, 2014 (54)	TAVR	TTE	e', E/e', E/A, DT, IVRT	None, Grade I, Grade II, Grade III	**Baseline** **12months post TAVR** e' 5.5±1.6 6.2±1.9 E/E' 17.4±7.4 15.9±6 IVRT 108.9±37.5 120.4 ±33.6 DT 204.1±73.7 224.2 ±62.5 E/A 1.16 ±0.77 1.16± 0.83 P=0.17 for e', P = NS otherwise DD grade III 24% 10% DD grade II 34% 26% DD grade I 42% 52% None 0 12% P=NS
Aslan, 2015 (55)	TAVR	TTE	E/e'	No	**Pre-operation** **7-days after TAVR**

					E/e'	13.7±4.6	11.5 ± 4.1	P< 0.001
Muratori, 2015 (358)	TAVR	TTE	E/A ratio, DT, e', E/e'	None, Grade I, Grade II, Grade III	***LVEF<50%***	**Baseline**	**12months**	
					DD grade ≥II	100%	58.8% *	
					LVEF ≥ 50%	**Baseline**	**12months**	
					DD grade ≥II	100%	87.1% *	
					* P < 0.001			

DD=Diastolic Dysfunction, AS=Aortic Stenosis, AVR=Aortic Valve Replacement, SAVR=Surgical Aortic Valve Replacement, TAVR=Transcatheter Aortic Valve Replacement, TEE=Transesophageal echocardiogram, TTE=Transthoracic echocardiogram, LA=Left Atrial, LVEF=Left Ventricular Ejection Fraction, LVED=Left Ventricular End Diastolic, DT= deceleration time, Vp=transmitral flow propagation velocity. E=peak early transmitral velocity, A= peak late transmitral velocity, e'= peak early mitral annular velocity Doppler, S= peak systolic pulmonary vein flow velocity, D= peak diastolic pulmonary vein velocity, CV=Cardiovascular, P/PM=Patient-Prosthesis Mismatch, HR= Hazard Ratio, OR=Odds Ratio (Permission from Kampaktsis et. al, Heart. 2017 Oct,103(19):1481-1487)

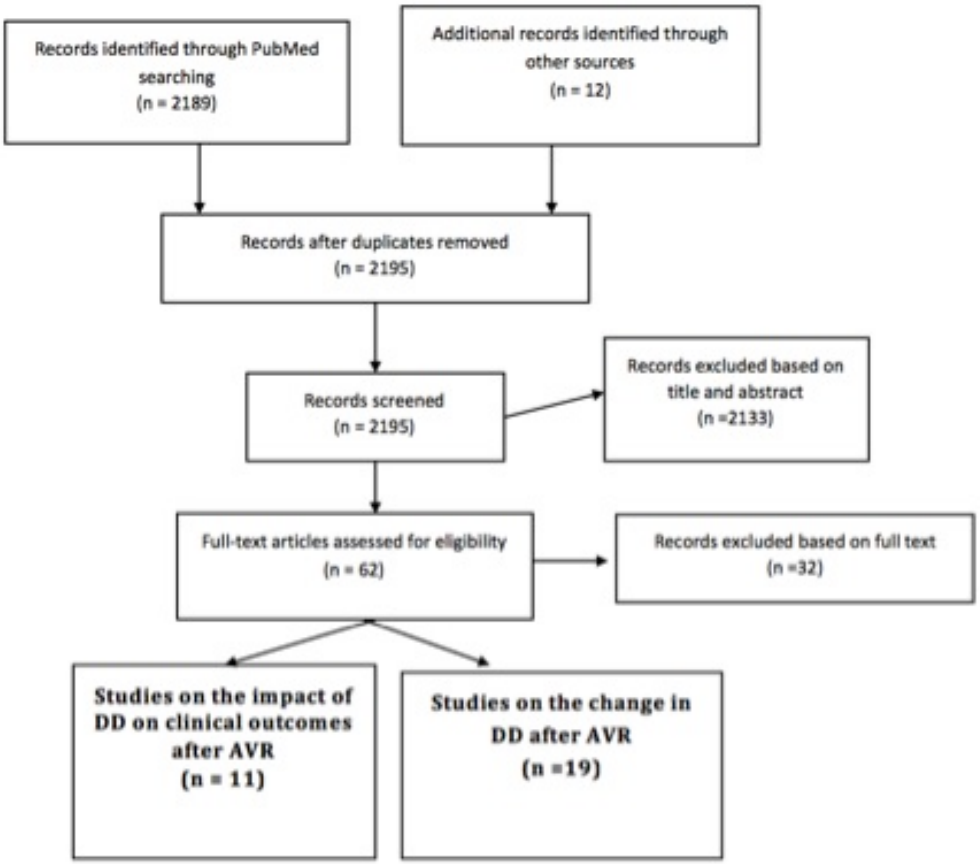
Supplemental Table 2. Univariate and multivariate regression models for all-cause mortality on a secondary analysis for the impact of diastolic dysfunction on patients who develop PVL after TAVR (n=144).

Variable	Univariate		Multivariate	
	HR	p	HR	p
DD=severe & post-TAVR AI≥mild	3.89 (1.76–8.6)	0.001	7.17 (1.28-40.17)	0.025
DD ≥moderate & post-TAVR AI≥mild	2.52 (1.22-5.23)	0.013	N/A	N/A
Post-TAVR AI	1.50 (0.97-2.31)	0.06	1.41 (0.64-3.13)	0.40
Pre-TAVR AI	0.77 (0.48-1.23)	0.28	0.91 (0.51-1.60)	0.73
DD grade	1.42 (0.86-2.34)	0.17	0.77 (0.30-1.97)	0.58
MR grade	1.18 (0.82-1.73)	0.37	0.87 (0.51–1.49)	0.86
LVEF (%)	0.99 (0.97-1.01)	0.35	1.01 (0.98-1.05)	0.51
PAPm (mmHg) *	1.032 (0.99-1.06)	0.06	1.02 (0.98-1.06)	0.47
eGFR	1.04 (0.67-1.61)	0.86	1.02 (0.99-1.05)	0.26
CVA	2.31 (0.95-5.64)	0.06	1.19 (0.25-5.68)	0.83

Multivariate model adjusted for age and gender. DD evaluated using a modified ASE/EACVI algorithm. PAPm obtained from diagnostic catheterization

AI = aortic insufficiency, CVA = cerebrovascular accident, DD = diastolic dysfunction, eGFR= estimated glomerular filtration rate (Cockroft-Gault formula), LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, MR = mitral regurgitation, PAP =pulmonary artery pressure (available for 125 patients), TAVR = transcatheter aortic valve replacement,

(Permission from Kampaktsis et. al Catheter Cardiovasc Interv. 2017 Feb 15;89(3):445-451.



Supplemental Figure 1. Study flow chart for systematic review of changes in diastolic dysfunction after aortic valve replacement and impact on outcomes

AS=Aortic Stenosis, AVR=Aortic Valve Replacement, DD=Diastolic Dysfunction
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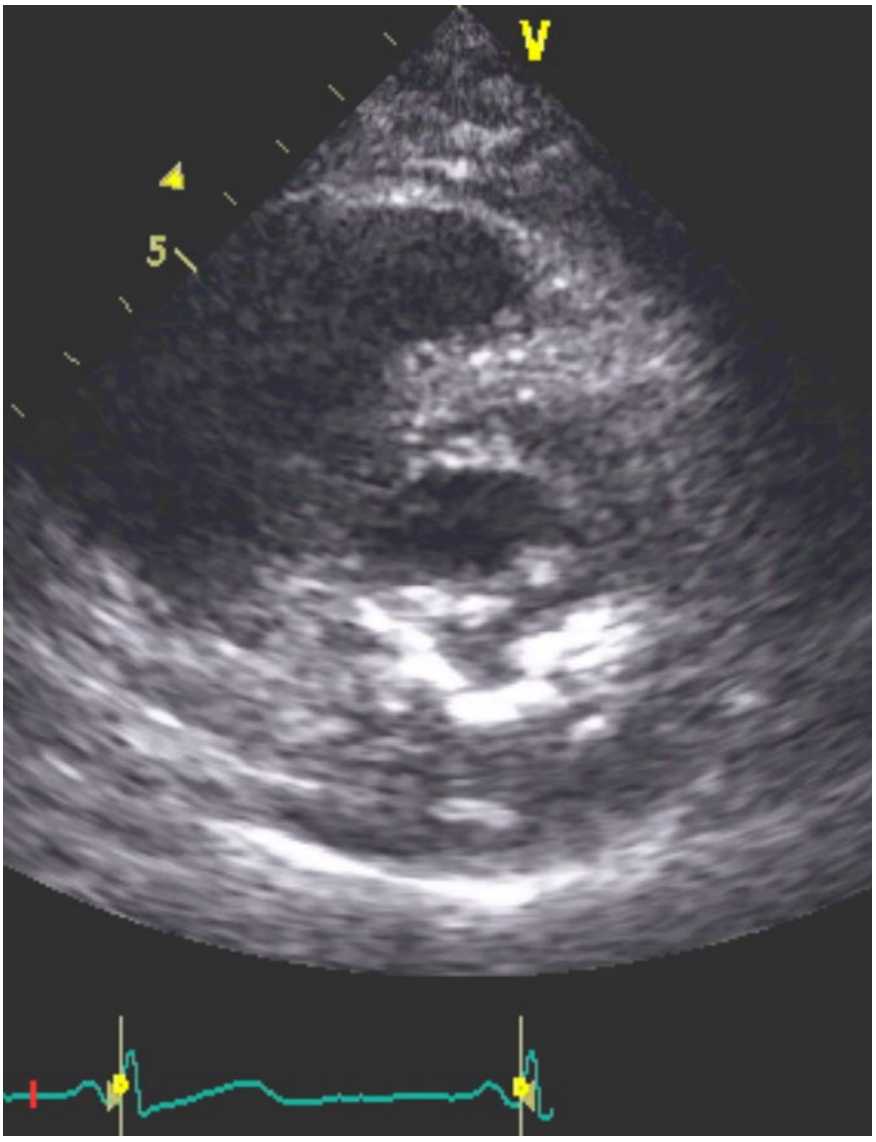
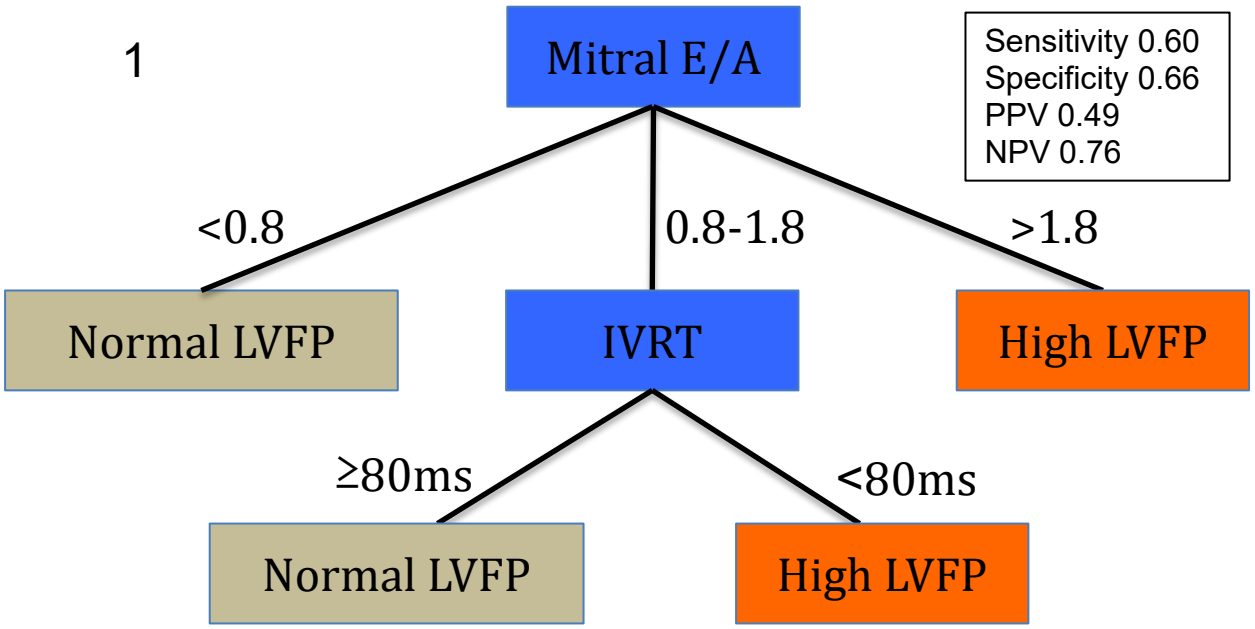
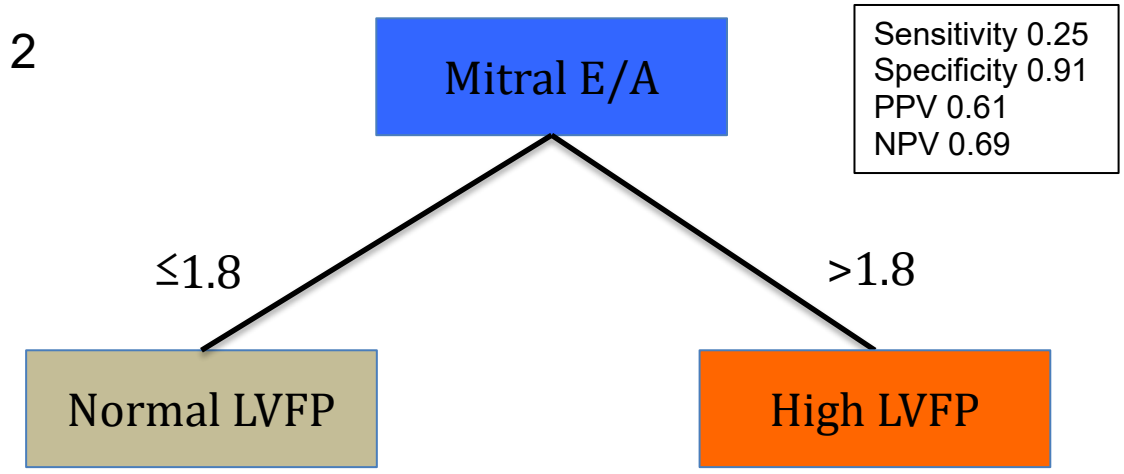


Supplemental Figure 2. Parasternal short-axis view of patient with severe aortic stenosis showing severe MAC involving the anterior and posterior mitral valve leaflets. Moderate-to-severe MAC was present in more than half of the patients in our TAVR cohort precluding the use of mitral annular tissue Doppler velocities for the evaluation of diastolic dysfunction.

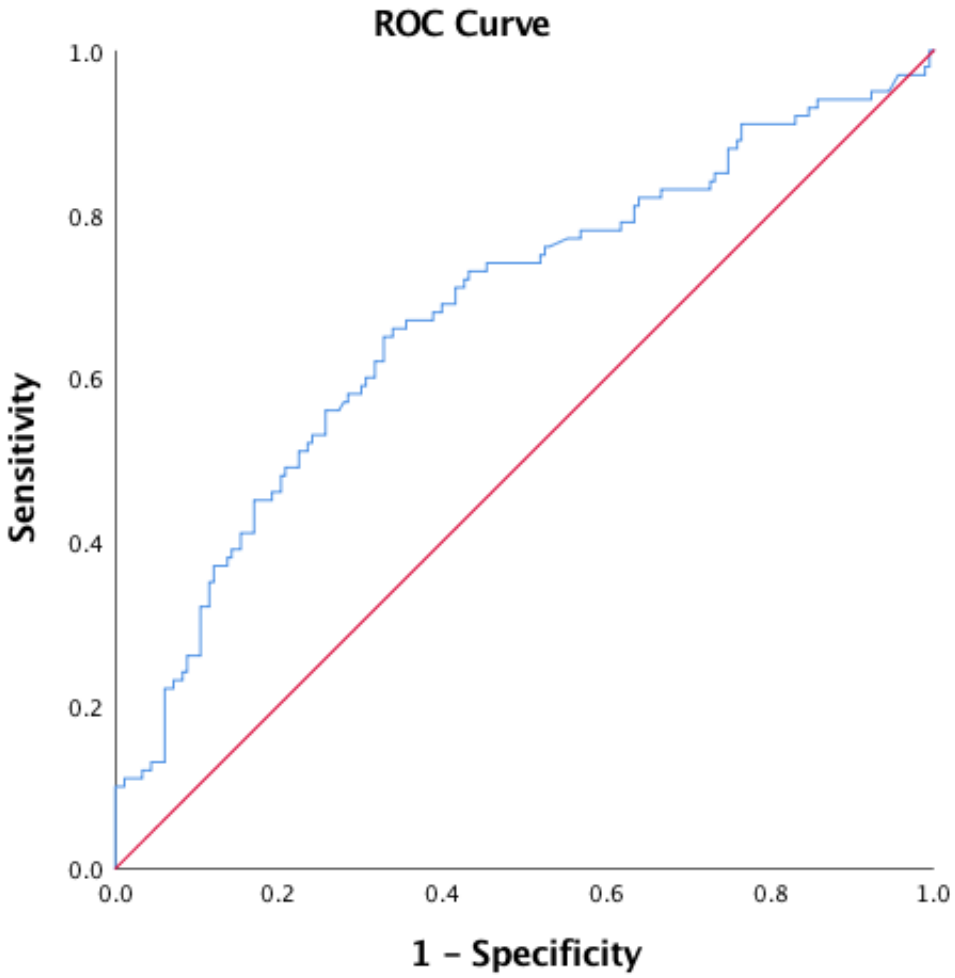
MAC=mitral annular calcification, TAVR=transcatheter aortic valve replacement





Supplemental Figure 3. Applied algorithms for estimation of left ventricular filling pressures 1) as proposed by Abudiab et al, 2) modified.

LVFP=left ventricular filling pressure, IVRT=isovolumic relaxation time, PPV=positive predictive value, NPV=negative predictive value
(Permission from Kampaktsis et al. Catheter Cardiovasc Interv. 2020 Apr 1;95(5):1024-1031)



Supplemental Figure 4: ROC Curve for high PCWP from E/A ratio. AUC for E/A ratio for high PCWP (>=18): 0.68

AUC=area under the curve, PCWP=pulmonary capillary wedge pressure
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