Aortic Stenosis: Multimorbidity and Myocardial Impact on Patients undergoing Transcatheter Aortic Valve Implantation.

Dr Kush P Patel
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PhD Thesis

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Declaration

I, Kush Prafull Patel confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Name: Dr Kush Prafull Patel **Date:** 02/11/22

For my parents, Vibha and Prafull who have been both an inspiration and driving force in all aspects of my life

And for my wife, Miriam, and my sister, Tulsi, for their unwavering support and encouragement

Abstract

Introduction

In aortic stenosis (AS), the myocardium remodels to compensate for the obstruction to forward flow before eventually decompensating, often acutely- termed acute decompensated AS (ADAS). Patients with AS often have other comorbidities, including coronary artery disease (CAD), cardiac amyloidosis (ATTR) and frailty which may also influence the myocardium and outcomes. This thesis examines the impact of multimorbidity on the myocardium and outcomes, diagnostic markers and decompensation in three patient populations: ATTR, CAD and ADAS.

Methods

To evaluate the impact of AS and ATTR on the combined phenotype AS-ATTR, I compared 4 prospective cohorts (n=583): elderly controls, severe AS, AS-ATTR and ATTR.

Using a single-centre, registry I retrospectively evaluated the impact o mong 1902 transcatheter aortic valve implantation (TAVI) patients, I assessed the impact of CAD stratified by location (left main stem (LMS) vs non-LMS) and territory (single-vessel vs multi-vessel) on mortality.

I examined the diagnostic ability of 3 commonly used metrics: Troponin T, ischaemic ECG and angina, to diagnose a type 1 NSTEMI in 273 AS patients with acute presentations.

I compared outcomes with TAVI in patients with ADAS vs non-ADAS. Within the ADAS cohort, I evaluated the prognostic role of a new echo based staging classification.

Results

Dual pathology with AS-ATTR is more closely related to ATTR than it is to AS, despite a similar burden of amyloid.

Only LMS CAD was independently associated with mortality (HR: 1.57) after the first year post-TAVI.

All 3 metrics have a low sensitivity and diagnostic ability (AUC 0.625, 0.559 and 0.692 respectively).

TAVI procedural complications and mortality were similar between ADAS and non-ADAS cohorts. However, ADAS independently predicted mortality at 30 days (HR

1.02). Among ADAS patients, advanced cardiac damage/dysfunction predicts mortality at 1 year (HR 1.853) whilst frailty predicts mortality at 2.4 years (HR 1.667).

Conclusions

This thesis has demonstrated the effect of dual pathology (AS-ATTR) on altering the resultant AS phenotype, the prognostic impact of multimorbidity (frailty and LMS CAD) in TAVI, the impact of AS on confounding common diagnostic pathways (NSTEMI) and identified a novel prognostic marker (ADAS).

Impact statement

Our understanding of AS has shifted from a disease of the valve to that including the myocardium and after this thesis- a spectrum of disease with the phenotype and outcomes influenced by multimorbidity and decompensation. Some of the challenges facing AS currently include appropriate patient selection (40-50% of TAVI in high risk patients are futile at 1 year), timing of valve replacement (up to 25% of patients acutely decompensate), and optimisation of health with additional therapies (coronary revascularisation and anti-ATTR medication). In order to refine our diagnostic and management pathways, a better understanding of the interplay between the myocardium, multimorbidity and outcomes is needed.

By examining the AS-ATTR phenotype and comparing it for the first time to healthy ageing, lone ATTR and lone AS, I provided evidence to supports the case for treatment with ATTR specific medications, in addition to valve replacement. By targeting patients with a lower burden of amyloid, ATTR-stabilising drugs such as Tafamidis may be more effective at improving outcomes for patients. This research has led to the establishment of an international, multicentre registry with 250 AS-ATTR patients pledged, to assess outcomes with ATTR-specific therapy and valve replacement. My work with CT contributed to defining the role of CT based extracellular volume (CT_{ECV}) quantification for the diagnosis of ATTR. I have now established a clinical screening pathway for ATTR using CT_{ECV}.

AS-related remodelling affects coronary haemodynamics and along with epicardial CAD renders the myocardium susceptible to ischaemia. My findings suggest that revascularisation is unlikely to be a prerequisite for TAVI in order to reduce procedural mortality. However, larger at risk coronary territories, such as LMS CAD, are associated with a higher long-term rather than short-term mortality. These patients may benefit from revascularisation on prognostic grounds. Further evaluation of coronary stenosis to guide revascularisation may be achieved using functional rather than anatomical imaging. I am setting up a multicentre study assessing the utility of CT-fractional flow reserve to identify prognostically important lesions and guide revascularisation.

Among patients presenting acutely with severe AS, differentiating between a type 1 NSTEMI and ADAS can be challenging. The former requires dual antiplatelet therapy upfront and invasive coronary angiography (ICA) ± revascularisation, whilst the later requires urgent valve replacement. Given the poor diagnostic ability of commonly

used metrics to identify a type 1 NSTEMI, alternative pre-angiographic screening is required to improve the diagnostic pathways for these patients. And given that all TAVI patients have a CT coronary angiogram, this could screen for obstructive CAD and inform further management.

ADAS represents a poor prognostic marker. Risk stratification for ADAS patients relies predominantly on myocardial damage/dysfunction at 1 year and frailty in the mid-term. And although TAVI is safe and effective in ADAS, mortality remains high in the short and long term. Stemming from these findings, I have devised a clinical pathway (ASTRID-AS) across 21 hospitals to expedite the investigations and treatment of patients with ADAS. I am testing the hypotheses whether time to treatment impacts on outcomes, by comparing ASTRID-AS patients to standard of care.

Acknowledgements

I would like to thank my supervisors, Prof James Moon, Dr Michael Mullen and Dr Thomas Treibel for their guidance, support, the various opportunities they provided me with and the resources they made available for me in order to complete this PhD.

I would like to thank Prof Andreas Baumbach, Dr Guy Lloyd, Dr Francesca Pugliese, Prof Anthony Mathur, Dr Simon Kennon and Dr Leon Menezes at Barts Heart Centre who provided me with their expertise on various aspects of my PhD and taught me a great deal about the clinical application of our research.

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My predecessor, Dr Paul Scully, played a crucial part in laying the building blocks for this PhD and teaching me about the intricacies of research methodology. Without him my work would have been very challenging.

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At the John Radcliff Hospital, Dr Nikant Sabharwal, Dr Jim Newton and Dr Andrew Kelion for their support and efforts in facilitating my research in Oxford.

Lastly, I would like to thank the TAVI nurses, imaging receptions, nuclear department receptionists and radiographers at Barts heart Centre and the John Radcliff Hospital for facilitating my research.

COVID statement

In April 2020, as the COVID pandemic spread, I was called back to clinical medicine to work in Intensive Care and Cardiology at St Bartholomew's Hospital. I did so for 6 months and returned to complete my PhD in October 2020. Again from January 2021 to the start of March 2021, for 2 months, I was recalled back to work in intensive care.

As a result of changes in clinical, research and daily life, my PhD has had to adapt and several aspects that I set out to achieve have changed. Recruitment for my main research arm (aortic stenosis and cardiac amyloidosis (ATTR)) was disrupted and fell short of what was expected.

Original PhD hypothesis

In elderly patients with severe aortic stenosis, referred for transcatheter aortic valve implantation (TAVI) this PhD will investigate whether:

1. AS-ATTR can be excluded clinically using ECG/Echo/biomarkers/CT and therefore permit DPD scanning for patients with high risk features for ATTR.
2. AS-ATTR is a separate disease entity to cardiac amyloid, AS and ageing alone.
3. AS-ATTR patients get different symptomatic/remodelling benefit from TAVI.

Original PhD methodology and changes due to COVID pandemic

Screening and recruitment: In TAVI clinic. COVID led to all clinics becoming virtual and patients were telephoned for consultation. This greatly curtailed recruitment.

Baseline investigations: DPD scintigraphy to diagnose ATTR at the time of their routine clinical CT scan. COVID resulted in CT scans taking place in local district general hospitals, reducing the opportunity to scan patients using DPD scintigraphy.

8 week follow-up: In TAVI clinic- take bloods for biomarkers, 6 minute walk test for functional assessment, quality of life and symptom questionnaire. COVID resulted in all TAVI clinics becoming virtual and patients no longer came to hospital, which meant I could not achieve my follow-up investigations, apart from asking questions via telephone.

1 year remodelling: By using clinical echocardiograms. COVID led to patients having echocardiograms at their local district general hospital restricting access to available echocardiograms for analysis.

1 year outcomes: phone call to assess symptoms and quality of life. Several of my recruited patients died because of COVID and as a result follow up was incomplete for many patients.

Recruitment target: 200 elderly TAVI patients and 100 elderly healthy participants for this PhD. Elderly patients were within the highest COVID risk group and majority were isolating. Any contact for clinical reasons needed to be kept to a minimum and our hospital policy was to stop any non-essential, non-COVID related research which prevented me from recruiting or performing any research.

Ethical permission: In order to recruit my patients/participants, I applied for ethics. However, COVID resulted in all non-COVID related ethics applications to be delayed. Consequently, my ethics took 1.5 years to get approval.

Using CT to screen for AS-ATTR: Only half of my recruited patients underwent CT. Further recruitment was stopped by the COVID pandemic. Consequently I could not recruit enough patients to develop CT as a screening tool for AS-ATTR.

The intermittent clinical commitments during the pandemic prevented timely follow up for patients that were already recruited.

Changes to PhD aims due to COVID pandemic

Only one of my 3 original study aims could be fulfilled: AS-ATTR is a separate disease entity to cardiac amyloid, AS and ageing alone. In addition to this hypothesis, my new aims are to investigate among patients undergoing TAVI, the impact of:

i) multi morbidity on clinical outcomes
ii) acute decompensated aortic stenosis on clinical outcomes

In doing so, this thesis will identify patient cohorts that may benefit from additional therapy, refine risk stratification, improve patient management pathways

Changes to PhD methodology due to COVID pandemic

I performed retrospective, observational research by developing various cohorts of patients with valvular heart disease. This was achieved by collating patient data using clinical records and analysing existing imaging. These cohorts include data on patient demographics, comorbidities, imaging parameters, procedural details and outcomes.

Index

Abbreviations

- 6MWT- 6 minute walk test
- ADAS- acute decompensated aortic stenosis
- AKI- acute kidney injury
- AIPW- augmented inverse probability weighting
- AS- aortic stenosis
- AR- aortic regurgitation
- AVR- aortic valve replacement
- BHC- Barts Heart Centre
- CAD- coronary artery disease
- CFR- coronary flow reserve
- CKD- chronic kidney disease
- CI- confidence intervals
- CMR- cardiac magnetic resonance
- CT- cardiac computed tomography
- ECV- extracellular volume
- GLS- global longitudinal strain
- hsTnT- high sensitivity Troponin T
- ICA- invasive coronary angiography
- LA- left atrium
- LDL- low density lipoprotein
- LGE- late gadolinium enhancement
- LOS- length of stay
- LV- left ventricular
- LVEF- left ventricular ejection fraction
- LVH- left ventricular hypertrophy
- LVM- left ventricular mass
- LVMi- left ventricular mass indexed
- MCF- myocardial contraction fraction
- MDT- multi-disciplinary meeting
- NT-proBNP- N terminal pro brain natriuretic peptide
- PPM- patient prosthesis mismatch

- RV- right ventricular
- RVESV- right ventricular end systolic volume
- RVEF- right ventricular ejection fraction
- RWT- relative wall thickness
- SAVR- surgical aortic valve replacement
- TAPSE- tricuspid annular planar systolic excursion
- TAVI- transcatheter aortic valve implantation
- VARC 2- valve academic research consortium 2
- VIC- valve interstitial cells
- VHD- valvular heart disease

1. INTRODUCTION

This chapter is based on the publication below:

***Patel KP**, Michail M, Treibel TA, Rathod K, Jones DA, Ozkor M, Kennon S, Forrest JK, Mathur A, Mullen MJ, Lansky A, Baumbach A. Coronary Revascularization in Patients Undergoing Aortic Valve Replacement for Severe Aortic Stenosis. JACC Cardiovasc Interv 2021;**14**:2083–2096.*

I was involved in the genesis, literature review, critical appraisal, image creation, writing, editing and manuscript creation.

***Patel KP**, Vandermolen S, Cooper J, Pugliese F, Ozkor M, Kennon S, Mathur A, Khanji MY Mullen MJ, Baumbach A, Awad WI.* Comparing outcomes between SAVR and TAVR in classical LFLG Aortic Stenosis. AJC, 2023

I was involved in the genesis, data collection, image creation, writing, editing and manuscript creation. Dr Vandermolen is joint first author and had a similar involvement to me. Dr Cooper performed the statistical analysis.

***Patel KP**, Aziminia N, Boubertakh R, Thornton GD, Eiros R, Moir S, Davies R, Manisty C, Bhattacharyya S, Lloyd G, Moon JC, Treibel TA. Global longitudinal strain is a more sensitive marker of remodelling and reverse remodelling than LVEF in patients with aortic stenosis aundergoing aortic valve replacement. Under review by JACC CVImaging*

I was involved in the genesis, data collection and analysis, statistical analysis, writing, editing and manuscript creation.

***Patel KP**, Treibel TA, Scully P, Fertleman M, Searle S, Davis D, Moon JC, Mullen MJ. Futility in TAVR: A search for clarity. Intervention Cardiology Reviews. 2021*

I was involved in the genesis, literature review, critical appraisal, image creation, writing, editing and manuscript creation.

*Treibel TA, **Patel KP**, Cavalcante JL. Extracellular Volume Imaging in Aortic Stenosis During Routine Pre-TAVR Cardiac Computed Tomography. JACC Cardiovasc Imaging 2020;**13**:2602–2604.*

I was involved in writing and editing this manuscript.

***Patel KP**, Chahal A, Mullen MJ, Rathod K, Baumbach, A, lloyd G, Treibel TA, Awad, WI, Ricci F, Khanji M. Acute decompensated aortic stenosis: State of the art review. Current Problems in Cardiology, 2022*

I was involved in the genesis, literature review, critical appraisal, image creation, writing, editing and manuscript creation.

1.1. Aortic stenosis

The aortic valve most commonly consists of 3 leaflets (although 1, 2 and 4 leaflets can occur) attached in a crown-like formation to the ventricular myocardium and the fibrous part of the anterior mitral valve at their basal portions and to the aorta at their apical portions. The aortic root houses the coronary ostia of which there are usually 2 (but can be less or more) supplying the left and right coronary arteries (figure 1 and 2) [1]. Aortic leaflets are composed of layers of valve interstitial cells (VIC) separated by fibrous tissue and lined with endocardium on both the ventricular and aortic surfaces [2].

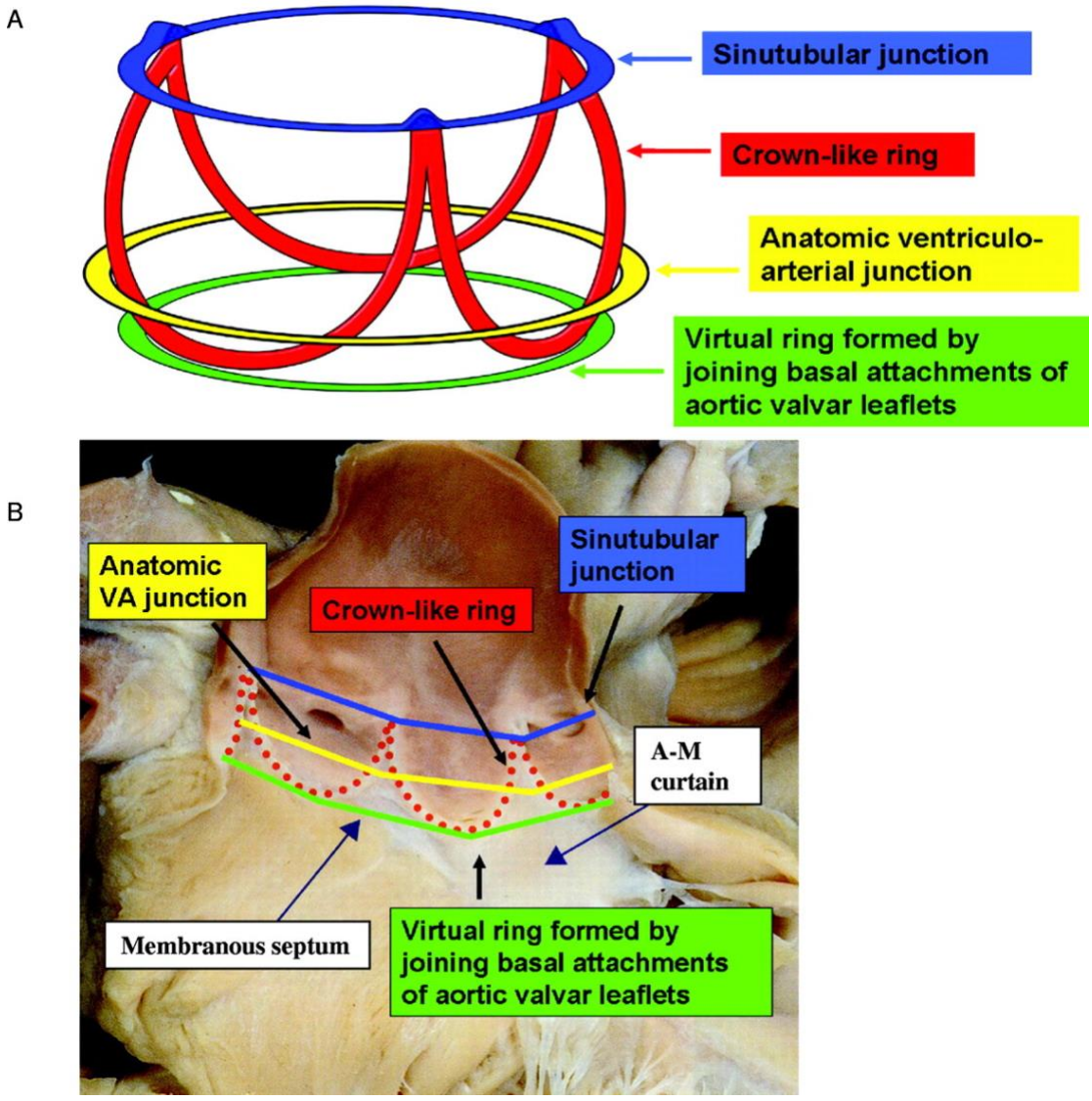


Figure 1: Aortic rings and relation between structures within the aortic root. Adapted from [1]

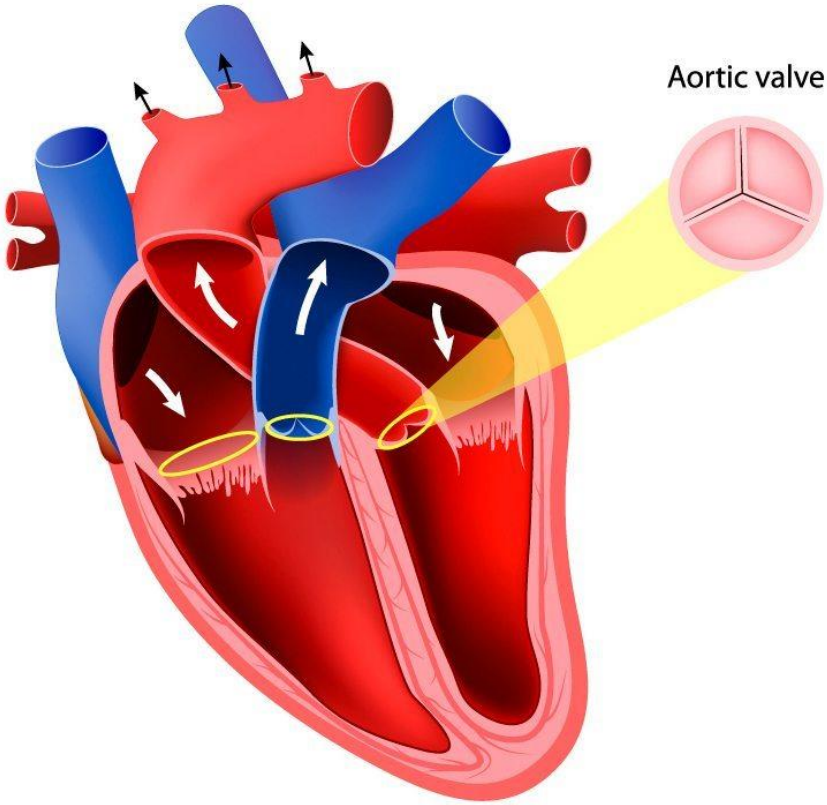


Figure 1: Normal location and en-face view of the aortic valve. Adapted from [3]

Aortic stenosis (AS) is characterised by a progressive stiffening of the leaflets and narrowing of the valve orifice, such that afterload on the left ventricle increases. Patients often develop symptoms of dyspnoea, angina, pre-syncope and syncope. If AS is left untreated it can be fatal. Treatment for AS is confined to aortic valve replacement (AVR) either using surgical aortic valve replacement (SAVR) or minimally-invasive transcatheter aortic valve implantation (TAVI).

1.1.1. Epidemiology of AS

The prevalence of AS increases with age and a meta-analysis of 9,723 patients >75 years old, found 12.4% had some degree of AS. However, the prevalence of severe AS was identified in 3.4% of patients [4]. Another report involving 11,911 patients from several epidemiological studies, found a prevalence of moderate and severe AS in 2.8% of participants [5]. Among screening studies, the OxVALVE study (n=2500) found AS in 1.3% of participants >65 years old, with 0.7% having either moderate or severe disease [6]. With an ageing population, the prevalence is set to increase [7].

1.1.2. Pathophysiology of AS

Risk factors for AS contribute to a complex and active process of progressive damage, change in composition and ultimately adversely affecting the function of the dynamic leaflets. Risk factors associated with AS are common to other cardiovascular diseases, most notably coronary artery disease. Age, male sex, active smoking, hypertension, Lipoprotein (a), low-density lipoprotein (LDL) cholesterol, chronic kidney disease, diabetes, obesity [8]–[11]. In addition several genetic loci are associated with AS [12], [13].

The initial damage to the endothelium on the aortic valve leaflets is believed to be secondary to increased mechanical stress and reduced shear stress [14]. This provides the impetus for lipoprotein (a) and oxidised LDL cholesterol to infiltrate the valve and stimulate inflammation [15]. Stimulated by the renin-angiotensin system, there is an increase in fibrosis. This forms the scaffolding for calcification [14], [16]. Microcalcification develops around the lipid deposits. The calcification promotes more inflammation and in a positive feedback loop both drive disease progression [17]. Calcification also drives further valve injury and in turn promotes more calcification. Differentiation of VIC into bone-forming osteoblast cells is key to this process and regulated by the several pathways [14]. The increase in valvular fibrosis and calcification increases the stiffness and reduces mobility such that there is a resultant obstruction to blood flow through the valve.

1.1.3. Assessment of AS

The severity of AS can be graded by several imaging modalities, including cardiac magnetic resonance imaging, computed tomography, invasive coronary angiography and echocardiography [18]. The latter is the most widely used and forms the basis of guidelines. Detailed explanations regarding how AS is graded by echocardiography are provided elsewhere [19]. Table 1 and figure 3 summarises the grading of AS based on haemodynamic and structural parameters.

	Units	Formula / Method	Cutoff for Severe	Concept	Advantages	Limitations
AS jet velocity	m/s	Direct measurement	4.0	Velocity increases as stenosis severity increase.	Direct measurement of velocity. Strongest predictor of clinical outcome.	Correct measurement requires parallel alignment of ultrasound beam. Flow dependent.
Mean gradient	mm Hg	$\Delta P = \sum 4v^2 / N$	40 or 50	Pressure gradient calculated from velocity using the Bernoulli equation	Mean gradient is averaged from the velocity curve. Units comparable to invasive measurements.	Accurate pressure gradients depend on accurate velocity data. Flow dependent
Continuity equation valve area	cm^2	$AVA = (CSA_{LVOT} \times VTI_{LVOT}) / VTI_{AV}$	1.0	Volume flow proximal to and in the stenotic orifice is equal.	Measures effective orifice area. Feasible in nearly all patients. Relatively flow independent.	Requires LVOT diameter and flow velocity data, along with aortic velocity. Measurement error more likely.
Simplified continuity equation	cm^2	$AVA = (CSA_{LVOT} \times V_{LVOT}) / V_{AV}$	1.0	The ratio of LVOT to aortic velocity is similar to the ratio of VTIs with native aortic valve stenosis.	Uses more easily measured velocities instead of VTIs.	Less accurate if shape of velocity curves is atypical.
Velocity Ratio	none	$VR = \frac{V_{LVOT}}{V_{AV}}$	0.25	Effective aortic valve area expressed as a proportion of the LVOT area.	Doppler-only method. No need to measure LVOT size, less variability than continuity equation.	Limited longitudinal data. Ignores LVOT size variability beyond patient size dependence
Planimetry of Anatomic Valve Area	cm^2	TTE, TEE, 3D-echo	1.0	Anatomic (geometric) cross-sectional area of the aortic valve orifice as measured by 2D or 3D echo.	Useful if Doppler measurements are unavailable.	Contraction coefficient (anatomic / effective valve area) may be variable. Difficult with severe valve calcification.

Table 1: Definition of severe AS based on commonly used echocardiographic parameters. Adapted from [19].

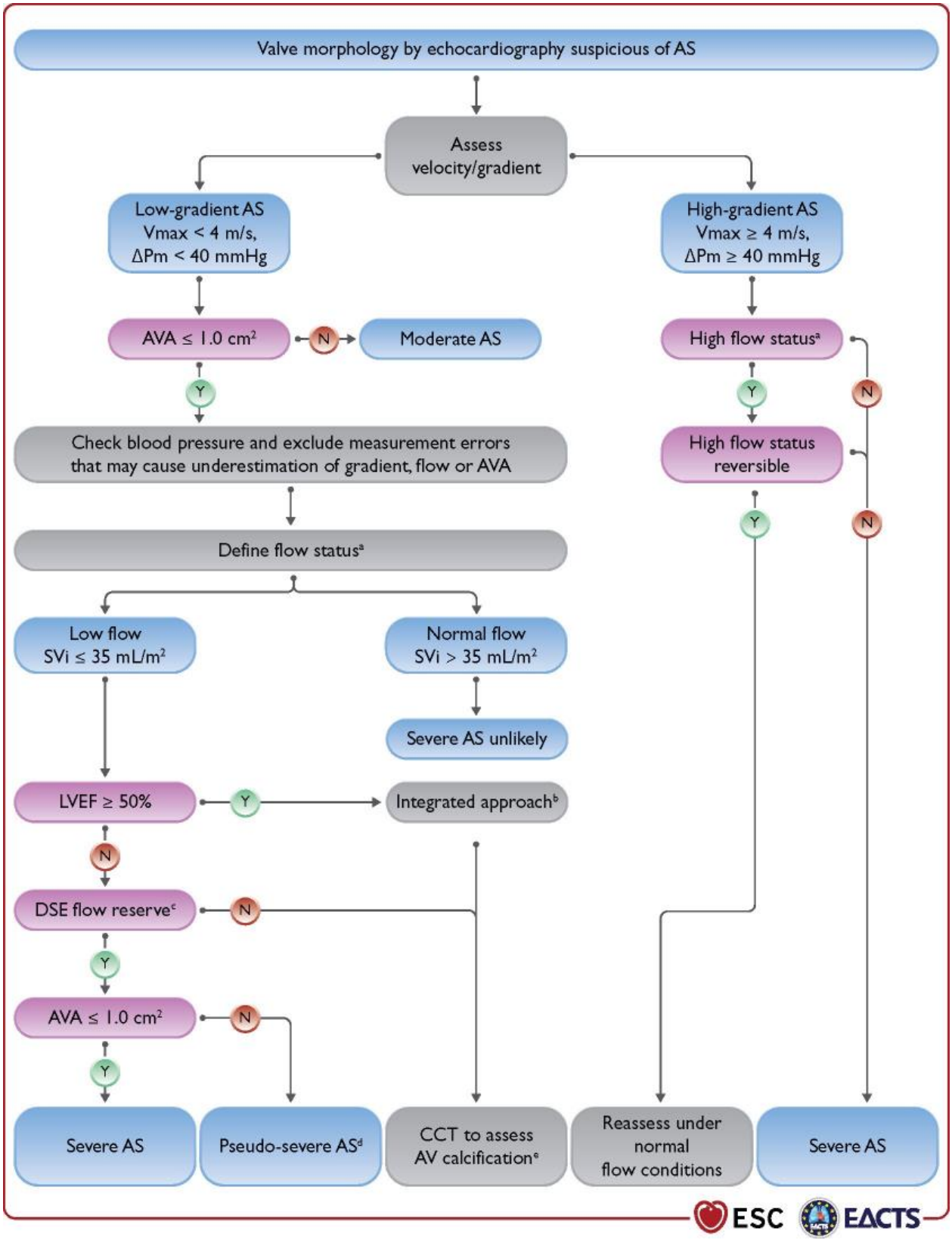

Valve morphology by echocardiography suspicious of AS
Assess velocity/gradient
Low-gradient AS Vmax < 4 m/s, ΔPm < 40 mmHg
High-gradient AS Vmax ≥ 4 m/s, ΔPm ≥ 40 mmHg
AVA ≤ 1.0 cm²
N
Moderate AS
Y
High flow status[a]
Y
N
Check blood pressure and exclude measurement errors that may cause underestimation of gradient, flow or AVA
High flow status reversible
Y
N
Define flow status[a]
Low flow SVi ≤ 35 mL/m²
Normal flow SVi > 35 mL/m²
Severe AS unlikely
LVEF ≥ 50%
Y
Integrated approach[b]
N
DSE flow reserve[c]
N
Y
AVA ≤ 1.0 cm²
N
Y
Severe AS
Pseudo-severe AS[d]
CCT to assess AV calcification[e]
Reassess under normal flow conditions
Severe AS
ESC
EACTS

Figure 3: Guideline recommendations for assessing severe AS using multimodality imaging. AS- aortic stenosis, AV- aortic valve, AVA- aortic valve area, CT- computed tomography, ΔPm- mean pressure gradient, DSE- dobutamine stress echocardiography, LV- left ventricle/left ventricular, LVEF- left ventricular ejection fraction, SVi- stroke volume index, V_{max} - peak transvalvular velocity. [a]High flow may be reversible in patients with anaemia, hyperthyroidism or arterio-venous fistulae, and may also be present in patients with hypertrophic obstructive cardiomyopathy. Upper limit of normal flow using pulsed Doppler echocardiography: cardiac index 4.1 L/min/m² in men and women, SVi 54 mL/m² in men, 51 mL/m² in women). [c]DSE flow reserve = >20% increase in stroke volume in response to low-dose dobutamine. [d]Pseudo-severe aortic stenosis = AVA >1.0 cm^2 with increased flow. [e]Thresholds for severe aortic stenosis assessed by means of CT measurement of aortic valve calcification (Agatston units): men >3000, women >1600 = highly likely; men >2000, women >1200 = likely; men <1600, women <800 = unlikely. Adapted from [18].

1.2. Myocardial involvement in AS

In patients with AS, the myocardium is directly affected by the increase in afterload. Additionally, several other diseases commonly associated with AS, have an impact on the myocardium. This results in myocardial remodelling and is a fundamental driver of symptoms, prognosis and affects other organ systems. Patients who undergo AVR, can benefit from reversal of remodelling to varying degrees. An understanding of this complex interplay between various insults and myocardial remodelling, the effect of remodelling on outcomes and the role of treatments in reverse remodelling is key to improving symptoms and prognosis for patients. Figure 4 illustrates the key factors associated with AS, their collective impact on the myocardium and the effect of treatments on reverse remodelling in patients with AS.

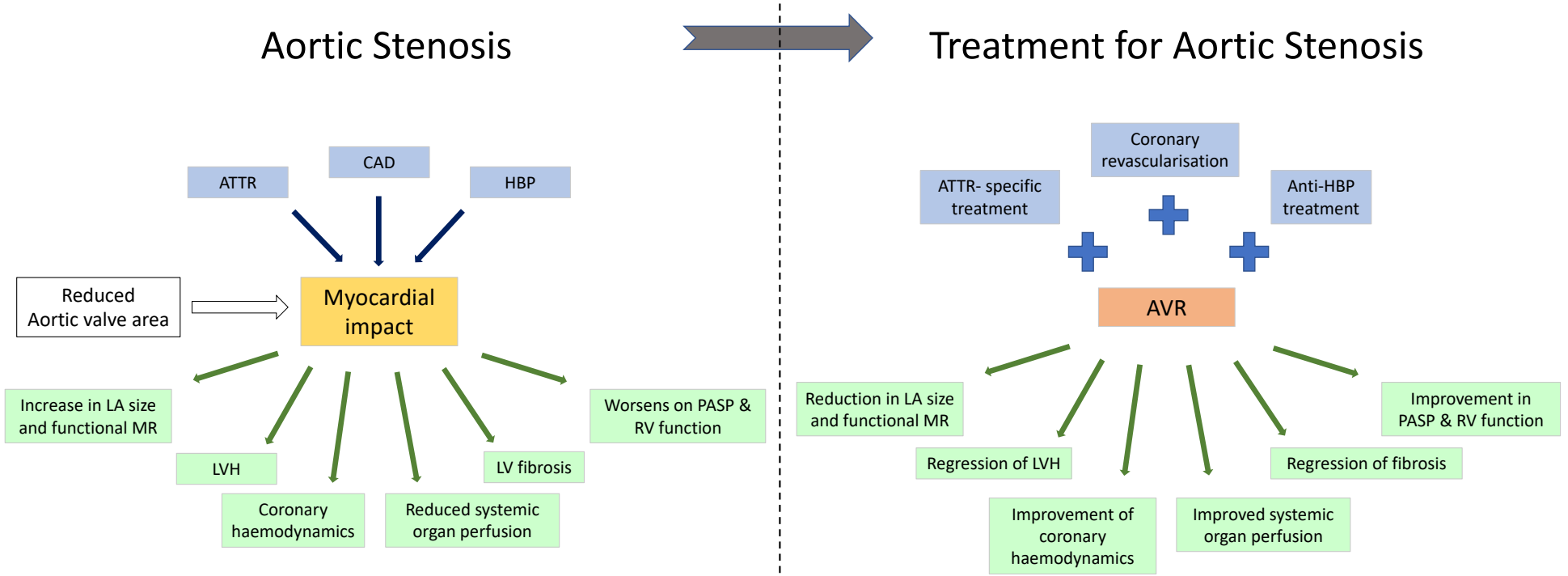


Figure 4: The myocardium in AS is affected by the reduced aortic valve orifice, obstructing blood flow through the valve. The myocardium is also affected by other diseases such as ATTR, CAD and HBP. The effect of these factors results in several pathological changes. With AVR, some of these changes can be reversed. Additionally treatments specific for other diseases may have an impact on the reversal of these changes. Overall, all these factors influence outcomes in patients with AS. ATTR- Transthyretin amyloidosis, CAD- coronary artery disease, HBP- hypertension, LA- left atrium, MR- mitral regurgitation, LVH- left ventricular hypertrophy, LV- left ventricle, RV- right ventricle, TR- tricuspid regurgitation, AVR- aortic valve replacement.

Figure 5 illustrates the main pathological changes that affect the myocardium in AS. These factors will be discussed in the following chapters.

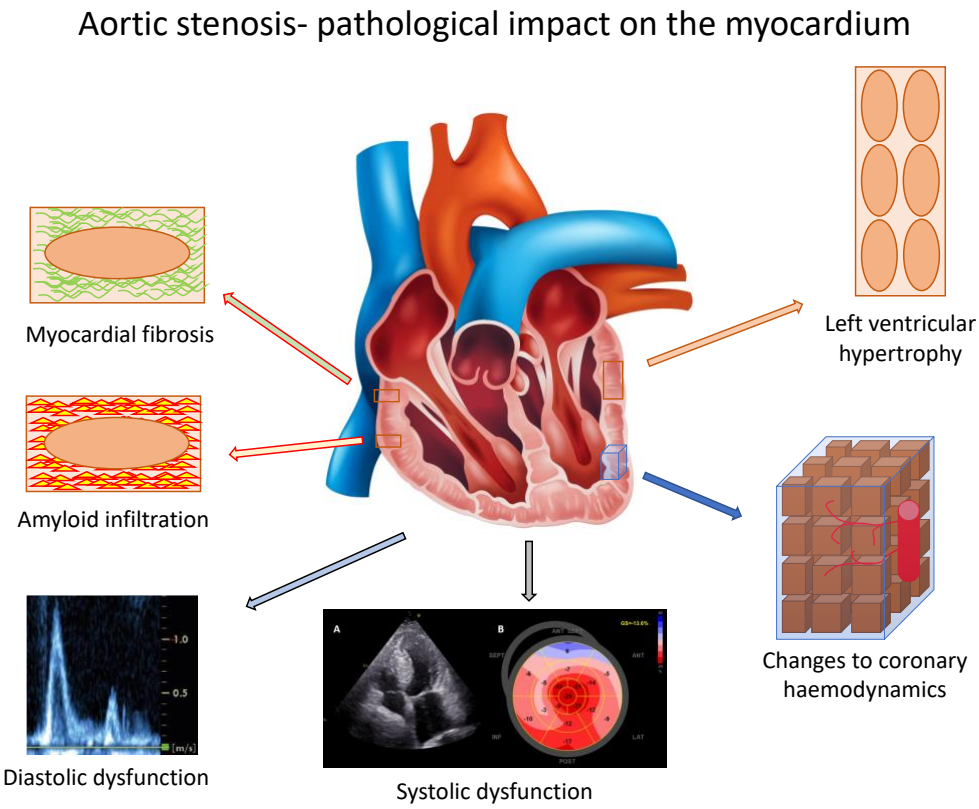


Figure 5: Pathological changes of the myocardium that take place in AS. Cross-sectional image of the heart obtained from www.vecteezy.com.

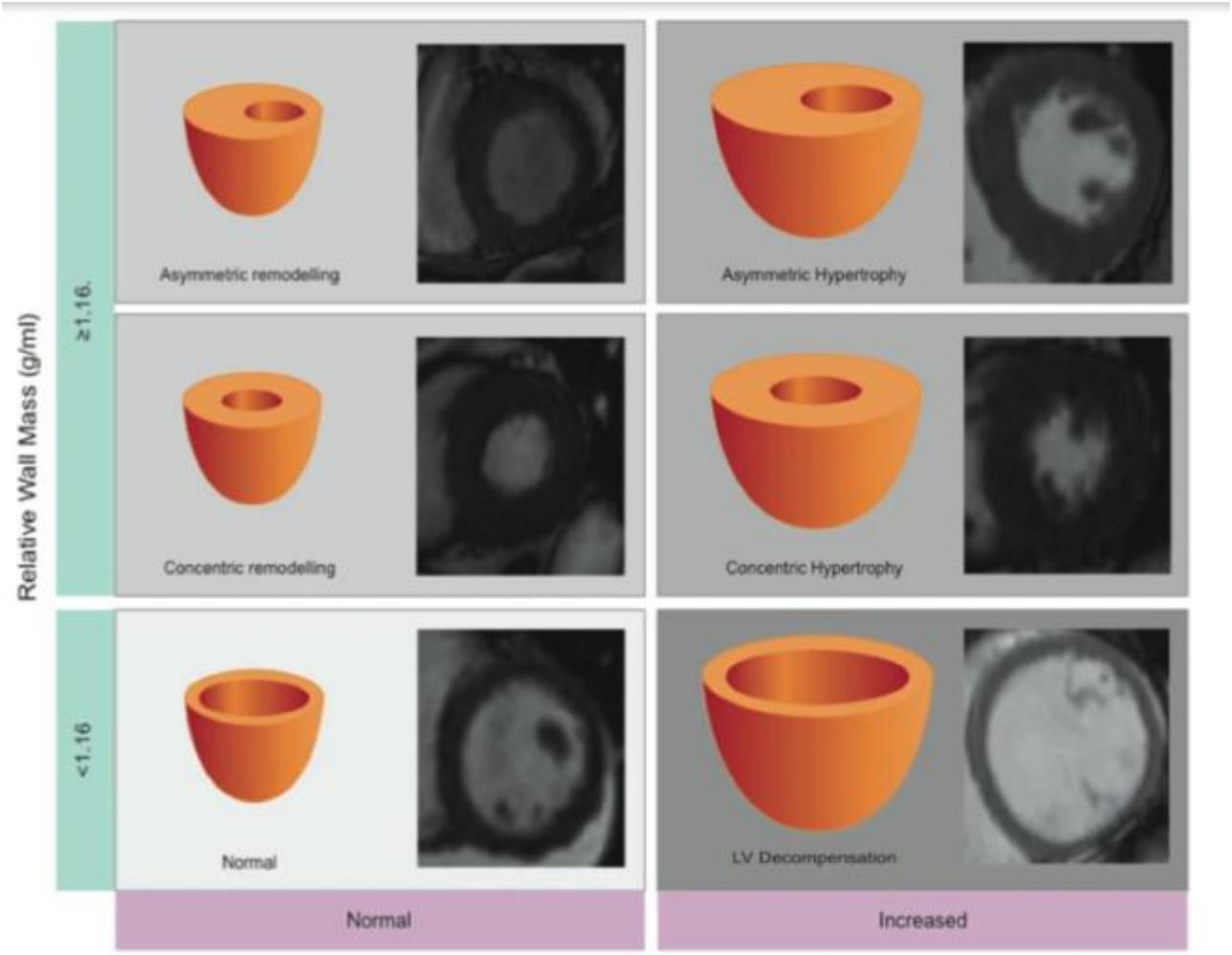
1.2.1. Left ventricular hypertrophy

The increased stiffness, thickening and calcification of the aortic valve results in reduced mobility and therefore opening during systole [20]. This subsequently increases afterload and systolic wall stress on the left ventricle. In order to normalise wall stress and maintain cardiac output against the resistant aortic valve, the myocytes undergo hypertrophy [21], [22]. Apart from afterload, other factors do contribute to the development of left ventricular hypertrophy (LVH) and include hypertension [21], [23], insulin resistance [24], diabetes [25], [26], obesity [26], [27], smoking [26] and chronic kidney disease (CKD) [28], [29]. Frequent co-existence between these risk factors makes it challenging to tease out the impacts of individual diseases on LVH [30].

LVH is measured using LV mass (LVM) that is often indexed to the body surface area of the patient (LVMi) and relative wall thickness (RWT) which is the sum of the thickness of two opposing ventricular walls as a proportion of the diameter of the LV cavity in diastole. Both LVMi and RWT take into account myocyte hypertrophy and extracellular space expansion. Based on these metrics, there are four recognised patterns of LVH (figure 6) [31]:

1) normal- normal RWT and normal LVMi
2) concentric remodelling- increased RWT and normal LVMi
3) concentric hypertrophy- increased RWT and increased LVMi
4) eccentric hypertrophy- normal RWT and increased LVMi

Amongst patients with increased RWT, remodelling and hypertrophy can also be asymmetrical rather than concentric [32].



	LV Mass Index	Indexed LVEDV	M/V	Asymmetric wall thickening	Ejection Fraction
Normal	=	=	=	✖	=
Concentric Remodeling	=	↓	↑	✖	=/↑
Asymmetric Remodeling	=	↓	↑	✔	=/↑
Concentric Hypertrophy	↑	=	↑	✖	=/↓
Asymmetric Hypertrophy	↑	=	↑	✔	=/↓
LV Decompensation	↑	↑	=	✖	↓

Figure 6: LV remodelling patterns based on RWT and LVMi. Adapted from [32]. LV decompensation is also referred to as eccentric hypertrophy.

The severity and patterns of LVH are associated with certain populations. The severity of AS is only partially related to hypertrophy [23], [32], [33]. Eccentric hypertrophy (also known as LV decompensation) is associated with a higher severity of AS and often considered an ‘end-stage’ form of AS remodelling [32]. Obesity has been associated with more eccentric and concentric LVH [27]. Asymmetric LVH is found in a quarter of patients and is associated, but not restricted, to older age and hypertension. The hypertrophy with asymmetric LVH is largely confined to the septum. Gender plays a prominent role in the development of LVH; males have higher LVMi than females [32], [34]. They also have more concentric and eccentric hypertrophy, whilst females have more normal geometry and concentric remodelling for the same severity of AS [34], [35]. LVH tends to increase over time at a faster rate in females, with risk factors such as diabetes and obesity demonstrating a greater impact on increasing LVH [26], [36]. Males tend to have larger LV volumes and less relative wall thickness. [34], [35]. Differences in the myocardial response to AS between sexes suggests a hormonal influence on remodelling. Studies have identified differences in type and amount of oestrogen receptors between males and females and between patients with AS and healthy controls. These receptors influence calcineurin and intracellular calcium availability, both of which are involved in the hypertrophic response [37]–[39].

There is some evidence to support a change in remodelling patterns from normal/concentric remodelling to concentric/eccentric hypertrophy. In patients with mild AS (n=80), normal/concentric remodelling accounted for 78% of patients at baseline. After a follow-up of 5.9 ± 1.8 years, patients had progressed to severe AS and normal/concentric remodelling pattern accounted for 37%. The inverse trend was observed for concentric/eccentric hypertrophy [23] (figure 7). Although another study did not demonstrated this [32].

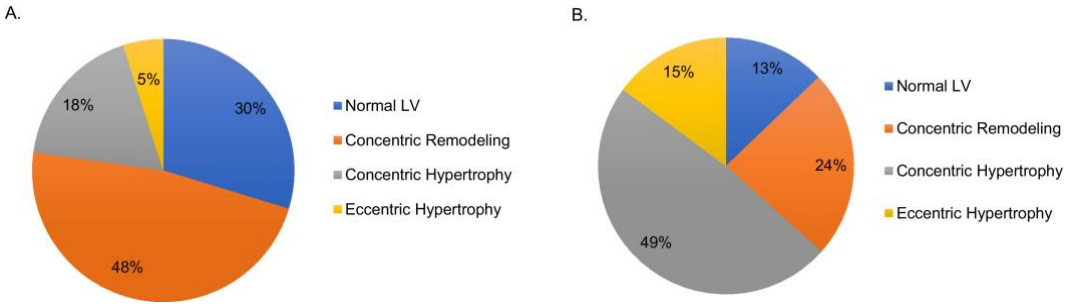


Figure 7: Changes in remodelling patterns at baseline with mild AS (A) and after 5.9 ± 1.8 years with severe AS (B) [23].

LVH is associated with diastolic dysfunction. The degree of myocyte hypertrophy is associated with a prolongation of relaxation time (Tau- the gold standard for measuring diastolic function- see section 1.2.4.) [40]. The relationship between left ventricular function and LVH is complex and dependant on which metric is used for measurement. Subsequently, there is some heterogeneity in the literature. Although LVH does facilitate adequate cardiac output against the increased afterload and wall stress, there is an inverse relationship between circumferential wall stress (a marker of afterload) and mid wall fractional shortening (a measure of cardiac function- see section 1.2.5.) [23]. Another study similarly demonstrated an inverse relationship between fractional shortening and wall stress. It also showed that differences in remodelling between males and females are associated with differences in LV wall stress and function, with higher values of fractional shortening in females than males. Figure 8 demonstrates these findings [35]. Comparatively, another study using LV micromanometry and quantitative cineangiography demonstrated opposite findings in 76 patients with AS. Reduced contractility was not dependant on whether or not LVH was adequate for the degree of wall stress, neither was it dependant on the degree of wall stress, but rather was inversely associated with the degree of LVH [41]. The concept of inadequate hypertrophy suggests that the degree of remodelling is less than what would be expected for a certain degree of afterload [42]. LVEF is strongly associated with the degree of circumferential wall stress which is determined by the RWT. Patients with high RWT demonstrated higher LVEF, and suggested that inadequate LVH is associated with impaired LVEF [43]. An important confounding factor in using LVEF in patients with high RWT is that they tend to have smaller LV volumes and therefore LVEF is maintained at a lower stroke volume.

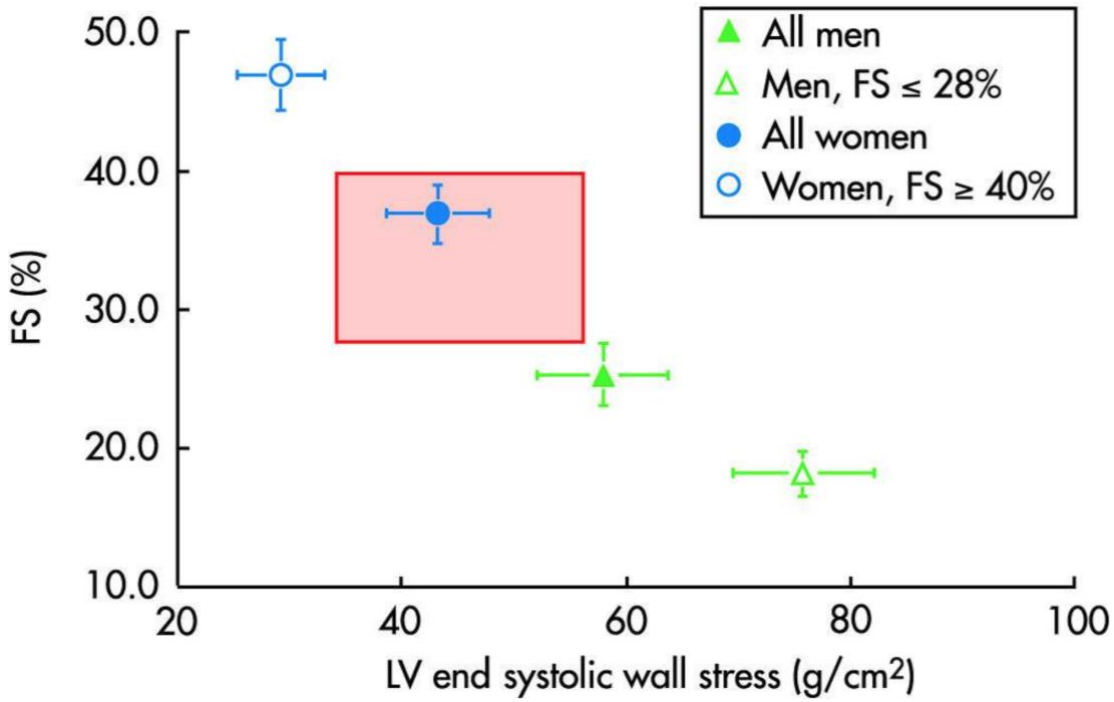


Figure 8: Association of wall stress and fractional shortening in patients with AS, according to sex. Adapted from [35]. FS- fractional shortening

Several studies have shown that LVH independently affects mortality in a severity-dependant manner [44]–[46]. In 3220 subjects from the Framingham heart study, LVM indexed to height independently predicted mortality at 4 years follow-up (relative risk (RR) for every 50g/m increase in LVM was 1.49, 95% CI: 1.2-1.85) [46]. In a larger study (n=10,406), males at high cardiovascular risk were followed by 5.9 ± 4.4 years and LVH was calculated using echocardiography. LVMi ≥149 g/m^2 was associated with a hazards ratio (HR) of 1.95; 95% CI: 1.74 to 2.17 compared to normal LVMi [44]. Studies remain divided on whether the pattern of remodelling has an influence on outcomes. One study demonstrated that mortality is not affected by relative wall thickness with similar outcomes in patients with concentric vs eccentric hypertrophy [44]. Whilst another study of 747 patients over a median follow-up of 6.4 years, demonstrated that concentric hypertrophy was associated with a higher mortality than the other remodelling patterns. This effect was only demonstrated in females (HR 1.56, 95% CI: 1.08-2.24; p=0.018) [47]. However, this has not been demonstrated in a similar study in which patients underwent SAVR, suggesting that medical management was associated with worse outcomes in patients with concentric hypertrophy but SAVR improves these outcomes [48]. RWT may have an

impact on patients with decompensated heart failure. A study including all patients with decompensated heart failure demonstrated higher mortality amongst patients with higher RWT [49].
LVM is also associated with an increase in heart failure events. The MESA study measured LVM using cardiac magnetic resonance imaging (more accurate than echocardiography) in 5098 subjects without known cardiovascular disease. The HR for heart failure for a 10% increase in LVM was 1.2, 95% CI: 1.0-1.4; p<0.01 [50].

At some point the degree of LVH exceeds that necessary for the amount of afterload and wall stress, resulting is inappropriately high LVH and may become a marker of cardiovascular risk. Cioffi et al investigated whether an excessive amount of hypertrophy for the degree of workload contributed to mortality. Inappropriately high LVH was defined as LV mass exceeding 10% of that expected from the patient's height, sex and stroke work, using the formula below:

Predicted LVM = 55.37 + (6.63*height$^{2.7}$) + (0.64* stroke work) - (18.1* gender)

In 218 patients with asymptomatic AS, followed up for 22 ± 13 months, 55.5% of patients had inappropriately high LVH. Mortality was significantly higher in this cohort compared to those with appropriate LVH (HR 3.08, 95% CI: 1.65-5.73) [45]. Among patients with hypertension and a lower than appropriate LVH (inadequate LVH) (n=21) cardiovascular death was similar to patients with appropriate LVH. The authors speculated that the former patients had increased sympathetic activity based on higher heart rate, contractility and cardiac index. This may have nullified any benefit from inadequate LVH [51]. Patients with inadequate LVH may develop reduced LVEF which is a result of afterload mismatch rather than impaired contractility [52]. This supports the concept of an appropriate cut-off for LVH in AS patients for any given stroke work/wall stress, above which cardiovascular risk increases.

1.2.2. Myocardial fibrosis

The extracellular space within the myocardium is composed of stromal cells, structural proteins- collagen and elastin, proteoglycans, glycoproteins,

glycosaminoglycans and the vascular compartment. It provides a means of communicating between myocytes, absorbs mechanical stress, provides structural integrity and helps in cardiac repair [53]. Disruption of its composition affects the heart's structure and function.

Myocardial fibrosis is the common pathological pathway in many cardiovascular diseases and is the result of an imbalance between synthesis, deposition and degradation of collagen fibres [54]. There are two forms of myocardial fibrosis that exist based on their initiating stimulus and topographical distribution. Reparative fibrosis is triggered after myocyte apoptosis and exists as microscars [54]. Autophagy and oncosis may also be the initiating stimulus [55]. Reactive fibrosis is triggered by non-apoptotic pathways and include mechanical stress, genetic mutations, endothelial inflammation and metabolic injury. This type of fibrosis exists as bands surrounding individual myocytes, bundles of cardiac muscle or within the perivascular space [54]. In AS, both reparative and reactive fibrosis can be found [56]. The initial trigger stimulates and activates fibroblasts, resulting in their differentiation into myofibroblasts. There are several pathways involved in this activation; however, angiotensin II-activated transformed growth factor- beta appears central [55]. Along with myofibroblasts, immune cells, vascular cells and myocytes are also important in the pathogenesis of fibrosis [54]. Myofibroblasts are responsible for producing collagen that makes up fibrosis. Two types exist: I and III. In AS, the ratio of type I:III is high due to excessive type I collagen [57]. There are sex-related differences in the expression of fibrosis with males producing higher levels of collagen than females [58], [59]. Males also tend to have worse architecture (cross-linking, endocardial fibrosis, and collagen volume fraction), which translates into increased myocardial stiffness [59].

In addition, to the amount and type of collagen, the degree of cross-linking of the collagen fibres determines diastolic function, exercise capacity and hospitalisation for heart failure [40], [60], [61]. In AS, this cross-linking is driven by oxidation via lysyl oxidase [62].

In AS, histological studies have identified three distinct patterns of fibrosis (figure 9):

1) Thickened endocardium with a massive fibrosis layer
2) Microscars in the mid-myocardium
3) Diffuse interstitial fibrosis

Fibrosis takes on a gradient, with higher densities in the subendocardial layer and less in the mid-myocardial layer [63]. This is postulated to follow similar distributions of wall stress, capillary density and pressure gradient [54], [64].

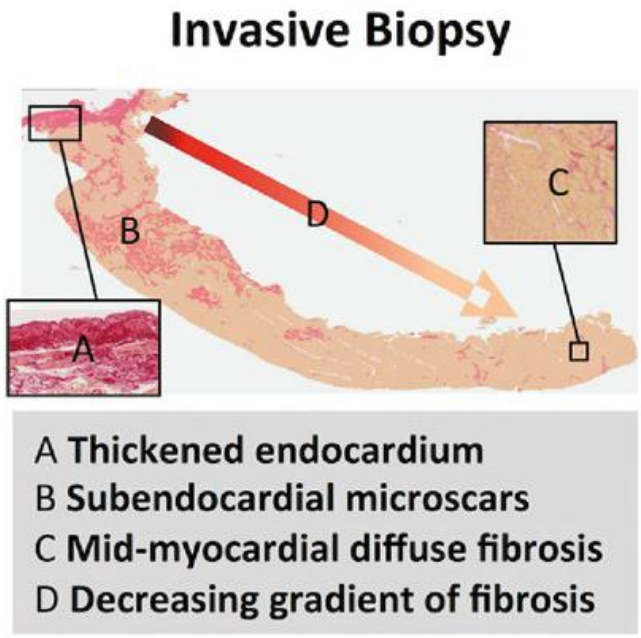


Figure 9: features of fibrosis seen on a myocardial biopsy (adapted from our study-RELIEF AS) [63]

Fibrosis has been shown to be associated with diastolic dysfunction and heart failure, despite a preserved LVEF. The degree of cross-linking and the severity of fibrosis correlates with diastolic dysfunction [33], [40], [57] but only weakly correlates with the severity of AS [33].

Non-invasive methods of quantifying fibrosis are very appealing, given the potential risks associated with an invasive biopsy. Cardiac Magnetic Resonance imaging (CMR) can identify both focal fibrosis using late gadolinium enhancement (LGE) and diffuse interstitial fibrosis using extracellular volume (ECV) quantification. Advances in cardiac computed tomography (CT) have also enabled the quantification of ECV. Details of both imaging modalities are discussed elsewhere [65]. In brief, contrast agents used in CMR (gadolinium based), and CT (iodine based) accumulate in the extracellular space and are washed out slowly from areas of fibrosis, enabling an estimation of the quantity of fibrosis and its location.

In AS, LGE has been shown to capture subendocardial scars and mid-wall fibrosis and represents both infarct-related and non-infarct scar (figure 10). It correlates with histologically-defined focal fibrosis [63] and is most commonly found at the basal septal and inferior walls [66], [67] (figure 11).

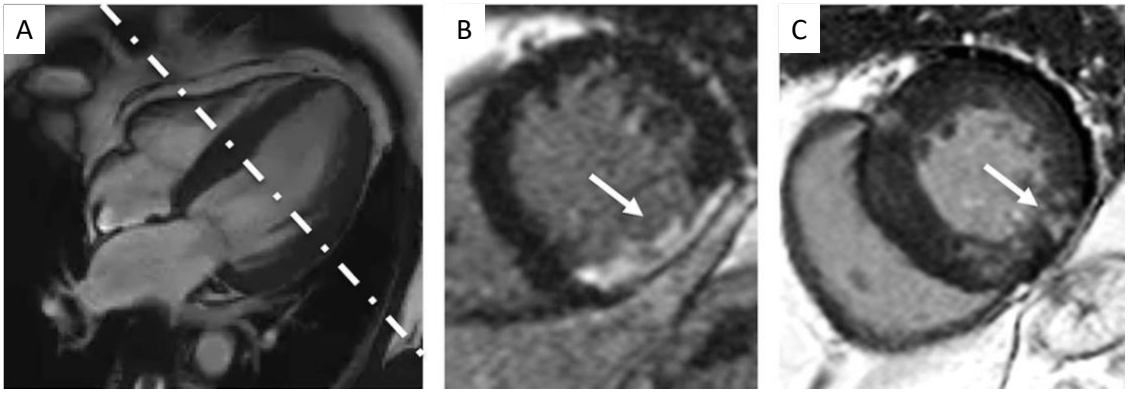


Figure 10: CMR imaging demonstrating **A**: a four chamber balanced steady-state free precession cine image with LVH. The white dotted line demonstrates the axis of acquisition of the short axis (**B** and **C**). **B**: LGE of a short axis slice in the mid ventricle showing transmural LGE of a full thickness myocardial infarct (arrow). **C**: LGE of a short axis at the mid ventricle showing patchy non-infarct LGE in the inferolateral segment (arrow) and more subtle LGE in the inferoseptum and right ventricular insertion points. Adapted from [68].

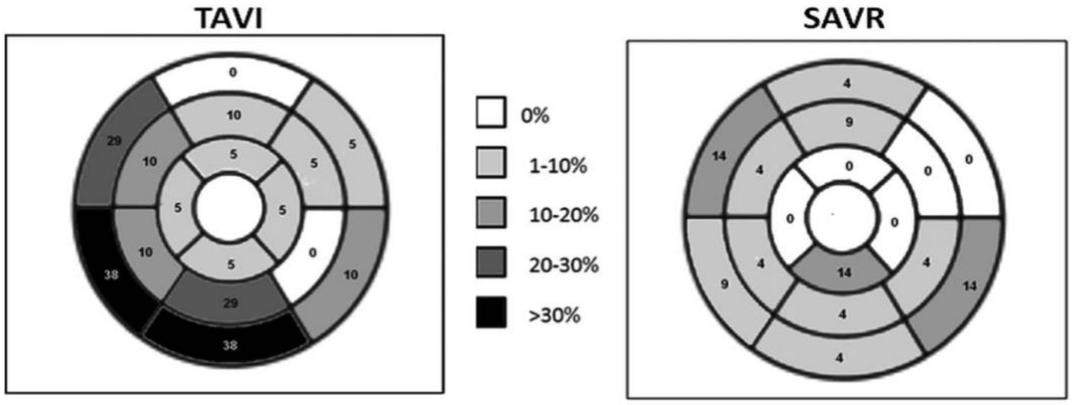


Figure 11: Increased LGE distribution in the basal septum and inferior wall Adapted from [66].

LGE defined fibrosis has been found to be an independent predictor of all-cause mortality [68]–[72]. An observational study of 143 patients with AS, identified mid-wall LGE as an independent predictor of mortality at 2.0 ± 1.4 years (HR: 5.35; 95% CI: 1.16 to 24.56; p = 0.03). Mortality in patients with LGE was related to cardiovascular causes in 4 out of 5 patients. LGE was also found in patients with moderate AS [70]. This suggests a prognostic role for the detection of fibrosis even among non-severe AS and explains the known increased mortality found among patients with moderate AS [71]. A multicentre study of 674 patients with AS who had CMR with imaging for LGE and followed up for a median of 3.6 years- many of whom had aortic valve replacement. The study showed that for every 1% increase in myocardial fibrosis, both all-cause and cardiovascular mortality increased; HR 1.11, 95% CI: 1.05-1.17; p<0.001 and HR 1.08, 95% CI: 1.01-1.17; p<0.001 respectively. The study also demonstrated that both infarct and non-infarct scar increased mortality [68]. A meta-analysis of 1151 patients with AS showed that focal fibrosis leads to an adjusted hazards ratio of all-cause mortality, at a mean of 1.1-3.6 years of 2.50; 95% CI: 1.64 to 3.83 [69]. The severity of fibrosis correlates well with NYHA status and longitudinal systolic function [67]. Focal fibrosis also correlates well with cardiac troponin I [73].

ECV quantifies the volume in ml or the fraction of the myocardium in percentage that constitutes the extracellular space. This includes structural proteins such as collagen which is of primary interest in AS. However, it also houses the vascular compartment which is known to influence ECV values [74]. Therefore, ECV measurements using CMR, and CT need to be interpreted with this in mind. Age appears to influence the degree of interstitial fibrosis in AS, with older patients demonstrating more fibrosis than younger patients with a similar severity of AS [75].

ECV is a prognostically important marker for all-cause mortality [33], [76]. One study demonstrated ECV independently predicts mortality after aortic valve replacement at a median of 3.8 years (HR per percent increase in ECV%: 1.10; 95% CI 1.02 to 1.19). The study demonstrated 52.7 deaths per 1000 patient years with an ECV% >29.1% [76]. Another study of 203 patients with varying severity of AS showed that increasing degree of diffuse fibrosis (measured using ECV indexed to body surface area: ECVi) was associated with a higher mortality rate. ECV was also independently associated with functional status measured using 6 minute walk test (6MWT) (relative change in 6MWT with 1% increase in ECV: -9.77, 95% CI: -17.0 to -2.58,

p=0.01) [33]. Among asymptomatic moderate to severe AS, ECV may not be prognostically important. A study on 174 patients found an ECV between 23-27% with no association to cardiovascular mortality, development of symptoms or major adverse cardiovascular events (MACE) [77].

1.2.3. Coronary haemodynamics

Alterations in coronary haemodynamics among AS patients are the result of an intimate relationship between the myocardium and its blood supply (figure 12). Myocardial remodelling in AS influences myocardial oxygen demand and supply. Demand is increased by the increase in LV mass [20]. Supply is restricted due to capillary rarefaction [78] and perivascular/interstitial fibrosis [63], increased LV afterload and reduced diastolic perfusion time [79] and coronary flow reserve (CFR) [80], [81].

In order to meet the increased myocardial oxygen demand at rest, patients with AS have lower microvascular resistance and greater resting vasodilatation and coronary blood flow than non-AS controls [79], [81], [82]. Consequently, there is reduced capacity for additional vasodilation of the coronary vasculature with further increases in myocardial oxygen demand during exercise or adenosine-induced hyperaemia. This accounts for the lower CFR among AS patients [81], [82] and is believed to be one of the main reasons that AS patients without obstructive coronary artery disease (CAD) develop exertional angina. Small coronary artery diameters and inadequate LV hypertrophy (LVH) may also contribute to angina [83]. The latter exists when adaptive hypertrophy is insufficient for the degree of LV pressure, resulting in high wall stress, which is an important determinant of myocardial oxygen demand [84]. Higher LV afterload increases pressure on intramural vessels- more so in the subendocardium than the subepicardium, stopping or reversing coronary blood flow during systole. As LV pressure reduces during diastole, coronary flow rapidly increases. In AS, associated LVH and diastolic dysfunction attenuate this rapid increase in diastolic flow. Additionally, the reactive hyperaemia associated with diastole causes vasodilatation of subepicardial vessels before subendocardial vessels, further limiting blood flow to the subendocardium [85]. This is further compounded by perivascular fibrosis and capillary rarefaction (the result of LVH without an equivalent increase in vasculature), which increases diffusion distances for oxygen, rendering the myocardium more susceptible to ischemia [86]. This sets

the stage for a vicious cycle, with ischemia leading to further fibrosis. While the majority of coronary flow and myocardial perfusion takes place during diastole, in AS, the fraction of the cardiac cycle spent in diastole is reduced compared to controls, as systole is prolonged by the time taken for blood to pass through a stenosed aortic valve [87]. During exercise induced tachycardia, diastolic perfusion time is further reduced, compromising blood supply [83]. Any “significant” epicardial CAD will compound this effect.

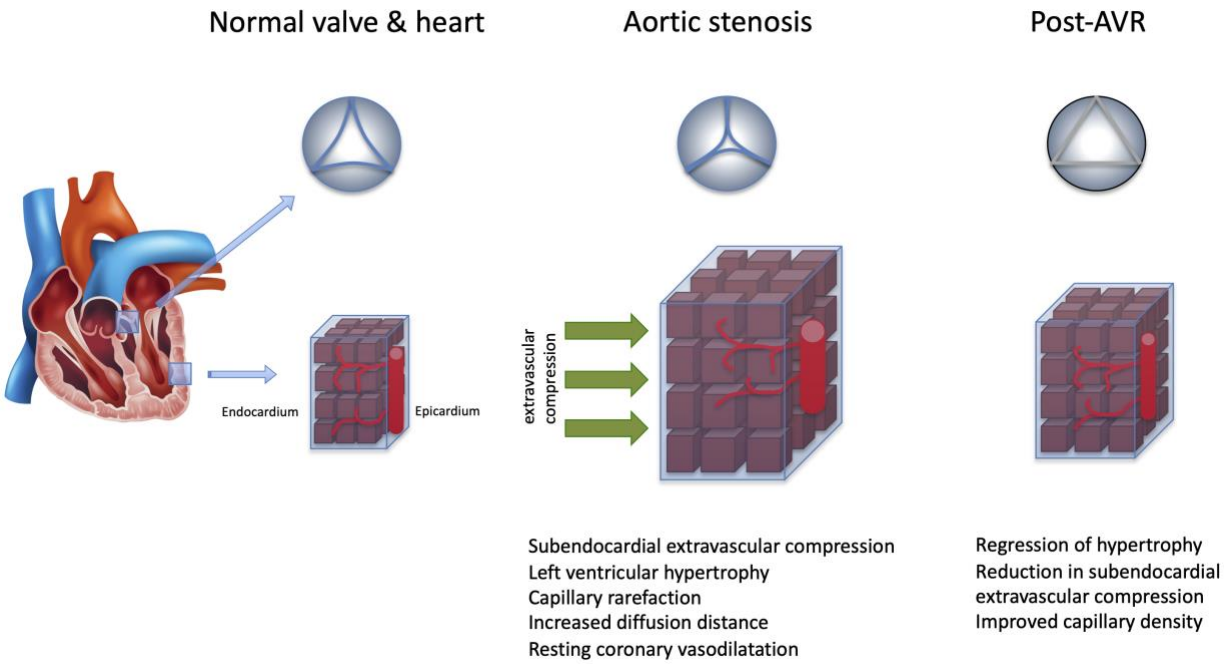


Figure 12: Myocardial remodelling changes related to aortic stenosis and reverse remodelling related to aortic valve replacement. Myocardial remodelling and an increase in afterload affect coronary demand and supply such that the myocardium (in particular the subendocardium) becomes susceptible to ischemia. After aortic valve replacement, afterload reduces and remodelling reverses to a certain extent, leading to a beneficial change in coronary haemodynamics and thus a reduction in ischemic susceptibility. Cross-sectional image of the heart obtained from www.vecteezy.com.

1.2.4. Diastolic dysfunction

1.2.4.1. Assessment of diastolic function

Diastology is defined by active myocardial relaxation and passive chamber stiffness. The gold standard in measuring diastolic function is LV end-diastolic pressure and time constant of LV relaxation (Tau). Both of which are measured using cardiac catheterization [88]. However, the most common investigation to assess diastology is

echocardiography which uses surrogates of these metrics to provide an estimation of diastolic function. Diastolic function is graded mild, moderate or severe based on tissue doppler and doppler flow indices [89] (figure 13). The size of the left atrium (LA) is also an important factor in assessing diastology. These metrics are dependent on the fluid status of the patient, RV-LV interaction, heart rate, heart rhythm, pericardial function and left atrial function. As a result they can vary with changes in any of these factors [88].

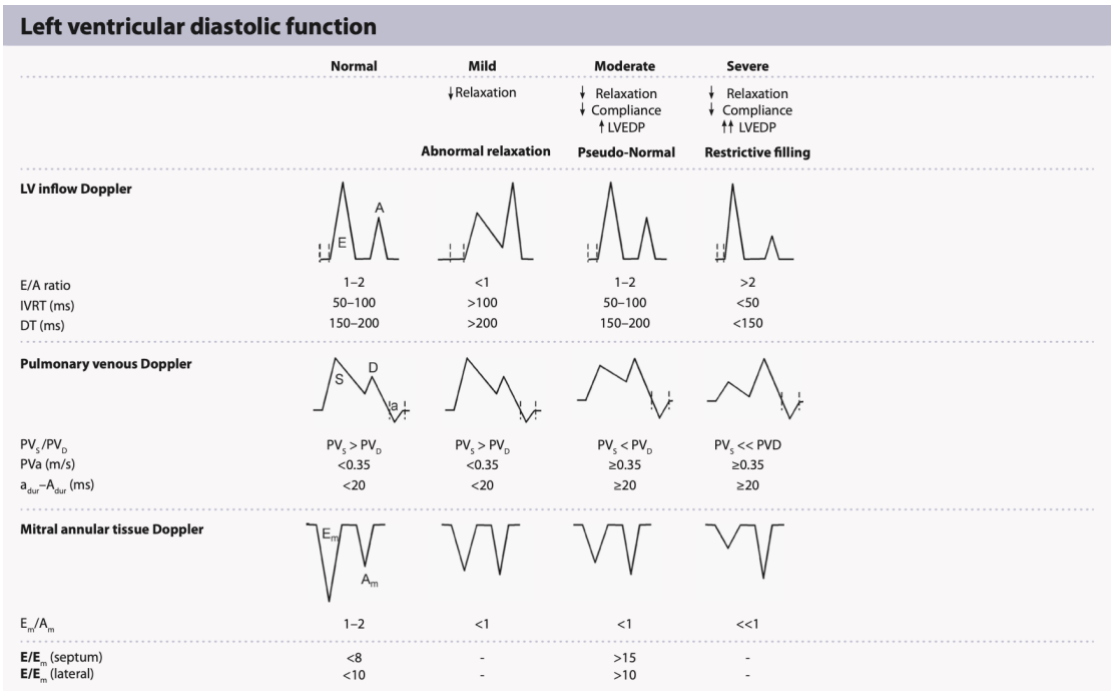


Figure 13: Grading of diastolic function according to doppler and tissue doppler measurements. Adapted from [89].

CMR can also provide similar estimates and has the advantage of better spatial resolution and enables tissue characterization. Myocardial remodelling in AS involves LVH and myocardial fibrosis, both of which affect myocardial relaxation and stiffness [90]. Age also appears to affect diastology, with older adults demonstrating a greater severity of LVH, stiffness and impaired relaxation for similar severities of AS to younger patients [75].

1.2.4.2. Impact of Diastolic function on outcomes in AS

Diastolic dysfunction is an important metric of mortality and adverse events in patients with AS. Average E/e', a marker of LV filling pressure, has demonstrated

strong independent prognostic value among 125 patients with inoperable severe AS (HR for mortality at 1 year: 2.34, 95% CI: 1.27-4.33; p=0.0072) [91]. Similarly among patients undergoing SAVR, diastolic dysfunction at baseline is independently associated with increased short and long-term mortality [92]. Amongst another cohort of SAVR patients, E/e' ratio was identified as an independent predictor of in-hospital mortality or major morbidity (defined as any of the following: all-cause death, stroke, renal failure, prolonged ventilation ≥48 hours, or need for reoperation) (HR 1.40, 95% CI: 1.03-1.78) [93]. A larger study of patients with any degree of AS followed up for 4.6 ± 4.1 years and investigated using exercise echocardiography at baseline, demonstrated that >grade 1 diastolic dysfunction was independently associated with death or the need for SAVR (HR 1.75, 95% CI: 1.13-2.71; p=0.012) [94]. Diastology measured using a combination of metrics has the advantage of a more accurate classification. Among 1383 patients undergoing SAVR for AS, LV filling pressure was estimated using E/e', e', RV systolic pressure and left atrial volume index. At a mean follow-up of 7.3 ± 3.7 years, increased LV filling pressure was an independent predictor of mortality (HR: 1.45, 95% CI: 1.16-1.81; p=0.005) [95].

Among TAVI patients, studies evaluating the prognostic utility of diastolic dysfunction at baseline have demonstrated discrepant findings. Some have shown that it is not associated with worse outcomes [96], [97], whilst others have demonstrated that it is [98], [99]. Differences in the nature of the studies (prospective, echo core lab vs retrospective), patient populations, variables used in regression models and procedural complications are likely to account for this discrepancy. A prospective study with echo core lab assessment demonstrated that increasing grades of diastolic dysfunction conferred higher mortality and hospitalization rates (1 year cardiovascular death and hospitalization with baseline grade 3 diastolic dysfunction: HR 2.73, 95% CI: 1.07-6.98; p=0.04) [98]. Even grade 1 diastolic dysfunction independently predicts mortality at 1 year compared to no diastolic dysfunction (HR 2.32, 95% CI: 1.15-4.66) and this effect can be seen as early as 30 days post-TAVI [99]. Diastolic function is associated with functional status in AS, with higher severity of dysfunction correlating to worse diastology [92], [96].

1.2.5. Systolic dysfunction

1.2.5.1. Assessment of systolic function

Systolic function can be assessed using various methods and technologies described in detail elsewhere [100]. The most commonly used metrics of systolic function in AS are left ventricular ejection fraction (LVEF), first-phase ejection fraction (EF1), strain imaging, myocardial contraction fraction (MCF), longitudinal excursion and fractional shortening. Other markers related to systolic function in AS, include stroke volume indexed and transvalvular flow rate. Diastolic dysfunction tends to precede systolic dysfunction measured using LVEF [101], [102].

LVEF is an insensitive marker of systolic function and should be interpreted with caution in AS. It does not consider changes in ventricular capacitance, which is particularly important in patients with LVH related remodelling. It is also load dependant and needs to be interpreted in the context of increased afterload related to AS [100]. Studies have demonstrated preserved LVEF in the setting of reduced cardiac function measured by EF1 and strain imaging [103], supporting the insensitivity of LVEF as a marker of cardiac function. However, clinical trials and guidelines continue to use LVEF to delineate populations and provide recommendations, mainly because it is the most commonly used metric to estimate systolic function and subsequently has the largest amount of evidence supporting its use [104].

Deformational changes in function may provide a better index of cardiac function. Strain imaging captures the change in regional and global wall motion through the cardiac cycle, in various planes- radial, longitudinal and circumferential. It is a more sensitive marker of contractility than LVEF, but similar to LVEF, is dependent on load [105]. Global longitudinal strain (GLS) worsens with increasing myocardial fibrosis and hypertrophy [67], [106], [107]. GLS tends to reduce early in the natural history of AS with compensatory increases/preservation of radial and circumferential strain [106]. A study of 43 patients with hypertensive LVH and normal LVEF, demonstrated reduced mid-wall circumferential shortening and longitudinal shortening. Whereas endocardial circumferential shortening was higher compared to controls [108]. Mid-wall shortening has demonstrated prognostic value in hypertensive patients with LVH, more so than LVEF. LVEF poorly correlates with AVA, LVMi and peak LV systolic pressure. Instead it demonstrates strong correlations with circumferential wall stress. A significant determinant of circumferential wall stress is relative wall thickness, with higher values associated with higher LVEF [43].

EF1 is a relatively novel marker of function based on the fraction of blood ejected between the time of aortic valve opening to the time of peak aortic flow. It is reduced in patients with AS compared to controls as the increased afterload and wall stress imposed by AS result in early myocardial dysfunction and prolongs the time to peak aortic flow [103]. 25% has been determined as the optimum cut-off to predict future AVR, heart failure and death [109]. Studies have demonstrated the prognostic value of EF1 among symptomatic and asymptomatic, moderate and severe AS, greater than that demonstrated by established prognostic markers [103], [109]. EF1 decreases with increasing AS severity, myocardial fibrosis content and global afterload [103].

Myocardial contraction fraction (MCF) is a volumetric measure of systolic function. It is the ratio of blood pumped out of the heart (stroke volume) indexed to the amount of LV myocardium (myocardial volume). The advantage of MCF over other metrics of cardiac function is that by indexing to myocardial volume, MCF is independent of geometric factors [110].

1.2.5.2. Low-flow, low-gradient AS

The narrower the valve orifice becomes, the greater the velocity of blood through that valve. The grading of AS is based on this transvalvular velocity, which is used to calculate pressure gradients (mean (MG) and peak gradient (PG)) and aortic valve orifice area (AVA) using the modified Bernoulli equation and the continuity equation respectively [111]. Around a third of patients with severe AS do not fulfil the classical criteria for severe AS- namely high flow, high gradient AS (peak velocity>4m/s, mean gradient ≥40mmHg and AVA≤1.0cm^2). Reduced flow through the valve usually accounts for the discrepancy between these metrics of AS severity, such that AVA is in the severe range whilst transvalvular gradients are not. Patients are further classified according to LVEF, with <50% considered as the cut-off for reduced systolic function in AS and termed as classical low-flow, low-gradient (LFLG) AS. LVEF can also be preserved (>50%) and associated with reduced flow termed paradoxical LFLG AS. Both are associated with increased mortality [112].

Myocardial fibrosis affects the transmission of force through the myocardium. Apart from the amount of fibrosis, the presence of cross linking of collagen fibres is associated with systolic dysfunction. One study demonstrated depressed LVEF

among patients with normal collagen volume fraction and increased cross linking compared to those with increased collagen volume but without cross linking [40].

1.2.5.3. Impact of systolic function on outcomes

Left ventricular systolic dysfunction (LVSD) independently increases mortality from heart failure and sudden cardiac death post-TAVI, with worse function conferring a higher risk [113]. However, transvalvular flow (measured as indexed stroke volume $\leq$35ml/m^2) may be a better prognostic marker than left ventricular ejection fraction (LVEF). This is supported by poorer outcomes in patients with paradoxical LFLG AS (where LVEF is normal) compared to high gradient AS and a study where low flow remained an independent predictor of mortality (HR 1.29; 95% CI 1.03–1.62) but LVEF and mean gradient did not [114]. Thus, the effect of low forward flow maybe more important than the mechanism causing it. It should be noted that despite poor outcomes compared to normal-flow, high gradient patients, those with LFLG have a better survival with TAVI than conservative treatment (HR 0.36, 95% CI: 0.24-0.55), p<0.001) [115]. This is the case for both classical LFLG AS (HR 0.43, 95% CI: 0.19-0.98; p=0.04) and paradoxical LFLG AS (HR 0.38, 95% CI: 0.16-0.87; p=0.02) [116]. Among survivors, functional outcomes at 1 year post-TAVI with low flow are comparable to normal flow patients [114]. LVEF<50% is an indication for AVR in asymptomatic severe AS [18]. However, several studies have demonstrated that a LVEF 50-60% is associated with a higher mortality compared to LVEF>60% [117], [118]. Therefore among patients with preserved LVEF, further refinement of risk is beneficial. Strain imaging is a more sensitive marker of LV systolic function than LVEF. Studies have demonstrated among patients with preserved LVEF, longitudinal strain can predict mortality over and above traditional risk factors (for every 1% increase in longitudinal strain HR 1.05-1.42; p<0.0001) [119], [120]. A marked impact on mortality was observed in patients with longitudinal strain <-12.1% compared to better strain values [120]. MCF has demonstrated prognostic importance among various papulations of AS and has improved risk prediction scores, offering an alternative metric for risk stratification [121], [122]. In an observational study of patients managed medically and surgically, decreasing tertiles of MCF at baseline predicted increasing risk of mortality at a follow-up of 80 months. The optimum MCF cut-off point for mortality prediction was identified as 41%. MCF improved risk

prediction greater in a model compared to other metrics of LV systolic function (LVEF, GLS, SV indexed) [122].

1.3. Treatment of AS

Current guidelines recommend treatment with either SAVR or TAVI in patients with severe AS [123]. Since its inception in 2002 [124], TAVI technology has advanced and outcomes improved, such that it is the main technique used for valve replacement. Treating AS with SAVR is reserved for patients where TAVI is inappropriate. The utility of TAVI has surpassed that of SAVR in many countries [125] and will continue to do so as its safety and efficacy is proven among lower risk patients [6,7].

However, as with many technological advancements, there are often non-responders- patients who do not benefit from the procedure due to adverse outcomes. It is usually after a wide-scale distribution of the technology that these sub-populations of non-responders are identified, leading to further refinements in patient selection criteria. Once identified, an understanding of the mechanisms causing the adverse events, stratification by potential response and defining alternative/additional therapeutic pathways that these sub-populations may benefit from is required. Adverse events with TAVI are related to:

1. the number and severity of comorbidities,
2. procedural factors, such as the type of access,
3. AS status, such as end-stage heart failure

AS is considered both a disease of the valve and the myocardium. For it is the response of the myocardium to the obstruction caused by AS, that is responsible for symptoms and adverse outcomes related to AS [34], [56], [63], [76].

1.3.1. Effect of AVR on left ventricular hypertrophy

AVR does result in regression of LVH but not back to normal levels. Regression of LVH is proportional to LVH at baseline (pre-AVR), with the largest gains seen among patients with the most LVH at baseline. The degree of regression at 1 year post-SAVR independently predicts long-term survival at 10 years [128]. This period represents the greatest rate of LVH regression post-SAVR [129]. The regression in LVMi is both a product of reduced cellular and extracellular matrix volume [56]. Among 22 participants (including AS and controls), a study concluded that at 81 ± 22

months post-SAVR, LVMi and muscle fibre diameter reduced gradually by 43% and 15% respectively, compared to baseline [130].

1.3.2. Effect of AVR on myocardial fibrosis

Most studies have demonstrated that aortic valve replacement does not resolve focal fibrosis. A study of 116 patients who had a repeat CMR, 1 year post-SAVR for AS, demonstrated no difference in LGE compared to baseline [56]. Another study in 58 patients, 9 months post-SAVR confirmed these findings [67]. However, a study comparing remodelling in TAVI vs SAVR showed that focal fibrosis reduces with TAVI but not with SAVR. At baseline the TAVI cohort had more LGE than the SAVR cohort and whilst LGE mass and percentage reduced at 6 months post-procedure in both, the reduction in the SAVR cohort was not statistically significant [66]. Focal fibrosis also precludes favourable reverse remodelling post-TAVI but does not appear to affect improvement in LVEF [131].

ECV post-AVR can either increase or decrease depending on the concomitant change in cellular hypertrophy. For example, one study demonstrated no change in ECV percentage at 1 year post-SAVR; however, ECV when measured as a volume did reduce. This can be explained by a larger reduction in cellular size compared to extracellular space (figure 14) [56].

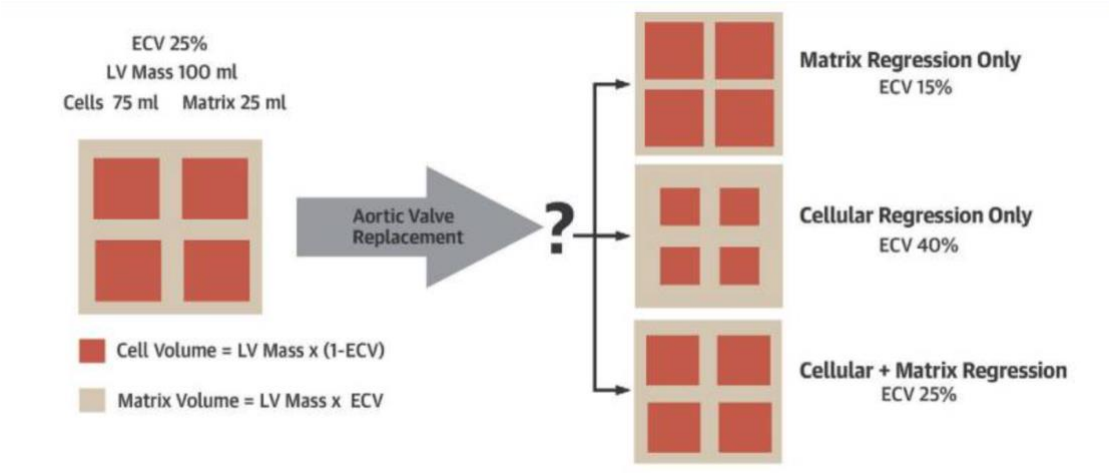


Figure 14: change in ECV depending on matrix and cellular regression (adapted from our study-RELIEF-AS) [56].

At 9 months post-SAVR, improvement in NYHA status was greatest among patients without focal fibrosis; with no improvement demonstrated among the subgroup with

severe fibrosis. Improvement in NYHA status was predicted by lower Euroscore and better longitudinal strain at baseline [67].

1.3.3. Effect of AVR on coronary haemodynamics

Figure 15 illustrates the changes associated with relief of AS and their effects on coronary haemodynamics. Several studies have demonstrated normalization in coronary haemodynamics following SAVR. Coronary flow profiles improve one-week post SAVR as systolic forward flow begins earlier in systole accompanied by an increase in diastolic time. These improvements are associated with improvements in energetics, oxygenation and circumferential strain [132].

Myocardial blood flow in the subendocardium, which is reduced in AS, improves as early as 2 weeks post SAVR [133] due in part to the reduction in LV wall stress that accompanies the relief of AS. At 6 months post SAVR, CFR improves due to a reduction in resting blood flow, the increase in hyperaemic myocardial blood flow, and the associated reduction in LVH [82]. However, even at 30 months post-SAVR, CFR may not completely normalize as hyperaemic blood flow can remain blunted [134].

Because CFR is dependent on diastolic perfusion time, severity of AS and LV afterload [79], [135], the presence of hypertension after SAVR is an important consideration as it contributes to LV afterload, preventing structural and functional changes that would improve myocardial blood flow.

The type of prosthesis used, and the presence of patient-prosthesis mismatch (PPM) also affect CFR. Stentless biological prosthesis closely resemble physiological geometry and diastolic flow patterns and do not result in diastolic leakage flow. Consequently, they can result in normalization of CFR values. Metallic prosthesis, on the other hand, result in less of an improvement in CFR. PPM can cause increased aortic flow turbulence and reduced coronary flow. However, compared to metallic prothesis, CFR with stentless biological prosthesis is not adversely affected by PPM [136].

TAVI results in reduced afterload and subendocardial compression, which subsequently increases systolic coronary flow at rest [86] and diastolic coronary flow during hyperaemia [86], [137], [138]. These hemodynamic changes are likely to account for the relief of angina in some patients immediately following TAVI [139].

Figure 12 summarizes the changes associated with relief of AS and their effects on coronary haemodynamics.

There is uncertainty regarding normalization of CFR post-TAVI with some studies suggesting immediate improvement post-TAVI [81] and others suggesting it is a long term phenomenon [86], [140]. Improvement in CFR is predominantly driven by a decrease in hyperaemic microvascular resistance, which increases vasodilatory capacity and hyperaemic blood flow. Post-TAVI aortic regurgitation may play a detrimental role in these changes [81], as it is known to reduce CFR and change phasic coronary flow from predominantly diastolic to systolic in a severity-dependent manner [141]. At rest, microvascular resistance and flow velocity remain unchanged immediately pre and post-TAVI as the driving forces- myocardial mass and capillary rarefaction are still present- requiring the compensatory vasodilatation at rest [81].

Given the overall improvements in coronary haemodynamics and in some cases angina post-TAVI, the significance of coexisting epicardial coronary stenosis needs to be carefully considered. A recent study sought to identify the 'predominant lesion' in patients with severe AS and coexisting coronary stenosis by comparing iFR in AS patients treated with TAVI to iFR in patients with coronary stenosis (without AS) treated with PCI. Their study was based on the concept that both AS and coronary stenosis independently affect microvascular resistance during the wave free period of diastole, such that low resistance indicates a higher severity of stenosis. In AS, resting microvascular resistance was low and subsequently increased following TAVI, signifying the role of AS in reducing coronary flow. This increase was independent of the severity of coexisting coronary stenosis. TAVI achieved a similar increase in microvascular resistance as stenting a coronary stenosis with an iFR>0.74. For an iFR ≤0.74, PCI achieved larger increases in microvascular resistance than TAVI, concluding that for any coronary stenosis with an iFR > 0.74, AS was the predominant lesion and TAVI achieved greater improvements in microvascular haemodynamics than PCI [142]. This study highlights how dual pathology (severe AS and coronary stenosis) influences coronary haemodynamics and the importance and feasibility of assessing the effect of each lesion. However, further validation of these physiological assessment tools is required to guide management. Until trial data emerges, revascularization decisions have to be made on a case-by-case basis, with functional data contributing to this decision.

1.3.4. Effect of AVR on diastolic dysfunction

Diastolic dysfunction tends to improve post-TAVI [96], [98], albeit slower than improvements in systolic function, as the former is more aligned with structural changes whilst systolic function also reflects afterload which is quickly reversed with AVR [143]. A large prospective study with echo core lab assessment demonstrated that 71% of patients showed an improvement in diastolic function by 1 grade or had grade 1 diastolic dysfunction at 30 days post-TAVI. These patients demonstrated lower cardiovascular mortality and hospitalisation at 1 year (HR: 0.39, 95% CI: 1.07-6.98; p=0.04) [98]. Among 358 patients who had a TAVI for severe AS, diastolic function improved at 6 months post-TAVI and this improvement was maintained at 1 year. Improvements in diastolic function are associated with improvements in NYHA status post-TAVI. LVEF does not appear to influence improvements in both diastology and NYHA; with similar improvements demonstrated in patients with both LVEF<50% and >50% at baseline. Patients that do not demonstrate any improvement in diastolic dysfunction demonstrated a higher mortality at 1 year post-TAVI compared to those who did [96]. Determinants of improvement in diastolic dysfunction are not well explored and warrant further investigation. The presence of cardiac amyloidosis, irreversible myocardial fibrosis and hypertension may account for this. The persistence of severe diastolic dysfunction (grade 3) is associated with a higher mortality at 1 year compared to patients who do demonstrate an improvement in diastolic dysfunction [96]. Post-TAVI aortic regurgitation (AR) plays a key role in reverse remodelling, impacts on mortality and demonstrates a significant interaction with baseline diastolic dysfunction. Patients with grade 3 diastolic dysfunction are less compliant to even low severity of post-TAVI AR, leading to increase in LV end diastolic pressure and associated with heart failure and death [144]–[146].

1.3.5. Effect of AVR on systolic dysfunction

LVEF increases post-SAVR as there is an immediate reduction in afterload [96], [130]. At 1 year post-TAVI, a study showed a mean change in LVEF from 38% to 51% [96]. Improvements in LVEF are seen in up to two-thirds of patients as early as 48 hours post-TAVI and continued up to over a year post-TAVI. Determinants of improvement in LVSD are high transvalvular gradient at baseline and the absence of a permanent pacemaker [147]. Using CMR, a study in 54 patients demonstrated a

moderate inverse correlation between improvement in LVEF at 27 ± 22 months post-SAVR and baseline severity of fibrosis (r= -0.47; p=0.02) [72].
Other markers of cardiac function also improve post-AVR- EF1 and strain [103], [148], [149]. Patients with no improvement in EF1 post-AVR had significantly higher focal fibrosis content and subsequently a higher mortality [103]. GLS and global circumferential strain (GCS) demonstrated an improvement at 3 months post-SAVR but not earlier [148]. Improvements in GLS are maintained at 12 months post-SAVR [149].

1.4. Utility of TAVI

TAVI emerged from the need to cater for the high-risk patient (defined as a society of thoracic surgery risk (STS) score >8-10% or Euroscore II of >15-20% [150]). Initial studies demonstrating better outcomes with TAVI compared to conservative treatment in such high-risk patients [151]. Compared to SAVR, TAVI resulted in a similar mortality rate, faster improvements in symptoms and different post-operative complication rates [152]. It was shown to be non-inferior to SAVR among patients at intermediate surgical risk (STS score of 4.5±1.6) [153]. TAVI has also shown promise among low-risk patients with better outcomes than SAVR [126]. Current guidelines reflect this by favouring TAVI over SAVR in patients at intermediate or high surgical risk [18], [154].

1.5. Futility in TAVI

Some patients either have a high mortality in spite of TAVI or receive no symptomatic/functional benefit from the procedure. In the CoreValve US Pivotal Extreme and High Risk trials, TAVI was futile at 1 year in 50.8% of patients; 30.2% were dead; quality of life (QoL) did not improve in 19.6%, and declined in 1.0% [155]. Similarly, the PARTNER high risk trial, showed that TAVI was futile in 40% of patients [156]. Although technological, operator and pathway improvements have reduced mortality and complications since its inception [157], TAVI remains expensive, invasive and carries risk. TAVI studies have primarily focused on identifying predictors of mortality and major adverse cardiovascular events, however many elderly TAVI patients value different treatment goals such as independence and QoL.

Guidelines define futility as a lack of survival or improvement in QoL/symptoms at 1 year post-TAVI and do not recommend intervention for AS if TAVI is deemed futile [154]. Although predicting outcomes and making management decisions can be challenging, it is becoming increasingly important as the utility of TAVI expands. The more comorbidities a patient has, the lower the chances of an improvement in physical and psychological quality of life and the higher the mortality rate. Additionally, the severity of these comorbidities is important, with higher severity generally pertaining a higher risk of futility. Futility should be considered especially in patients whose health is affected primarily by comorbidities other than AS. It is important to consider certain comorbidities that can reverse post-TAVI (e.g. coronary haemodynamics), despite conferring excess risk. Whilst others may not be reversible (e.g. cardiac amyloidosis). Quantifying the contribution of specific comorbidities to a patient's symptoms can facilitate better prediction of symptomatic improvement and allow patient expectations from TAVI to be managed. Therefore, both patients and clinicians need to be clear about the potential improvements that TAVI can provide. Although our understanding of comorbidities and their impact on TAVI outcomes has improved, there is still a need to refine our prediction tools and better understand the impact of TAVI on QoL and function, such that this rapidly growing technology is targeted towards those patients who are likely to gain the most benefit and avoided amongst those where it will be futile.

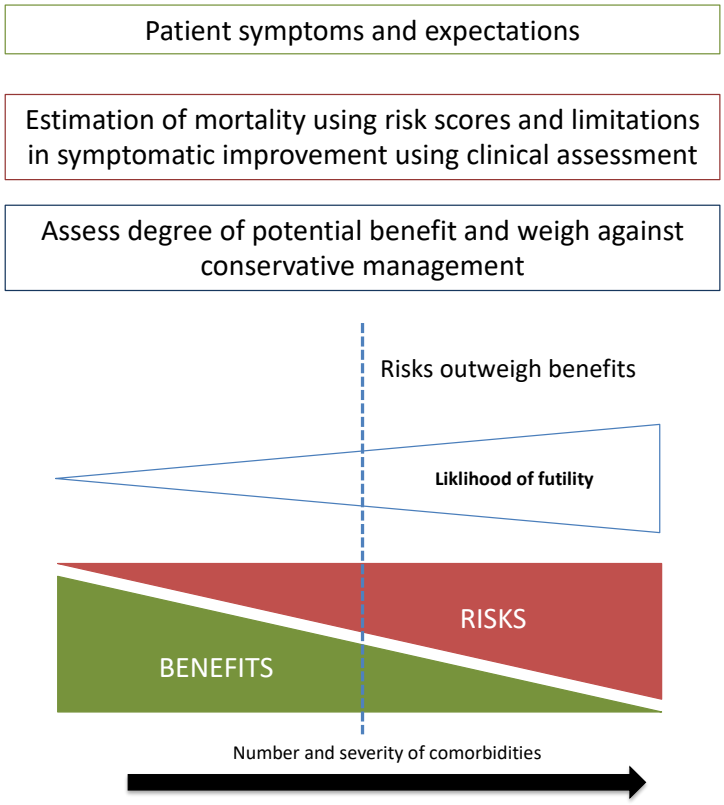


Figure 15: Benefit versus risk and the determination of futility of TAVI.

The balance between benefits and risk of TAVI dictates the decision to perform a TAVI, with increasing number and severity of comorbidities resulting in increased risk of futility. The risk of futility in TAVI should be judged within the context of a patient's symptoms, through clinical evaluation and the use of established scoring systems. The multi-disciplinary team should then provide the framework to make a management decision. This model underpins the importance of shared decision-making that should involve the patient. The decision is made at a certain time point and should be compared with conservative management. In figure 15, the blue dotted line represents the halfway point between benefits and risks, where the risk of futility increases with the accumulation of risk and dissipation of benefit.

1.6. Coexisting aortic stenosis and transthyretin cardiac amyloidosis (AS-ATTR)

In this thesis, I have used the term AS-ATTR to define the coexistence of aortic stenosis and wild-type transthyretin cardiac amyloidosis (Perugini grade 2 and 3).

Perugini grade 1 ATTR is often considered subclinical and where I discuss Perugini grade 1 AS-ATTR, I have clearly made this distinction. A summary of the nomenclature used in this thesis and by the wider cardiology community is shown in figure 16.

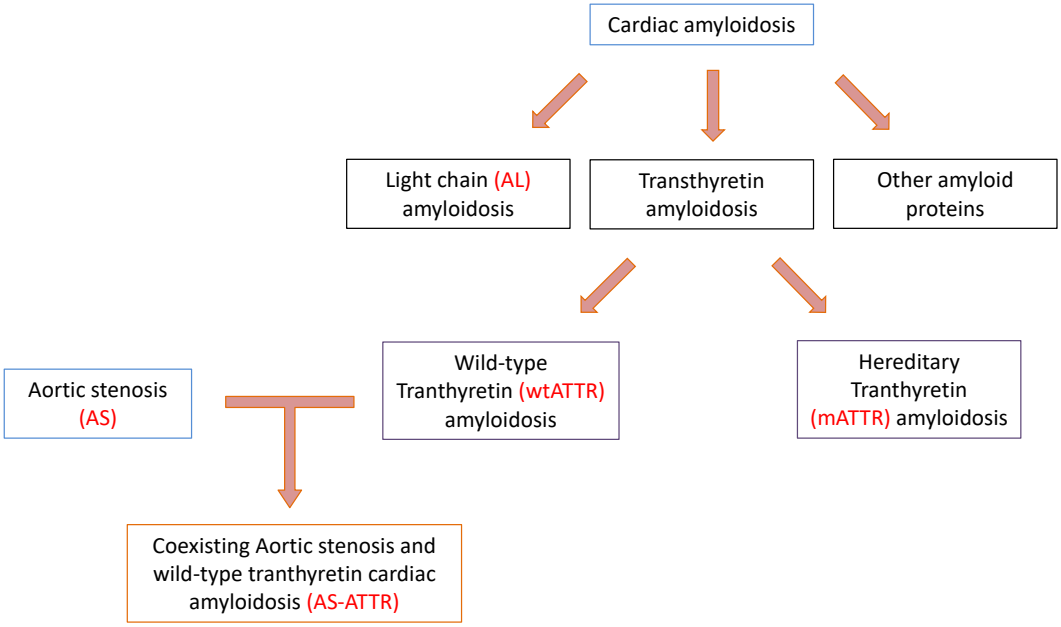


Figure 16: Subtypes of cardiac amyloidosis and common nomenclature used

1.6.1. Epidemiology

Over the past five years, several studies have reported a high prevalence of coexisting ATTR among patients with AS; between 8-16% [158]–[161]. Our study [158], that of Castano et al [160] and Nitsche et al [161] were prospective observational studies recruiting all comers (age cut-off>75 for Scully et al and >65 years for Castano et al) with severe AS referred for a TAVI. The diagnosis of ATTR was made using bone scintigraphy. Cavalcante et al [159] retrospectively identified ATTR among patients with AS (85% had severe AS) using a CMR. One study examined the prevalence among patients undergoing SAVR using a combination of histology and bone scintigraphy and revealed a lower prevalence of 4% [162].

1.6.2. Wild-type transthyretin cardiac amyloidosis (ATTR)

Cardiac amyloidosis is caused by the deposition of insoluble folded proteins within the cardiac architecture. There are several types of cardiac amyloid proteins of which transthyretin (ATTR) and light chain (AL) are the most common [163]. Transthyretin normally acts as a carrier for retinol binding protein and thyroxine. Majority of transthyretin is produced by the liver with smaller amounts produced by the choroid plexus and retinal epithelial cells [164]. It is a tetramer of four beta sheet rich monomers that dissociate into monomers and aggregate in tissues [165]. The transthyretin proteins get embedded within the extracellular space of the myocardium resulting in a restrictive cardiomyopathy [164] (figure 17). ATTR is further classified into wild type (wtATTR) or hereditary/mutant (mATTR), based on the absence or presence respectively, of point mutations within the transthyretin gene. mATTR is common among certain populations such as the Val122Ile phenotype which is found in 3.5% of African-Americans [166]. Whereas wtATTR is commonly found among elderly patients; 25% of older adults had wtATTR at autopsy [167], [168]. However, the true prevalence within the general population is unknown.

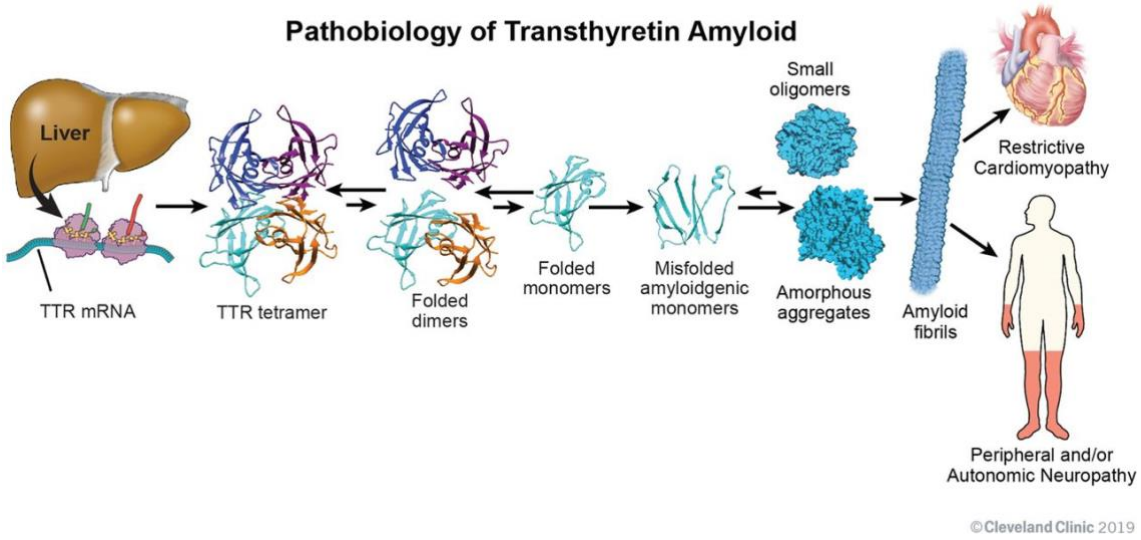


Figure 17: The pathobiology of transthyretin amyloid. From production in sources such as the liver of its stable tetrameric form to dissociation of monomers and misfolding resulting in amyloid fibrils. Adapted from [164].

1.6.3. Diagnosis of ATTR

The need to diagnose wtATTR is increasingly becoming important for several reasons; it is commonly associated with other diseases such as aortic stenosis and

heart failure with preserved ejection fraction [158], [169]. Secondly, it is increasingly being recognised that wtATTR can mascaraed as other diseases, given its propensity for increased left ventricular wall thickness and diastolic dysfunction- aortic stenosis, hypertrophic cardiomyopathy and hypertensive heart disease [170]. Thirdly, with the advent of new therapies, both symptoms and prognosis can improve [171]. This recognition along with new diagnostic modalities and probably an ageing population have contributed to an increase in the prevalence of wtATTR [164] (figure 18).

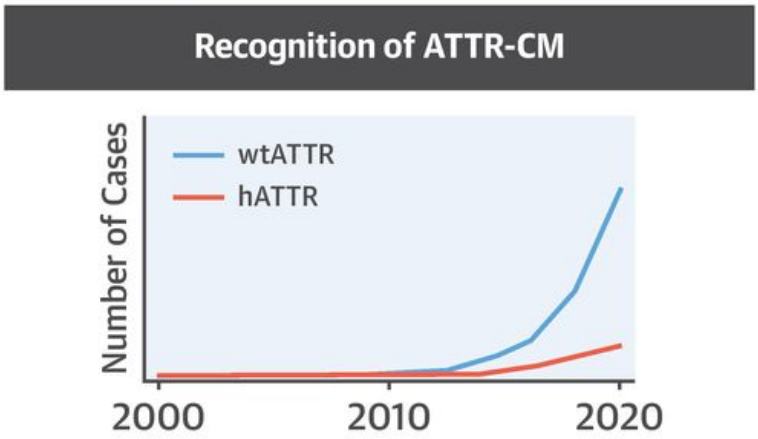


Figure 18: Prevalence of ATTR over time. Both wtATTR and hATTR have seen increases in prevalence due to increased awareness, widely available diagnostic modalities and most likely an ageing population. Adapted from [164].

Traditionally wtATTR was diagnosed using histological examination of an endomyocardial biopsy. Although this remains the gold standard, the practicality of performing biopsies in elderly patients, many of whom are frail with comorbidities remains challenging. Additionally, there exists a complication rate and the procedure is susceptible to sampling error [172]. Cardiac biopsy is now reserved for patients where imaging is equivocal and the diagnosis uncertain or in the presence of a monoclonal gammopathy to differentiate from AL amyloidosis [173]. However, several non-invasive imaging modalities provide alternative options with high diagnostic accuracy.

1.6.3.1. Echocardiography

Echocardiography is usually the first cardiac imaging investigation that patients with cardiac-related symptoms will have. It is relatively cheap, widely available and provides a wealth of data on cardiac and valvular structure and function. In ATTR, echocardiography can demonstrate increased wall thickness, diastolic dysfunction, atrial enlargement (figure 19 and 20). These markers have high specificity for cardiac amyloidosis but low sensitivity. On the other hand, deformational imaging, particularly global longitudinal strain (GLS) has shown good diagnostic performance, especially when combined with ejection fraction (EF/GLS: area under the curve 0.95; 95% CI: 0.89–0.98) [170]. Longitudinal strain is disproportionately reduced at the base and mid ventricle more than at the apex resulting in apical sparing pattern (figure) [174].

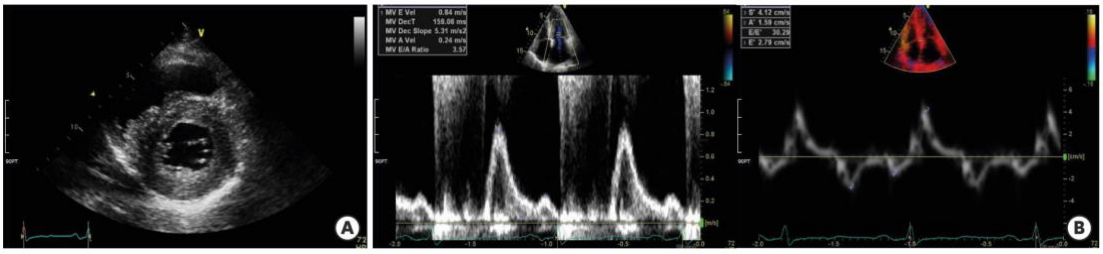


Figure 19: Echocardiographic features of ATTR. (A) Parasternal short axis view demonstrating thick LV walls (B) Doppler study of mitral inflow (left image) demonstrating a restrictive filling pattern with a high E/A ratio and tissue doppler study of septal mitral annulus (right image) showing low e′ velocity [175].

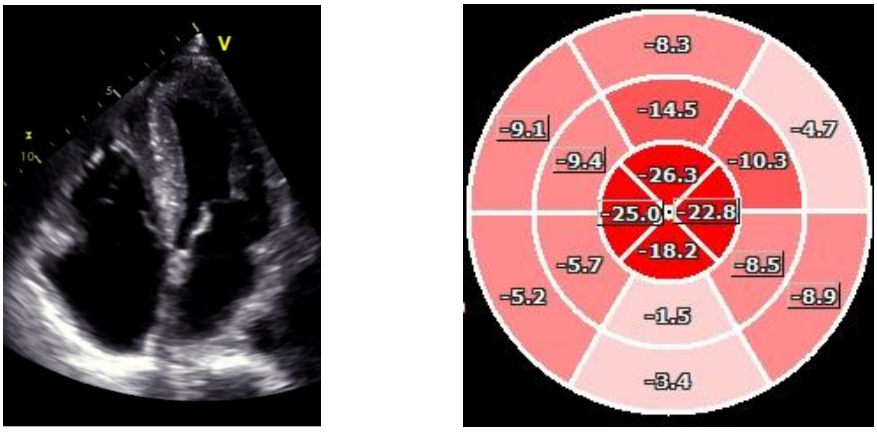


Figure 20: Echocardiographic features of ATTR. Left image illustrates an apical 4 chamber view with enlarged atria and thick ventricular walls. Right image illustrates the classical apical sparing pattern obtained from longitudinal strain analysis. The

dark red areas of the apex indicate good function, whilst the paler red areas indicate poor function at the base and mid LV.

1.6.3.2. Cardiac Magnetic Resonance (CMR)

CMR allows tissue characterisation whilst providing detailed, reproducible images of cardiac structure and function. Exploiting the kinetics of the extracellular contrast agent, gadolinium, three distinct patterns can be seen in amyloidosis based on late gadolinium enhancement: none, subendocardial and transmural- demonstrating increasing amyloid burden and worse prognosis [176]. T1 mapping utilises the magnetic properties of different tissues in health and disease to provide a quantitative measure of T1 relaxation time. It can be represented using pre-contrast T1 (native) which has good diagnostic performance for ATTR (area under the curve of 0.85 [95% CI: 0.77 to 0.92]) and is a marker for early disease [177]. However, native T1 mapping cannot differentiate between oedema, infiltration or fibrosis). An alternative that uses T1 mapping is extracellular volume quantification (ECV), which measures the percentage of free water within the extracellular space. It is more specific for infiltration than native T1 mapping, has a high diagnostic performance for ATTR (area under the curve of 0.91 (95% CI: 0.87 to 0.94)) and is independently predictive of mortality [178]. Figure 21 shows the different sequences used in CMR in patients with normal hearts compared to ATTR and AL amyloidosis.

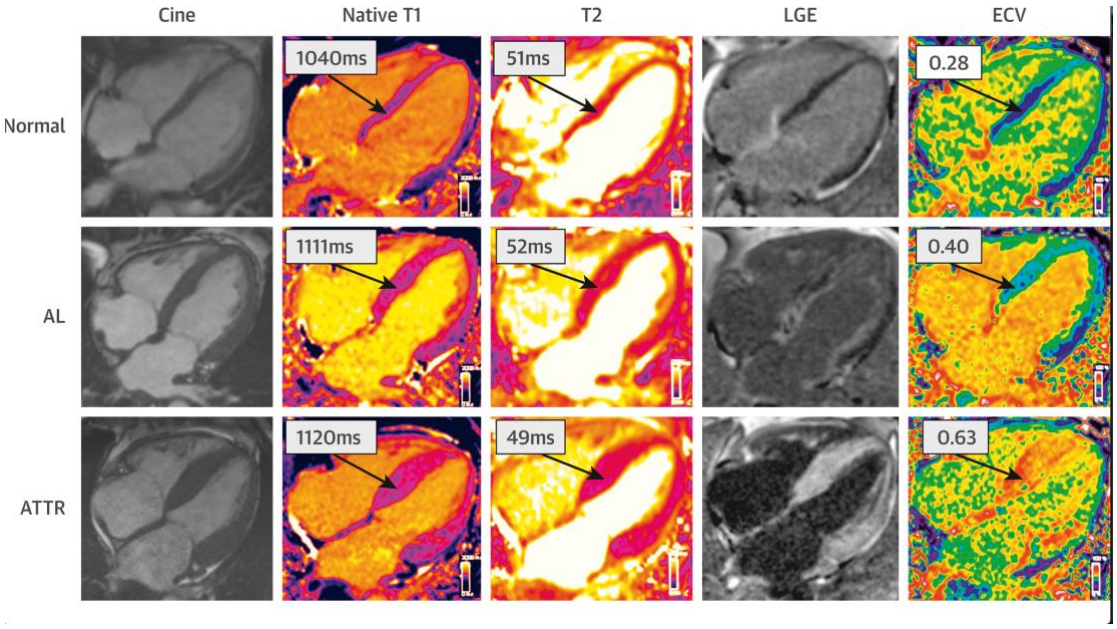


Figure 21: CMR sequences showing the differences in patients with normal hearts compared to ATTR and AL amyloidosis [179].

1.6.3.3. Bone/Cardiac scintigraphy

Bone scintigraphy using Technitium (^{99m}Tc)- labelled pyrophosphate (PYP), 3-diphosphono-1,2-propanodicarboxylic acid (DPD) or hydroxymethylene diphosphonate (HMDP), can diagnose ATTR with high accuracy [180]–[182]. Despite a sensitivity reported around 100%, the specificity of bone scintigraphy ranges between 86-96% [180], [183]. This false positive rate can be accounted for by cases of AL amyloidosis. In order to increase the specificity to 100% for ATTR, guidelines recommend performing bone scintigraphy with simultaneous evaluation for a plasma cell dyscrasia- the absence of which confirms ATTR. The latter is usually achieved by performing serum and urinary immunofixation and evaluating serum for free light chains and urine for Bence Jones proteins [173], [183].
The substrate that the radiotracer binds to is yet unknown but maybe influenced by the calcium content [182]. Bone scintigraphy involves the peripheral injection of the radiotracer, followed by a set delay and imaging using either single photon emission computed tomography (SPECT), planar or a combination of the two. There are several ways to quantify the bone scintigram:

1) Perugini grading is a visually based assessment of cardiac uptake relative to the long bones (femur and humerus). Grading ranges from 0 indicating no cardiac uptake of the radiotracer to 3- with higher grades correlating with more cardiac uptake relative to the long bones (figure 22).

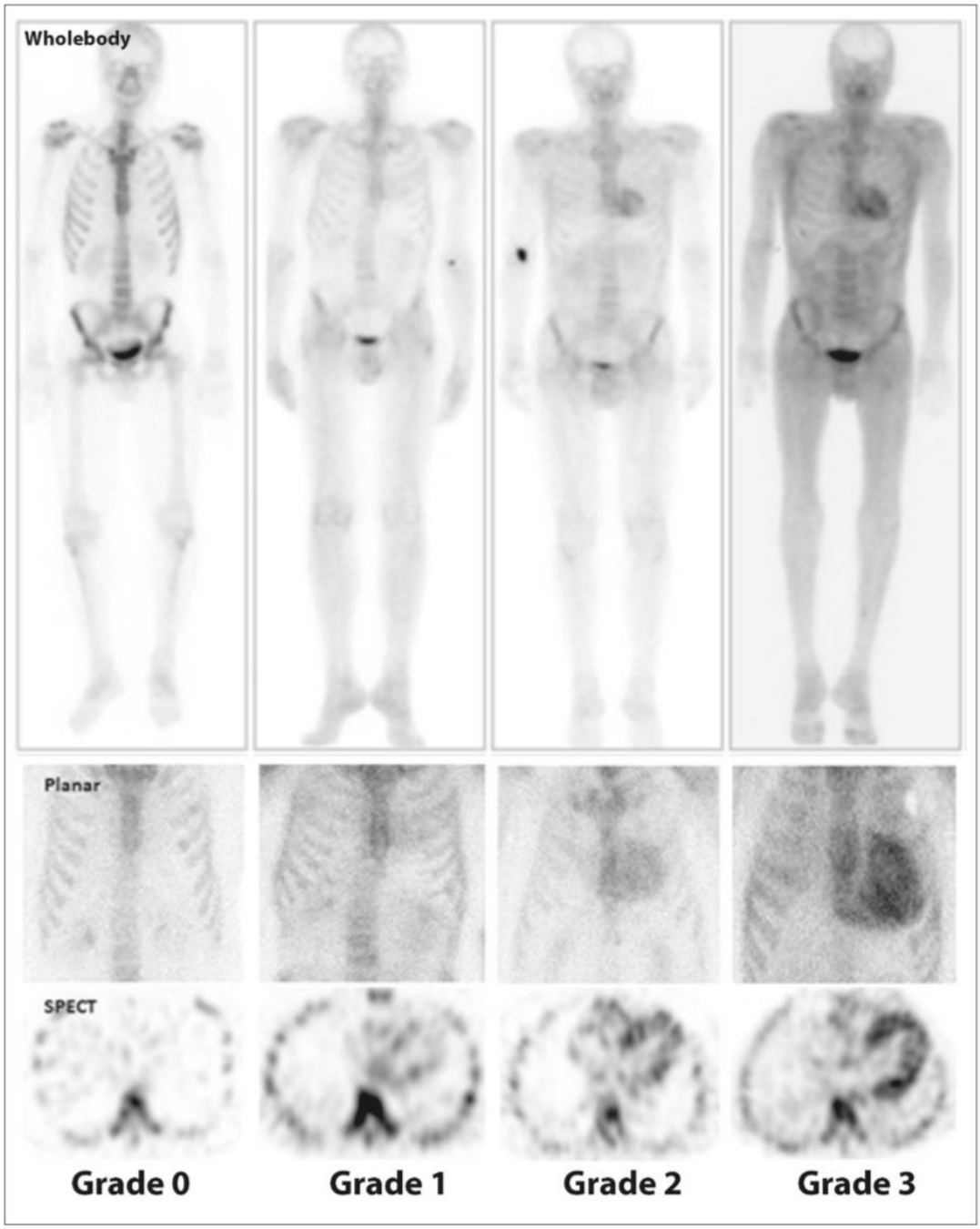


Figure 22: Perugini scoring demonstrating whole-body planar and SPECT images of Perugini grade 0 through to 3, representing increasing cardiac uptake of radiotracer. Adapted from [184].

2) Heart to contralateral ratio is a semi-quantitative measure of absolute counts over the heart compared to the opposite side of the chest, over the lung (figure 23). It is derived using a region of interest on planar images and expressed as a ratio; with ≥1.5 diagnostic of ATTR [182].

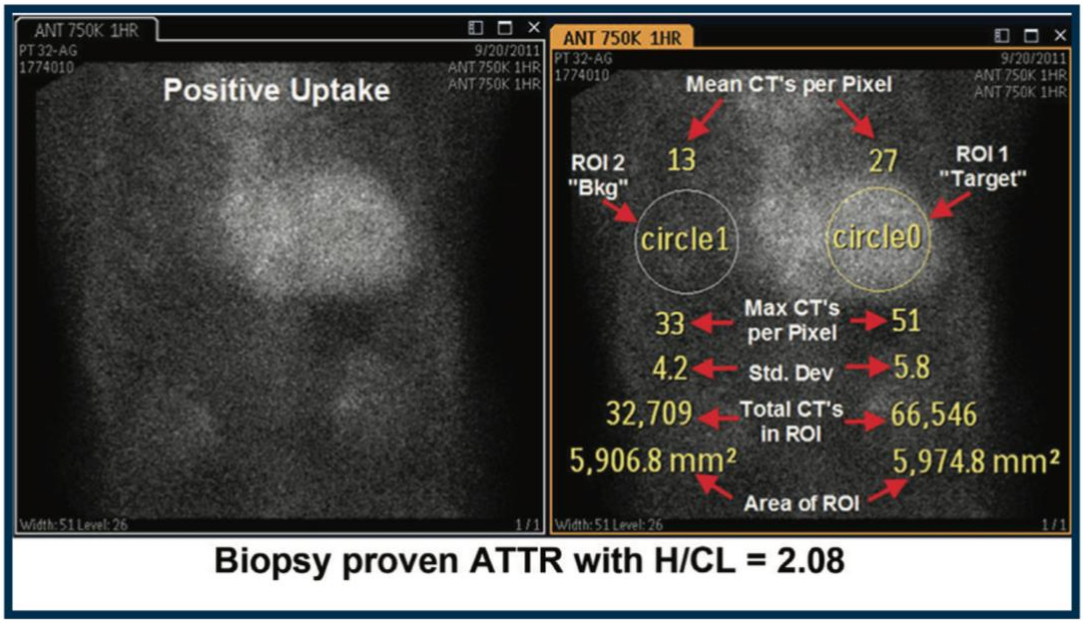


Figure 23: heart to contralateral ratio in a patient with biopsy proven ATTR. The figure shows the two regions of interest (ROI) drawn on opposite sides of the chest- one over the heart where absolute counts are higher and one over the lung. The ratio of the total counts from each ROI is 2.08- diagnostic of ATTR. Adapted from [185].

3) Standardised uptake value (SUV) is an objective semi-quantitative measure of the radiation burden of a tissue (figure 24). By measuring the radioactivity of a certain area and taking into account, radiotracer injection dose, timing of radiotracer injection in relation to SPECT acquisition and patient demographics, peak SUV can be quantified. We have evaluated its diagnostic utility in cardiac amyloidosis by developing an SUV retention index and demonstrating better differentiation between Perugini grading compared to planar quantification [186].

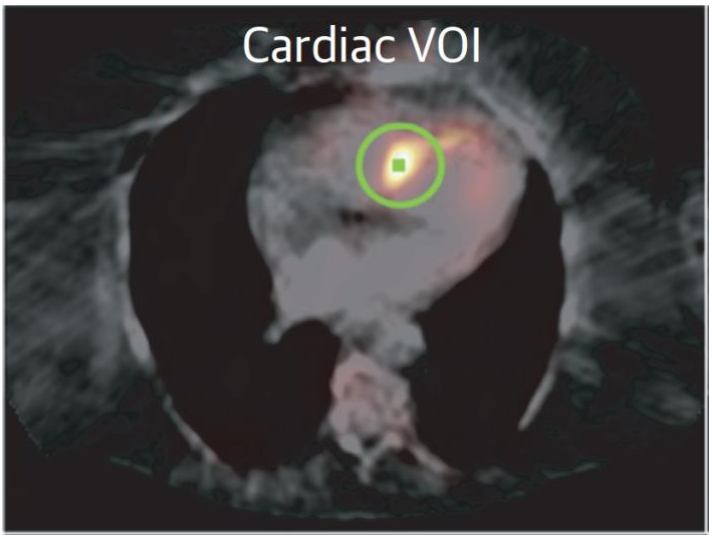


Figure 24: SUV quantification using a region of interest over the brightest part of the cardiac uptake. Adapted from our work [186]

1.6.3.4. Positron Emission Tomography (PET)

PET imaging had been used successfully to detect ATTR with various tracers: C-Pittsburgh compound B (^{11}C PiB) [187] ^{18}F-florbetapir [188] and ^{18}F-florbetaben [189]. However, further work is required before this modality can be utilised clinically.

1.6.4. Extracellular matrix in AS and ATTR

In addition to fibrosis, the ECM is the site of amyloid fibril accumulation by all types of cardiac amyloidosis. Transthyretin amyloidosis in particular, accumulates in large quantities and similar to myocardial fibrosis, reduces cardiac compliance, impairs diastolic and systolic function and affects cardiac conduction [164].

Until recently, myocardial fibrosis could only be identified using histological examination of a biopsy specimen. Now CMR can identify both focal and diffuse fibrosis with good correlation to histology (see section1.6.3.2.) [190].

1.6.4.1. Extracellular volume quantification by CT

Although CMR is the gold standard for non-invasive tissue characterization, imaging takes time, expense limits its availability, claustrophobic patients find it challenging and cardiac devices restrict its use. Computed tomography (CT) provides a cheaper and faster alternative. Based on similar principles to CMR, ECV derived by CT (ECV_{CT}) has demonstrated good correlation with CMR [191], [192] and fibrosis seen

on histology [193]. Higher ECV_{CT} values are associated with worse markers of cardiac structure and function in patients with systolic heart failure [194] and cardiac amyloidosis [192]. It has also demonstrated strong diagnostic capability for identifying cardiac amyloidosis [195]. And for an additional ~2.3mSv of radiation and ~4 minutes of scanning time, ECV_{CT} presents a potentially viable screening tool to identify ATTR [196].

1.6.5. The phenotype of AS-ATTR

The high prevalence of coexisting AS-ATTR, suggests the possibility of an interaction between the two diseases such that one increases the prevalence of the other. Although speculative, this hypotheses requires a few conditions to be fulfilled; firstly, the prevalence of ATTR in the general population must be lower than it is in the AS population. Secondly, the phenotype of AS-ATTR should be different to both individual diseases- AS and ATTR. Thirdly, a mechanistic link explaining how one disease interacts with and facilitates the initiation or progression of the other is important.

Defining the phenotype that is AS-ATTR is also important from a diagnostic and therapeutic perspective, as new therapies are available for both conditions and therefore requires a robust screening tool to identify AS-ATTR. Characterising AS-ATTR will identify features unique to this phenotype, map out the extent of overlap between the two diseases and also illustrate how severe the phenotype is compared to individual diseases. It will provide evidence for whether or not ATTR specific, AS specific therapy or a combination of the two should be used. It will also provide biological insights into the development of this phenotype.

1.7. Coexisting coronary artery disease and aortic stenosis

Coronary artery disease (CAD) is of particular interest among TAVI patients for three reasons. Firstly, it is highly prevalent; 38-65% [197]–[202]. Secondly, as TAVI expands into lower risk cohorts and life expectancy increases, coexistent coronary disease will become increasingly prevalent and intervention for acute and chronic coronary syndromes will increase in frequency. In addition, the TAVI bioprosthesis can affect access to the coronary ostia, raising concerns about its management. Thirdly, unlike other comorbidities, CAD is amenable to treatment with revascularization and medications. If CAD impacts on outcomes of TAVI patients,

appropriate management can be initiated. Fourthly all patients undergo some form of coronary evaluation pre-TAVI, providing the ideal opportunity for screening and managing coexisting CAD.

1.7.1. Assessment of coronary stenosis

The evaluation of an epicardial coronary stenosis involves considerations regarding the approach (anatomical vs. functional), the vessels involved (single vessel vs. multi-vessel), and the contribution of the microvasculature. Patients with AS often undergo several investigations, both invasive and non-invasive as part of their work-up prior to aortic valve replacement. Each of these can provide valuable data on coronary anatomy or the effect of CAD.

1.7.1.1. Non-invasive assessment of coronary stenosis

Data is limited to small studies that address the safety, feasibility and diagnostic accuracy of functional, non-invasive imaging. The potential risks of hypotension and arrhythmias with stress testing, discourages studies in the field, which is consequently not recommended in AS patients by guidelines [154]. Among non-AS patients, revascularization of moderate to severe ischemia has not shown to improve outcomes compared to medical therapy [203]. This casts doubt over the role of perfusion testing (stress echocardiography, cardiac magnetic resonance (CMR) and myocardial perfusion scintigraphy) among AS patients, where myocardial hypoperfusion and inducible functional abnormalities can be due to AS-induced supply-demand mismatch (cellular hypertrophy, capillary rarefaction, changes in coronary haemodynamics), epicardial coronary stenosis or a combination (see section 1.2.3.). Differentiating between the two aetiologies can be challenging [204]. Stress echocardiography in AS patients (n=50) demonstrated a sensitivity of 85% and specificity of 96.5% to localize >50% stenosis on invasive coronary angiography [205]. Single photon emission computed tomography (SPECT) has been shown to predict significant CAD (defined by angiographic stenosis of either >50 or 70%) with a sensitivity of 85-100% and specificity of 71-91%. However, these were small studies and validation in larger cohorts is required. Adverse events were minimal and in one study were similar to a control group. Overall, SPECT perfusion imaging was deemed to be safe [205]–[209]. Positron Emission Tomography (PET) imaging has also been safely used in a small cohort of AS patients with CAD [210]. Although

stress CMR has been performed in patients with AS [211], and has been shown to be safe in a relatively large study [77], its diagnostic accuracy for detecting obstructive CAD in patients with AS has not been evaluated. Studies evaluating outcomes based on perfusion (ideally combined with anatomical data) compared to anatomically-guided revascularization in patients undergoing AVR, are needed.

With increased availability and advances in CT, many centres are changing their practice and using it as the primary screening tool for CAD in patients with AS, whilst reserving invasive coronary angiography (ICA) if CT is inconclusive [212]. This strategy can reduce ICA among a high risk population by up to 37% [213]. The diagnostic accuracy of CT can reduce with higher coronary calcium burden, which is very common among patients with AS [214]. Vasodilators and chronotropic medications that are often used for CT coronary angiography are often avoided due to safety concerns in patients with AS undergoing CT, which can result in suboptimal imaging. However, a recent study (n=42) employing computed tomography derived fractional flow reserve (CT-FFR) has shown that sublingual glycerol trinitrate and beta-blockers/ivabradine can be administered without resulting in adverse events [215]. CT-FFR is a promising imaging modality that has gained considerable adoption for the evaluation of CAD in non-AS patients, as it provides both anatomical and functional data. A prospective, single centre study has demonstrated its safety and feasibility in patients with AS. 92% of the CCT data was interpretable for CT FFR analysis. Compared to invasive FFR, per-vessel analysis of CT-FFR demonstrated sensitivity, specificity, positive predictive value, negative predictive value of 73.9%, 78.4%, 68.0%, 82.9% respectively and a diagnostic accuracy of 76.7% [215]. Larger, multi-centre studies are needed to validate these findings.

1.7.1.2. Invasive assessment of coronary stenosis

There is substantial evidence to support the use of intracoronary measurements to determine the functional significance of a coronary lesion in non-AS patients and their use is recommended to guide revascularization for intermediate lesions [216]. Fractional flow reserve (FFR) and instantaneous wave free ratio (iFR) both measure the pressure gradient across a coronary lesion during hyperaemia and the wave-free period of diastole respectively. The pressure difference across a coronary lesion is influenced by microvascular resistance, which changes during hyperaemia. This raises two limitations of FFR, that need to be acknowledged. First, the effect of

adenosine in patients with AS is often blunted, calling into question whether true FFR values can be obtained in patients with AS [217]. Secondly, there is uncertainty about the change in hyperaemic microvascular resistance pre- and post-TAVI and hence FFR, with studies showing discrepant results. Some studies demonstrate a reduction [81], [138], [142], [218], some an increase [219], [220], and others minor to non-significant changes in post-TAVI FFR compared to pre-TAVI FFR values [220]–[223]. Further studies are needed to clarify this. By contrast, iFR obviates the need for pharmacological hyperaemia and recent studies have shown that iFR measurements remain similar pre and post-TAVI [221], [224]. This makes iFR a potentially attractive alternative to FFR in patients with AS. Although, iFR has been compared to FFR among AS patients in a small study [224], larger studies with outcome-driven data are required to establish appropriate cut-off points for intervention. Among patients with borderline FFR or iFR values, small changes can reclassify the functional severity of lesions and caution is required when interpreting these values [220], [222]. Quantitative flow ratio (QFR) which assesses the functional significance of a coronary stenosis without the use of a pressure wire or drug-induced hyperaemia is an alternative to FFR and iFR. It is based on computational assessment of the passage of contrast during diagnostic coronary angiography. One study in severe AS patients demonstrated that when compared to FFR, QFR has a good diagnostic ability for identifying functionally relevant coronary stenosis, with an accuracy of 81% and an area under the receiver operating characteristic curve of 0.88 (95% CI: 0.82-0.93) [225]. These physiological metrics have been used with both SAVR and TAVI to evaluate the effect of AS and valve replacement on coronary haemodynamics and outcomes.

1.7.2. Revascularization in aortic stenosis

Guidelines for revascularization in non-AS patients make a distinction between revascularization for symptoms and prognosis depending on the site and extent of CAD [216]. These have been clinically extrapolated to the AS population to guide revascularization. However, in this unique patient group, it is key to understand the impact of revascularization in this cohort with the available evidence.

1.7.2.1. Revascularization with SAVR

A systematic review showed that CAD among patients undergoing SAVR increases the risk of early mortality, but this included a heterogeneous collection of studies. Unadjusted mortality was higher among patients undergoing SAVR and concomitant coronary artery bypass grafting (CABG) compared to isolated SAVR [226]. However, two studies have demonstrated that, after propensity matching, mortality was similar in both cohorts, suggesting the differences in reported unadjusted mortality rates can be accounted for by existing comorbidities [227], [228]. Furthermore, two observational retrospective studies involving patients with AS and coexisting CAD, treated with combined CABG and SAVR had significantly reduced early and late mortality compared to the SAVR-only group [229], [230]. The prognostic benefit was evident in both coronary stenosis >50% and >70% [230] (table 1).

PCI can also be performed safely as part of a hybrid procedure in patients undergoing SAVR without increasing the risk of short term mortality [231], providing an alternative to CABG and SAVR [232]. Bleeding complications remain a concern with hybrid procedures due to the need for dual antiplatelet agents [231], however performing PCI on the day of or day prior to SAVR may reduce bleeding rates, potentially because platelets activity is not completely inhibited by the time of SAVR [233].

1.7.2.2. Revascularization with TAVI

With the rapid adoption of TAVI, the assessment and management of CAD is becoming increasingly important. A key advantage of TAVI over SAVR is that PCI with TAVI can be performed separately, whereas CABG needs to be performed at the same time as SAVR. Several non-randomized studies and a meta-analysis have demonstrated that CAD does not affect short and mid-term outcomes in patients undergoing TAVI, with similar outcomes among patients treated medically and those with PCI [197]–[199], [201], [202], [234]–[237].

In the short-term, post-TAVI myocardial injury, determined by serum biomarkers is independently influenced by significant CAD, with complex CAD having a greater impact [238], [239]. However, revascularization even in patients with severe CAD (high SYNTAX scores) has not demonstrated an improvement in short-term outcomes, suggesting that it is not a pre-requisite pre-TAVI [236], [240]–[242]. However, in the mid-term, some studies do suggest a mortality benefit with a selective revascularization strategy, especially among patients with a high SYNTAX

score) [197]–[199], [201], [202], [234]–[237]. Studies addressing the completeness of revascularization have yielded conflicting results- with some demonstrating that incomplete revascularization is associated with increased cardiovascular events [236], [242], [243], whilst others demonstrating that it does not [198], [237], [240], [241]. Several of these studies were limited by low patient numbers, short follow-up and differences in cohorts based on lesion location, angiographic severity, atherosclerotic burden, comorbidities and the definition of incomplete revascularization. Further studies are needed to provide clarity on this.

Recent results from the ACTIVATION study, a randomized controlled trial evaluating the safety and efficacy of medical therapy to PCI in coronary vessels with >70% stenosis prior to TAVI, demonstrated similar short-term outcomes. Among 235 patients, (Canadian Cardiovascular Society (CCS) class 0-2), PCI compared to no PCI, had similar rates of mortality and rehospitalization at 1 year (41.5 vs 44%; p=0.067) and higher bleeding rates (44.5 vs 28.4%; p=0.02) [244]. It should be noted that patients in this study had low symptom burden, the recruitment target (n=310) was not met, and PCI was guided by angiographic stenosis severity.

Several studies have investigated the role of physiology-guided revascularization in patients with CAD and AS. In a single-centre, observational study, FFR-guided PCI was shown to be superior to angiographically-guided PCI in patients undergoing TAVI. The authors reported better major adverse cardiac and cerebrovascular event–free survival in the FFR-guided group compared to the angiography-guided group (hazard ratio 0.4; 95% confidence interval 0.2–1.0; p=0.035) at 2 years following TAVI [245]. The NOTION-3 [246] and FAITAVI [247] trials are currently underway to assess the role of FFR in guiding revascularization pre- TAVI.

1.7.2.3. Timing of revascularization

Among patients who present acutely, the predominant lesion (AS vs CAD) needs to be identified in order to guide further management. This can be challenging as both acute decompensated aortic stenosis (ADAS) and acute coronary syndromes (ACS) can present with an increase in cardiac troponin, ECG changes and similar symptoms [248]. Clinical evaluation, coronary angiography and echocardiography are all required to differentiate between the two presentations. If ACS is the predominant condition, PCI should be undertaken first. However, if ADAS is the predominant condition, valve replacement should be undertaken first, with studies

supporting the feasibility of TAVI in ADAS [249], [250]. Figure 25 describes factors that support revascularization decisions either pre-, peri- or post-valve replacement.

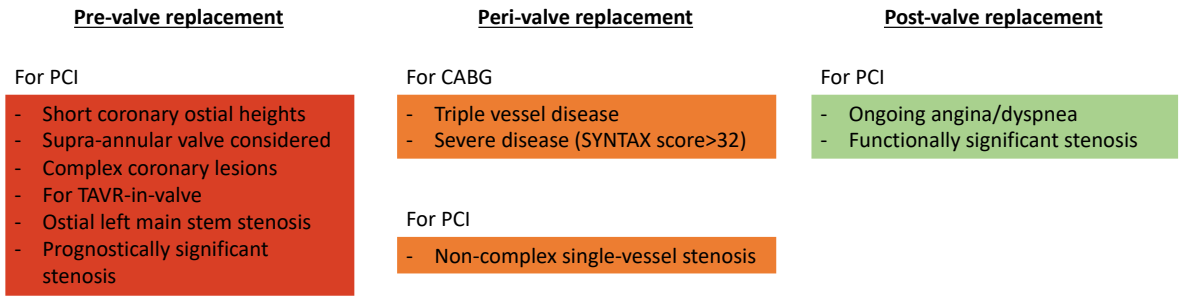


Figure 25: factors that favour a particular revascularization strategy

1.7.2.3.1. Peri-procedural revascularization

For surgical patients, CABG at the time of SAVR makes clear sense given the risks of reoperation. CABG has proven its prognostic superiority over PCI in patients with triple vessel and severe CAD (SYNTAX score>32) and should sway the decision away from percutaneous and towards surgical treatment [251], [252]. Among TAVI patients however the timing is less clear. Alternatively, PCI can be performed concomitantly with TAVI where there is the inherent benefit to the patient of a 'single procedure' and hospital admission. Timing considerations include the risk of acute kidney injury among patients with pre-existing renal function and should be individualized [253]. In both settings, the need to withhold dual antiplatelet therapy (DAPT) in the event of TAVI-related bleeding or vascular complications can be potentially dangerous. Evidence from observational studies suggest that staging PCI at least 30 days pre-TAVI can reduce bleeding and vascular complications [254]. A nationwide registry showed that performing concomitant TAVI and PCI during the same admission can increase mortality compared to TAVI alone (10.7% vs 4.6%; $p<0.001$ respectively) [255].

1.7.2.3.2. Post-TAVI PCI

As aortic valve replacement often leads to symptom improvement (angina/dyspnoea), among patients where equipoise/uncertainty remains, a strategy of initial valve replacement (at least in the case of TAVI), with revascularization deferred until after the TAVI if symptoms persist, may also be reasonable. This maybe more applicable to younger and lower risk patients. The evidence supporting

a post-TAVI PCI strategy is based on the studies in section 1.7.2.2. that concluded that neither CAD nor revascularization adversely affects short-term outcomes post-TAVI.

However, performing PCI after TAVI can be technically challenging as access to the coronary ostia can be partially obstructed by the native leaflets, the prosthetic valve's commissural posts or skirt, especially in the case of a supra-annular self-expanding prosthesis [256]–[258]. Although, more recent studies have reported high success rates for PCI post-TAVI (>95%), regardless of valve prosthesis type [259]–[261]. Challenging cases may require modifications to PCI technique [256], and benefit from CT angiography to assist in planning PCI [261] and pre-TAVI simulation to assess the effect of the prosthesis on coronary haemodynamics and its position relative to the coronary ostia [262]. When performing TAVI, optimising commissural alignment in order to maintain access to the coronary ostia is feasible with some valves and is especially important for supra-annular bioprosthesis [263]. If there is a risk of coronary obstruction, electrosurgical laceration of the native or bioprosthetic valve leaflets can be performed using the BASILICA technique [264]. Alternatively PCI can be performed pre-TAVI.

1.7.2.3.3. Pre-TAVI PCI

Although revascularization pre-TAVI can reduce the ischemic burden during rapid pacing for valve deployment [265], [266], the evidence discussed in section 1.7.2.2. suggests that neither CAD nor revascularization affect hard procedural outcomes with TAVI. Prognostic lesions that will require revascularization should be considered for PCI pre-TAVI, especially if there are any high-risk features present (figure 25). PCI should also be considered pre-TAVI in patients with anatomical and procedural characteristics that may render PCI challenging post-TAVI.

Coronary access is an increasingly important issue in lower risk patients. As life expectancy exceeds valve durability, TAVI-in-TAVI or TAVI-in-SAVR is required, increasing the risk of coronary ostial obstruction by pinning the old bioprosthetic leaflets against the sinotubular junction with the new valve. This is more of a concern with the taller Corevalve/Evolut R/Pro valves than the Sapien 3 valves and among surgical bioprosthesis- stentless valves and valves with leaflets sutured on the outer side of the stent frame [267]–[269]. In patients considered for the prosthesis mentioned above, PCI should be considered pre-TAVI or pre-TAVI-in-valve.

Additionally, PCI for complex coronary anatomy that requires extra support and advanced techniques maybe easier without having to manipulate around a TAVI [270]. Patients with short coronary ostial heights and narrow sinus of Valsalva may also benefit from pre-TAVI PCI [271], [272].

Although, the safety and efficacy of PCI in patients with AS, including for complex coronary lesions, was similar to patients without AS in one study [273], the potential risk of hemodynamic instability still exists and needs to be carefully considered [274], [275]. Ostial left main stenosis is a recognized high-risk feature associated with coronary obstruction during TAVI requiring unplanned left main PCI. This is associated with increased mortality even if PCI is successful. These patients should be considered for pre-TAVI PCI or measures taken to protect the left main stem during TAVI [269]. As discussed above, bleeding risk and the need to withhold DAPT in the setting of a TAVI-related complication needs to be considered with pre-TAVI PCI. Adopting a staged procedure with PCI preceding TAVI by several months can reduce the risk of stent thrombosis if DAPT need to be withheld [276].

1.8. Acute decompensated aortic stenosis

Current guidelines recommend treatment with SAVR/TAVI in patients with severe symptomatic AS [123]. The development of symptoms is associated with a dismal prognosis without intervention [277], with a mortality rate as high as ~3%/month [151]. Patients are usually monitored at regular intervals using serial echocardiograms and clinical evaluations until such a time is reached. However, this approach has several flaws; firstly, assessing symptoms can be challenging; as patients may not sufficiently exert themselves in order to illicit symptoms or they may not recognise their symptoms and claim to be asymptomatic (7). Secondly, severity of AS can also be challenging to establish with up to a third of patients having discordant echocardiographic findings (8). Lastly, the rate of progression of AS severity is variable and can be as quick as a reduction in aortic valve area of $0.5cm^2$/year (9). Adopting a ‘watchful waiting’ approach can lead to many patients with AS progressing without adequate monitoring and a timely intervention. Some patients present with symptoms of AS at rest or on minimal exertion- dyspnoea, angina or syncope, requiring hospital admission, coined acute decompensated aortic stenosis (ADAS) (figure 26- in orange). These patients are in the final stages of AS.

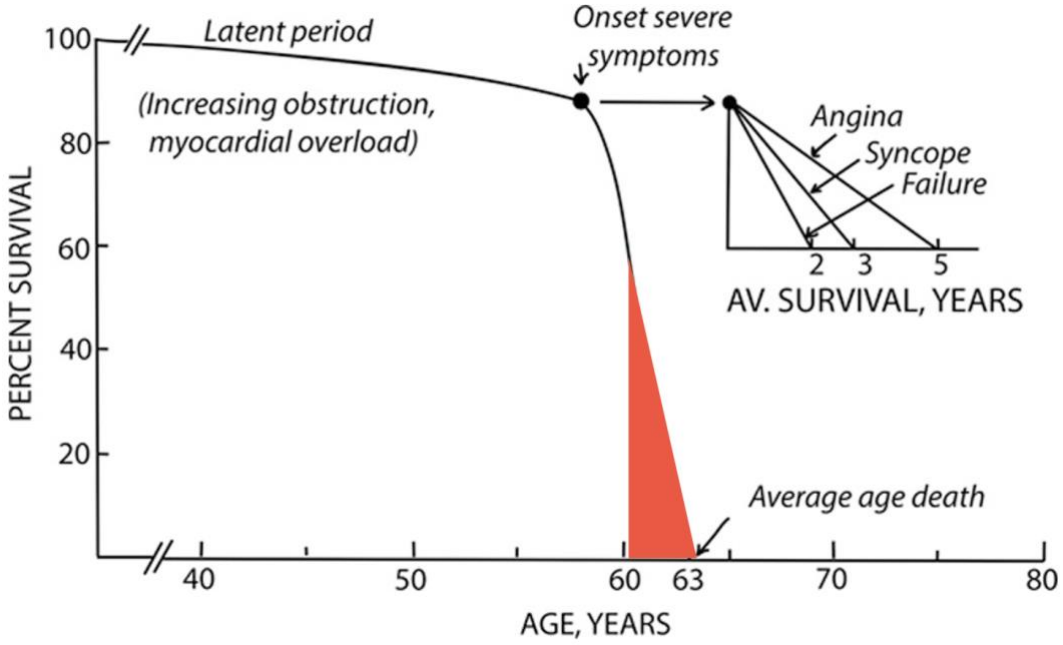


Figure 26: The natural history of AS. The orange zone represents patients towards the final stages of AS who present with ADAS. Adapted from Braunwald's original image [277].

1.8.1. Impact of ADAS

ADAS is surprisingly common, affecting 7-23% of all patients having a TAVI [250], [281]. Compared to patients undergoing an elective TAVI, ADAS patients have a significantly higher mortality rate (2 fold increase in 30 day mortality), rate of acute kidney injury (twice as high) and longer hospital length of stay (2 fold longer) [250]. ADAS is defined by debilitating symptoms related to AS (syncope, angina with minimal exertion or at rest and/or dyspnoea at rest). The condition frequently warrants hospitalisation and urgent valve replacement. Although TAVI has been performed safely in these patients, outcomes are worse than patients without decompensation; at 1 year post-TAVI, mortality is between 15.3-29.1%.[249], [250], [282] Traditional markers of futility described above predict mortality in ADAS: AF, oxygen-dependant lung disease, low body surface area (a marker of sarcopenia/malnutrition), previous cardiac surgery and poor renal function [250]. However, there is a large degree of overlap in baseline characteristics between ADAS and non-ADAS patients, making it challenging to differentiate and therefore predict futility.

Among patients presenting with acute decompensation is a subgroup with cardiogenic shock. Data on TAVI within this subgroup is limited to small case series. Device success is reportedly high (94%), However, Valve Academic Research Consortium (VARC) 2 defined early safety endpoints were reached in 35% [283] with 30 day mortality of 12-24% [283], [284]. At 1 year, mortality is reported at 26% and related to non-cardiovascular causes in the majority of patients. However, among survivors, TAVI did improve symptoms; 91% were NYHA 1/2 [283]. For patients with ADAS, non-randomised data suggest that TAVI is a better therapeutic option than balloon aortic valvuloplasty [282], [284].

1.8.2. Pathophysiology of ADAS

The mechanisms that lead to ADAS have not been adequately explored. However, possible theories can be drawn from studies in acute heart failure and acute decompensation in hypertensive heart disease. Acute pulmonary oedema is the result of fluid redistribution and in many cases fluid excess. It is mediated through the complex activation and interaction of the neuro-hormonal system, inflammation, renal failure and endothelial dysfunction commonly associated with a background of diastolic and/or systolic dysfunction; features that coexist in AS [285], [286]. In hypertensive heart disease, chronic exposure to high systolic pressures lead to an increase in both ventricular and vascular elastance such that the cardiovascular system becomes sensitive to small changes in preload and afterload, which can easily lead to acute heart failure [287]. AS represents a similar model to hypertensive heart disease, with an increase in afterload and may follow a similar pathophysiological mechanism to decompensation. In addition, many patients have vascular resistance that leads to a ‘double-hit’ to the ventricles. Evidence from the UNLOAD trial assessing the impact of sodium nitroprusside in patients with decompensated aortic stenosis and reduced LVEF, showed a beneficial effect of the vasodilator in increasing cardiac output, suggesting a role played by increased vascular resistance in patients with ADAS [288].

2. Aims of the PhD

2.1. Overarching aims

The aim of this thesis is to investigate among patients undergoing TAVI, the effect of:

i) comorbidities that impact on the myocardium,

ii) acute decompensated aortic stenosis

In doing so, this thesis will:

iii) identify patient cohorts that may benefit from additional therapy

iv) refine risk stratification

v) improve patient management pathways

Three populations will be evaluated in depth: those with coexisting ATTR, those with coexisting CAD and those presenting with ADAS. Frailty is an overarching phenotype present in all these populations and will be evaluated as well. Within these populations, I will assess the impact of the condition on outcomes and identify features associated with adverse outcomes and characterise the resultant pathology in terms of presentation, myocardial structure and function.

These cohorts are characterised by their involvement of the myocardium and can be divided into:

1. Infiltrative: patients with coexisting wild-type transthyretin cardiac amyloidosis (wtATTR)
2. Blood supply: patients with coexisting coronary artery disease
3. Decompensation: patients who present with acute decompensated aortic stenosis (ADAS).

All three conditions are prevalent, and little is known about their presentation, phenotypic characteristics, impact of TAVI on their natural history and their optimum management. These sub-populations are important as interest is growing and therapies do exist for their treatment. Figure 27 demonstrates the layout of my PhD.

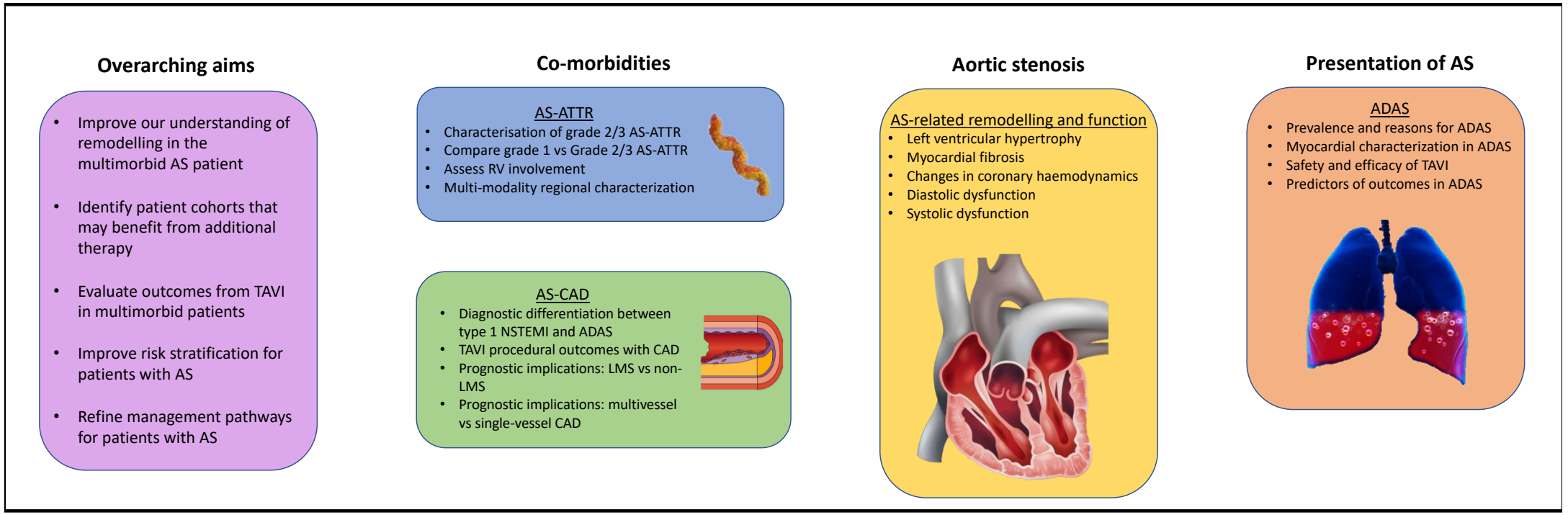


Figure 27: A roadmap of my aims and an outline of the topics that I covered for my PhD.

2.2. Workstream hypotheses

Topics in bold are completed and presented in this thesis report. Within each population I will have the following hypotheses:

1) AS-ATTR

I. Characterisation of AS-ATTR

A. Grade 2/3 AS-ATTR represents dual pathology and a severe phenotype that combines the characteristics of AS and ATTR

B. Grade 1 AS-ATTR is phenotypically milder to grade 2/3 AS-ATTR

C. The right ventricle is adversely affected in AS-ATTR

D. Regional uptake of DPD radiotracer is associated with structural and functional changes

2) AS-CAD

I. Acute presentation of AS-CAD

A. Common diagnostic metrics used to predict a myocardial infarction are inaccurate in patients with AS

II. Outcomes of AS-CAD

A. CAD does not adversely affect procedural and short outcomes in patients undergoing TAVI

B. Mortality in AS-CAD is related to the myocardial area at risk

3) ADAS

I. Outcomes with ADAS

A. TAVI is safe and effective in ADAS

B. ADAS is independently associated with mortality

II. Characterisation of ADAS

A. A more advanced stage of cardiac structure and function is predictive of mortality in ADAS

3. Materials and methods

3.1. Ethical approvals

Several ethics were developed de novo and amended during this PhD to facilitate the establishment of several research cohorts.

3.1.1. EVINCI- Evaluation of Integrated Cardiac Imaging

EVINCI (REC reference: 10/H0721/79) is an umbrella ethics under which my study of AS-ATTR was conducted. This ethics required two amendments (version 8 and 9) that I carried out in order to facilitate the recruitment of TAVI patients for the identification of coexisting ATTR.

3.1.2. POCA- Prevalence and Outcomes of transthyretin Cardiac Amyloidosis in cardiac disease and ageing

Succeeding EVINCI was the POCA ethics (REC reference: 20/LO/0315), that was created in order to assess the prevalence of ATTR among 3 populations- valvular heart disease (VHD), cardiac devices, and healthy elderly participants. These ethics allowed a multi-modal imaging and biomarker assessment of patients with DPD scintigraphy as the main diagnostic tool. They also permit the longitudinal follow-up of patients to evaluate important outcomes such as death and procedure related complications. I wrote these ethics and obtained approval in July 2020.

3.1.3. BSIR- Barts Structural Interventional Registry

The BSIR ethics (REC reference: 21/NW/0182), were created in order to setup cohorts of patients with VHD at Barts Health NHS Trust. These ethics allow the use of clinically acquired data for any patient with any type and severity of VHD who has ever been cared for at Barts Health NHS Trust. These ethics also allow for the derivation of outcome data from NHS digital such as cause and date of death, cause and date of hospitalisation and any cardiac procedure. I wrote these ethics and obtained approval in September 2021.

3.2. Establishment of research cohorts

By accumulating patient data using clinical records I have been able to setup several cohorts of patients with valvular heart disease. These cohorts include data on patient

demographics, comorbidities, imaging parameters, procedural details and outcomes.

3.2.1. Structural interventional cohort

This cohort consists of patients with VHD treated or referred by/to the structural heart team at BHC. Patient data was collected prospectively onto a designated Microsoft access database according to pre-specified variables. These categories are defined according to NICOR based definitions [289] and the VARC 2 criteria [290]. Additional data required for research was retrospectively identified manually from hospital-based sources and added to the access-based database. I established this cohort along with the clinical team at BHC. So far, several sub-populations have been derived from this cohort:

- Vascular access in TAVI
- Bicuspid aortic valve stenosis
- Coronary artery disease in TAVI patients
- Acute decompensated aortic stenosis
- Aortic stiffness in TAVI patients
- Mitral regurgitation
- Low-flow, low-gradient AS

3.2.2. Echocardiography cohort

This cohort consists of patients with VHD and treated either medically, surgically or via transcatheter intervention. Echocardiography details were delineated form reports and additional measurements made retrospectively. I established this cohort along with other research fellows. Several sub-populations have been created from this cohort:

- Bicuspid aortic valve stenosis
- Acute decompensated aortic disease
- Moderate aortic stenosis
- Mitral regurgitation
- Mixed aortic valve disease

3.2.3. Surgical cohort

Patients with VHD treated surgically at BHC were included into this cohort. Data for

this cohort was collected prospectively. The database included details about demographics, comorbidities, surgical procedural details and complications. Additional data on imaging parameters was obtained retrospectively from the hospital's data warehouse. The data was linked to the NHS spine to obtain mortality data. Several sub-populations have been derived from this cohort:

- Low-flow, low-gradient AS
- Mixed aortic valve disease

3.2.4. ATTRact AS cohort

Patients were prospectively recruited for an observational study assessing the prevalence, characterisation and outcomes coexisting ATTR and AS (details in section 3.3.). My predecessor, Dr Paul Scully recruited 200 patients, to which I added 117 patients. These patients were well characterised using a multi-modality imaging and biomarkers and followed up for >2 years. This cohort formed the basis of the AS-ATTR research I have carried out in my PhD.

3.2.5. Other cohorts

In order to compare AS-ATTR to elderly controls and ATTR, I obtained data from other research cohorts. From the National Amyloidosis Centre, I obtained prospectively collected data on patients with ATTR. From the SABRE cohort, I obtained prospectively collected data on elderly controls. This included demographics, biomarkers, comorbidities and echo data. I retrospectively collected ECG, strain and other echo data.

3.3. Patient recruitment

To assess the prevalence of ATTR among patients with AS and evaluate their outcomes following aortic valve replacement, I recruited patients using the EVINCI ethics at BHC and the John Radcliff Hospital, Oxford. Patients were referred for a TAVI, >75 years of age and provided written informed consent. Patients were identified using clinic and CT lists and multi-disciplinary team meetings. All patients had a set of baseline investigations, many had AVR and were followed by at regular intervals post-AVR. A schematic of the research investigations carried out is illustrated below (figure 28).

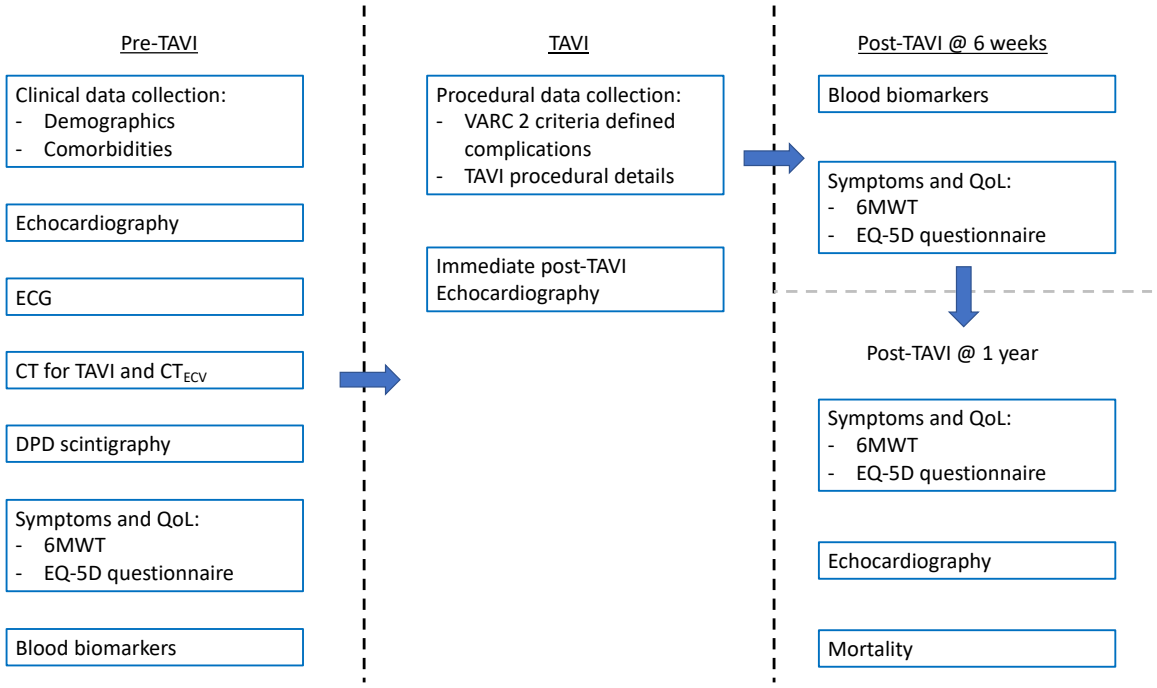


Figure 28: schema of research investigations and data collection for the AS-ATTR study

3.3.1. Baseline investigations

3.3.1.1. Biomarkers

All subjects had NT-proBNP and high sensitivity Troponin-T (hsTnT) measured at the time of recruitment which often coincided with their DPD scintigram or their CT scans.

3.3.1.2. DPD scintigraphy

All patients underwent DPD scintigraphy. The imaging protocol at the JRH and SBH consisted of an early (5 minutes) and late (3 hours) planar whole-body image. Scans were performed using aligned protocols and Perugini scoring; with grade 0 being negative, grade 1 to 3 increasingly positive as previously described [181]. Among positive patients, further assessments (serum free light chain ratio and monoclonal immunoglobulin in the serum and urine by immunofixation) to rule out AL amyloid and genotyping identified wild-type transthyretin cardiac amyloidosis based on international guidelines [291].

3.3.1.3. Echocardiography

All patients underwent transthoracic echocardiography by experienced accredited echocardiographers. Different machines and software were used at different sites for image acquisition. Chamber and valve quantification was performed according to international recommendations [292]. Cardiac parameters were measured using EchoPAC software (GE Healthcare, Wauwatosa, WI, USA). Left ventricular (LV) mass was calculated using methodology described previously [293]. Myocardial contraction fraction (MCF) was derived from the ratio of stroke volume over myocardial volume. Strain analysis was derived using Image Arena 4, TomTec software. Global longitudinal strain (GLS) was calculated using apical four, three and two chamber 2D images for the LV and the four chamber 2D image for the RV.

3.3.1.4. Symptom and quality of life assessment

All patients had symptoms graded according to the New York Heart Association (NYHA) and Canadian Cardiovascular Society Angina classifications. Additionally, patients had a 6 minute walk test (6MWT) to determine how far they could walk before they developed symptoms or in 6 minutes (the earliest of the two). Patients also completed an EQ-5D questionnaire that provides a subjected assessment of their quality of life (QoL).

3.3.1.5. Electrocardiography

ECGs were assessed for conduction disease (first degree heart block and left /right bundle branch block (LBBB/RBBB)), low amplitude (all limb leads with an amplitude <0.5mV), left ventricular hypertrophy (LVH) (Sokolov-Lyon criteria- sum of largest R wave in V5/V6 plus S wave in V1>35mm) and when combined with echocardiography, the voltage/mass ratio (Sokolov-Lyon length divided by LV mass) [294], [295].

3.3.1.6. Computed Tomography and CT_{ECV}

All CT scans were performed on a Somatom FORCE scanner (Siemens Healthineers, Erlangen, Germany). The TAVI work-up CT involves a topogram, calcium score, timing bolus, gated CT coronary angiogram (CTCA) acquired retrospectively and a FLASH whole body (lung apices down to the lesser trochanters). No additional contrast was used for research scan which included a baseline axial shuttle mode pre-contrast and a pseudo-equilibrium axial shuttle mode

(both triggered 250ms after the R wave), at 3- and 5-minutes post-contrast (following the FLASH whole body scan). Extracellular volume was calculated using Hepacare software (Siemens Healthineers) which included averaging of the axial shuttle mode datasets (3-4, depending on heart rate) to improve image quality and reduce noise. The averaged baseline image was then subtracted from the averaged 3- and 5-minute post-contrast images and registered with the CTCA image. A region of interest was placed in the LV blood pool on the CTCA image and the hematocrit inputted, generating a myocardial ECV map via the formula: ECV_{CT} = (1–hematocrit) x (ΔHU_{myo} /ΔHU_{blood}), where ΔHU is the change in Hounsfield unit attenuation pre- and post-contrast (i.e. $HU_{post\text{-}contrast}$ – $HU_{pre\text{-}contrast}$) [296]. Reports of CT_{ECV} are not reported in this thesis as data collection is still ongoing.

3.3.2. Post-TAVI investigations

Patients initially were followed up between 4 and 8 weeks post-TAVI at BHC. At this time, I collected data on:

- Symptoms and QoL
- Blood biomarkers

However, this clinical follow up was stopped due to COVID and patient geographical inconvenience. As a result, I only obtained symptoms and QoL data over the phone between 4-8 weeks post-TAVI in majority of patients.

At 1 year post-TAVI, I called recruited patients and obtained data on symptoms and QoL. I also obtained mortality data and if available their 1 year echo data.

4. Results: Characterisation of AS-ATTR

This chapter is based on the publication below:

***Patel KP**, Scully PR, Nitsche C, Kammerlander AA, Joy G, Thornton G, Hughes R, Williams S, Tillin T, Captur G, Chacko L, Kelion A, Sabharwal N, Newton JD, Kennon S, Ozkor M, Mullen M, Hawkins PN, Gillmore JD, Menezes L, Pugliese F, Hughes AD, Fontana M, Lloyd G, Treibel TA, Mascherbauer J, Moon JC. Impact of afterload and infiltration on coexisting aortic stenosis and transthyretin amyloidosis. Heart BMJ Publishing Group Ltd; 2021*

I was involved in the genesis, data collection and analysis, statistical analysis, writing, editing and manuscript creation.

4.1. Background

Previous studies have compared AS-ATTR to AS and noted important differences between the two populations. AS-ATTR is more prevalent among males 62-91% and patients are generally older [mean age of AS-ATTR patients 86-88 years undergoing TAVI, with a younger age among SAVR patients 75 (69-85) years vs mean age of AS patients: 70-83 years]. Compared to AS patients, AS-ATTR patients showed some structural differences, namely thicker LV walls and higher LV mass and functional changes, namely lower stroke volume, higher prevalence of low-flow, low-gradient AS, and reduced longitudinal function (table 2).

Parameter	Castano et al [160] (n=151)	Cavalcante et al [159] (n=113)	Scully et al [158] (n=200)
Study type	Prospective	Retrospective	Prospective
Diagnostic modality	^{99m}Tc-PYP	CMR	^{99m}Tc-DPD
Prevalence of AS-ATTR (%)	16	16	13
Male (%)	91.7 vs 63.0	89 vs 56 *	62 vs 48 *
Age (years)	86.3±5.7 vs 83.3±6.3	88±6 vs 70±14	88±5 vs 85±5
Grade of ATTR	Grade 2 or 3= 24	N/A	Grade 1= 31% Grade 2= 69%
LV septal wall thickness (cm)	1.3 vs 1.1	1.8±0.5 vs 1.3±0.3	1.4±0.3 vs 1.3 ±0.2
LV posterior wall thickness (cm)	1.1±0.4 vs 0.9± 0.2	N/A	1.3±0.4 vs 1.1±0.2
LV mass indexed (g/m^2)	130 vs 98	105±21 vs 73±21	136±36 vs 118±38
LVEF (%)	48 vs 56	43±17 vs 52±18	54±14 vs 54±11 *
LV stroke volume indexed (ml/m^2)	30 vs 36	33±10 vs 44±13	34±10 vs 38±11 *
Longitudinal function (lateral s') (cm/s)	4.0 vs 6.6		6 vs 2
Paradoxical LFLG AS (%)	8.3 vs 7.3	78 vs 45	15%
Classical LFLG AS (%)	29.2 vs 10.5		9%
LV E/A ratio	2.3 vs 0.9	N/A	1.28 (0.75-2.15) vs 0.78 (0.68-1.22)

Table 2: Characteristics of AS-ATTR patients compared to AS patients from 3 studies. * indicates p>0.05.

A universal issue with all these studies is that they compared AS to AS-ATTR and not to ATTR or similar aged controls. Therefore, whilst conclusions can be drawn about AS-ATTR from the above studies they are incomplete.

4.1.1. Clinical significance of Perugini grade 1 vs grade ≥2 AS-ATTR

Castano et al reported the first prospective case series of AS-ATTR and the entire study population had a visual score (same as perugini grade) ≥2 [160]. Our study

reported both Perugini grade 1 and 2 patients, without any grade 3 patients [158]. Among the wider cardiology community, there is a consensus that Perugini grade 1 represents bystander disease, that is unlikely to be clinically significant. This has affected clinical practice in many places, particular North America, where grade 1 is not considered ATTR. This is endorsed by professional bodies such as the American Society of Nuclear Cardiology [185] and therefore is purposely excluded from studies [297]. The rationale behind this stems from several studies that have demonstrated that majority of patients with ATTR are grade ≥2.

Rapezzi et al, assessed DPD visual grade in 63 patients with known hereditary ATTR. This group was divided into patients with and without echocardiographic evidence of cardiac amyloid involvement (thickened LV walls). The study found that all patients with cardiac involvement on echocardiography had a DPD visual grade ≥2 and only 3 patients (13%) without cardiac involvement on echocardiography had a visual grade ≥2 [298]. Bokhari et al studied PYP visual grade among patients with AL (n=12), wild-type ATTR (n=16) and hereditary ATTR (n=17). They found that no (0%) wild-type ATTR patients, 1 patient (6%) with hereditary ATTR and 10 patients (83%) with AL amyloid had a visual grade of 1 [182].

The counter-argument to this consensus of grade 1 being clinically insignificant, is that the Perugini grading system has not been found to be prognostic. Hutt et al evaluated survival in 605 patients with either wild-type or mutant ATTR, diagnosed using DPD scintigraphy) from a tertiary referral centre, demonstrating that there was no difference between patients with grade 1, 2 or 3. However, grade 0 had a better prognosis compared to the other grades [299]. Similarly, Castano et al, showed in 171 patients (121 with ATTR), using PYP scintigraphy, that there was no difference in mortality between grade 2 and 3. None of their patients had grade 1 ATTR. However, a H/CL ratio of >1.6 was prognostic and predicted a worse survival (HR: 7.9, 95% CI: 1.7-37.3; p =0 .01) [297]. This would suggest that grade 1 has a similar significance to grade 2/3.

Less evidence is available for patients with AS-ATTR. The clinical significance of grade 1 is unknown. Characterisation of this phenotype and comparison with grade 2/3 will provide valuable data on its relevance.

4.1.2. Characterisation of AS-ATTR

The high prevalence of coexisting AS-ATTR, suggests the possibility of an interaction between the two diseases such that one increases the prevalence of the other. Although this is speculative, this hypotheses requires a few conditions to be fulfilled; firstly, the prevalence of ATTR in the general population must be lower than it is in the AS population. Secondly, the phenotype of AS-ATTR should be different to both individual diseases- AS and ATTR. Thirdly, a mechanistic link explaining how one disease interacts with and facilitates the initiation or progression of the other is important.

Defining the phenotype that is AS-ATTR is also important from a diagnostic and therapeutic perspective, as new therapies are available for both conditions and therefore requires a robust screening tool to identify AS-ATTR. Characterising AS-ATTR will identify features unique to this phenotype, map out the extent of overlap between the two diseases and also illustrate how severe the phenotype is compared to individual diseases.

4.1.3. The right ventricle in AS-ATTR

As described above, aortic stenosis increases LV afterload resulting in its remodelling. As the disease progresses, the right ventricle can be affected with reduced function being the most commonly reported finding for RV involvement. This also has prognostically implications with several studies demonstrating worse outcomes with RV involvement [300], [301]. The pathophysiological explanation for RV involvement in AS is based on the interdependence of the LV and RV such that the pressure overload and remodelling of the LV can affect the structure and function of the RV [301].

In patients with ATTR, RV involvement is common (96% of patients have some degree of late gadolinium enhancement). With increasing DPD grades of ATTR, RV mass and RVESV increase with a corresponding decrease in RVEF [302]. Both AS and ATTR affect the RV. One would expect that the RV in AS-ATTR is affected by 2 pathologies- AS and ATTR therefore demonstrating more adverse features (increased wall thickness, reduce function) than any single disease alone.

4.1.4. Regional characterisation of AS-ATTR

Regional differences in AS-ATTR using global longitudinal function (GLS) have yielded mixed results; one study failed to demonstrate relative apical sparing

(apex/average of base and mid) or an apex to base gradient [160], whilst another study only demonstrated an apex to base gradient [161]. Some believe AS-ATTR does not have apical sparing because of AS-related changes [303]. In ATTR, an apical sparing pattern is seen with GLS and is a useful diagnostic and prognostic marker [174], [304]. Late gadolinium enhancement using cardiac magnetic resonance has shown a similar pattern [305] and so has ^{99m}Technetium-Pyrophosphate (PYP) scintigraphy. The later assessed amyloid deposition and demonstrated prognostic implications of apical sparing [306]. In AS, an apex to base gradient of GLS has been described, although to a lesser extent than in lone amyloid [174], [307]. However, its clinical utility is unknown.

The apical sparing pattern described using GLS in ATTR, has three possible explanations; the base has more amyloid deposition, increased myocyte death and/or less diversity of myocyte and matrix orientation [308]. In patients with AS, fibrosis accumulates in the extracellular space as part of the remodelling process [63]. Regional fibrosis accumulation may contribute towards apical sparing.

In AS-ATTR, both individual diseases are likely to influence its structure, function and subsequently its natural history and outcome. Using multimodality imaging I evaluated regional GLS and hypothesesed that the apical sparing pattern is influenced by amyloid deposition, fibrosis and myocyte death.

4.2. Specific methodology

Characterising AS-ATTR has so far been done by comparing AS-ATTR with AS. This provides an incomplete picture of the phenotype as comparison has not been performed with what is considered normal for this particular elderly demographic and with ATTR. Characterising the phenotype of AS-ATTR can only be suitably performed by comparing AS-ATTR with AS, ATTR and the normal, elderly cardiac phenotype in a 2x2 factorial design (table 3).

	AS present	AS absent
ATTR present	AS-ATTR	ATTR
ATTR absent	AS	Normal elderly control

Table 3: 2x2 factorial design to characterise AS-ATTR

4.2.1. Study population

Four prospectively recruited cohorts were combined: older age controls from the Southall And Brent REvisited (SABRE) study [309]. AS and AS-ATTR from the Role of Occult Cardiac Amyloid in the Elderly with Aortic Stenosis (ATTRact AS) study and a Vienna General Hospital study and ATTR from the UK National Amyloid Centre (NAC) registry. Table 1 shows the 2x2 matrix cohort model that was used for this study. AS, AS-ATTR and ATTR cohorts consisted of screened patients with complete data. The older age cohort provided age-expected comorbidities, matching that of the patient cohorts. All participants provided informed consent and each study was approved by a local research ethics committee. Patients, as part of the patient and public involvement programme for valvular heart disease, were involved in the design of this study. Participants had demographic data, cardiac biomarkers (NT-proBNP, high-sensitivity Troponin-T), electrocardiography, echocardiography and clinical data collected. Wild-type transthyretin cardiac amyloidosis was identified in all patients using bone scintigraphy and exclusion of AL amyloidosis in accordance with international guidelines [291].

4.2.1.1. SABRE cohort

A sample of elderly, European origin patients, without significant valvular heart disease, history of myocardial infarction or known heart failure was selected to provide a population-based, older age control cohort which was matched to the disease cohorts on age and ethnicity. This cohort did not have DPD scintigraphy.

4.2.1.2. AS-ATTR cohort

This cohort comprised of patients recruited from two prospective observational studies: ATTRact AS (a two-centre (John Radcliff Hospital (JRH), Oxford, UK and St

Bartholomew's Hospital (SBH), London, UK), study of patients 75 years or older with severe AS referred for a transcatheter aortic valve implantation (TAVI) recruited between October 2016 and February 2019 (NCT03029026)) and a study from Vienna General hospital (VGH) (recruited consecutive patients referred for a TAVI between October 2017 and January 2019). Consenting patients underwent pre-TAVI ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy to identify coexisting amyloid. Further assessments in positive DPD patients (serum free light chain ratio and monoclonal immunoglobulin in the serum and urine by immunofixation and genotyping) identified wild-type transthyretin cardiac amyloidosis based on international guidelines [291]. For hypotheses A and C, I only considered patients with wild-type transthyretin cardiac amyloidosis, Perugini grade 2 and 3, named as AS-ATTR and did not include those with Perugini grade 1. This resulted in two cohorts: 359 patients with AS and 36 patients with AS-ATTR. For hypotheses B, I compared grade 1 AS-ATTR (n=16) to grade 2/3 AS-ATTR (n=36)

4.2.1.3. ATTR cohort

The NAC is a tertiary referral centre in the UK. For this study I included consecutively referred, newly diagnosed patients with wild-type transthyretin cardiac amyloidosis, Perugini grade 2 and 3, (lone-amyloidosis), totalling 107 patients. Diagnosis of wild-type transthyretin cardiac amyloidosis was based on international guidelines [291]. Patients with coexisting mild-moderate AS (n=4) and Perugini grade 1 (n=2) were excluded.

4.2.2. Biomarkers

All subjects had NT-proBNP and high sensitivity Troponin-T (hsTnT) measured at their index consultation. For hypotheses D, the correlation between hsTnT and imaging parameters was assessed to provide insights into the association between myocyte death and regional differences in myocardial structure and function.

4.2.3. DPD scintigraphy

All patients (not older age controls) underwent DPD scintigraphy. The imaging protocol at the JRH, NAC and SBH consisted of an early (5 minutes) and late (3 hours) planar whole-body image. Scans were performed using aligned protocols and Perugini scoring; with grade 0 being negative, grade 1 to 3 increasingly positive as

previously described [181]. Among positive patients, further assessments (serum free light chain ratio and monoclonal immunoglobulin in the serum and urine by immunofixation) to rule out AL amyloid and genotyping identified wild-type transthyretin cardiac amyloidosis based on international guidelines [291]. Patients with Perugini grade 1 were excluded from hypotheses A and C but included for hypotheses B.

4.2.4. Echocardiography

All patients underwent transthoracic echocardiography by experienced accredited echocardiographers. Different machines and software were used at different sites for image acquisition. Chamber and valve quantification was according to international recommendations [292]. Cardiac parameters were measured using EchoPAC software (GE Healthcare, Wauwatosa, WI, USA). Left ventricular (LV) mass was calculated using methodology described previously [293]. Myocardial contraction fraction (MCF) was derived from the ratio of stroke volume over myocardial volume. Global longitudinal function (GLS) was acquired using strain imaging in the apical 4, 3 and 2 chamber views and is an average of all 17 segments.

4.2.5. Standardized Uptake Value (SUV)

SUV quantification is explained in detail elsewhere [186]. In brief, SUV is a dimensionless index that provides a semi-quantitative index of DPD tracer uptake relative to the general body. This was obtained using
Corridor 4DM (Invia, Ann Arbor, Michigan, USA) as a 17 segment model. The apex (17^{th} segment) was ignored for this study as it is prone to partial voluming effects due to its thinness.

4.2.6. Extracellular Volume (ECV) fraction

20 of the 34 patients with AS-ATTR included in this study had ECV quantification using computed tomography. Detailed methodology is published elsewhere [196]. In brief, a baseline (pre-contrast) and 3 minute post-contrast image was acquired. Acquisitions were triggered at 250ms after the R-wave. Along with the coronary angiogram and patient's haematocrit, ECV fraction was calculated using the formula below and expressed as a percentage.

$$ECV = (1 - Haematocrit) \times \frac{\Delta HU\ myo}{\Delta HU\ blood}$$

∆HU myo- change in Hounsfield units (pre vs post-contrast) in the myocardium, HU blood- change in Hounsfield units (pre vs post-contrast) in the blood.

The data was obtained as a 17 segment AHA model of which the apex (17th segment) was ignored for this study as it is prone to partial voluming effects due to its thinness.

4.2.7. Study endpoints

For hypotheses A, end-points were selected as markers of myocardial damage, structure and function. The primary end-point was NT-proBNP, based on its prognostic value in patients with AS and ATTR. The secondary endpoints used were:

a) left ventricular mass indexed as it is a marker of amyloid burden and a frequent consequence of remodelling in AS.
b) Myocardial contraction fraction (MCF) and global longitudinal strain (GLS) as markers of LV systolic function
c) E/A ratio to assess LV diastolic function
d) Tricuspid annular planar systolic excursion (TAPSE) to assess RV systolic function
e) High sensitivity Troponin T (hsTnT) as a marker of myocardial damage
f) Carpal tunnel syndrome as a marker of systemic ATTR involvement

For hypotheses B, demographics, comorbidities, ECG, biomarkers and echocardiographic variables were all compared between grade 1 and grade 2/3 AS-ATTR.

For hypotheses C, RV remodelling and function were compared across all four cohorts.

For hypotheses D, CT_{ECV}, GLS and SUV were compared between patients with AS-ATTR and AS. Regional differences between base, mid and apex was compared within the AS-ATTR and AS populations separately.

4.2.8. Statistical analysis

Continuous data describing the sample are summarised as mean ± standard deviation or median (interquartile range) for skewed data; categorical data are summarised as frequencies (percentages). Unless stated otherwise, a 2-sided p value of <0.05 was considered significant.

4.2.8.1. Analysis for hypotheses A

Results from the four diagnostic groups were compared using multivariable regression modelling with covariate adjustment to control confounding. Results are presented as marginal means and 95% confidence intervals (CI). Covariates were chosen as potential confounders based on *a priori* evidence indicating correlations with both exposure and outcome. Covariates were sex, age, diabetes, hypertension, high cholesterol and chronic kidney disease. Additional sensitivity analyses were performed to check the results of the regression modelling, using augmented inverse-probability weighting (AIPW) to achieve confounder balance across the four groups. AIPW is a statistical approach that combines propensity-based inverse probability weighting (where the contribution of an individual's data is weighted by the propensity score) and regression adjustment. AIPW has the advantage that it is 'doubly robust', such that only one of the two methods need be correctly specified to obtain an unbiased effect estimator [310].

Additional data on comorbidities, ECG and echocardiographic findings are provided in table 5. These parameters were not included in the main analysis and are presented to provide a more complete description of each cohort, rather than for inferential purposes. All statistical analyses were performed using SPSS statistics software (V26, IBM, Chicago, IL) or Stata SE (15.1, StataCorp LLC, College Station, Texas). For the primary outcome (NT-ProBNP) a two-sided p value of <0.05 was considered significant. Inferences on other outcomes were made based on the means and 95% confidence intervals.

4.2.8.2. Analysis for hypotheses B

Data were compared between the two cohorts using Independent student's T test for parametric data, Mann-Whitney U test for non-parametric data and Chi squared (or Fischer's exact test if appropriate) for categorical data.

4.2.8.3. Analysis for hypotheses C

Data were compared across all four groups using a one-way ANOVA for parametric data or the Kruskal-Wallis test for non-parametric data.

4.2.8.4. Analysis for hypotheses D

Comparisons between two regions were performed using the paired student's t test. Correlation was compared between parameters using linear regression. Data were compared between the base and the apex using the Wilcoxon signed-rank test or between all three regions (base, mid and apex) using Friedman's test for dependable non-parametric data.

4.3. Results for hypotheses A: Grade 2/3 AS-ATTR represents dual pathology and a severe phenotype that combines the characteristics of AS and ATTR

4.3.1. Study population

Baseline characteristics of the four prospective cohorts are shown in table 4, and 5 and figure 29. Patient demographics for the four cohorts were:

1) Older age controls (AS negative, ATTR unlikely) cohort (n=81) was 69% male, median age of 82 (80, 84) years,

2) AS (i.e. ATTR negative, severe AS) cohort (n=359) was 49% male, median age of 85 (80, 88) years,

3) AS-ATTR cohort (ATTR positive, severe AS) cohort (n=36) was 61% male, median age of 88 (85, 92) years with Perugini grade 2 identified in 33 patients (92%) and grade 3 in 3 patients (8%).

4) ATTR (ATTR positive, AS negative) cohort (n=107) was 94% male, median age of 80 (75, 84) years. Perugini grade 2 was identified in 104 patients (97%), grade 3 in 3 patients (3%).

AS-ATTR patients with Perugini grade 1 were excluded from this study (n=16). The AS-ATTR cohort was older than all three other cohorts ($p<0.005$ for trend) but between AS and ATTR for male predominance (61%; $p<0.005$ for trend).

		Aortic stenosis	
		Present	**Absent**
ATTR	**Present**	AS-ATTR (n=36) 61% male, age 88 (85, 92) years. Perugini grade 2 in 33 patients (92%) and grade 3 in 3 patients (8%)	ATTR (n=107) 94% male, age 80 (75, 84) years. Perugini grade 2 in 104 patients (97%), grade 3 in 3 patients (3%)
	Absent	AS (n=359) 49% male, age 85 (80, 88) years	Older age controls (n=81) 64% male, age 82 (80, 84) years

Table 4: Study population according to the presence or absence of aortic stenosis and amyloidosis and the demographics of each cohort.

Variable	Older age controls (n=81)	AS (n=359)	AS-ATTR (n=36)	ATTR (n=107)
Ischemic heart disease (%)	19 (23)	162 (45)	14 (40)	19 (18)
Diabetes Mellitus (%)	12 (15)	95 (27)	6 (17)	22 (21)
Hypertension (%)	44 (54)	299 (83)	28 (78)	28 (26)
High Cholesterol (%)	45 (56)	75 (43)	8 (36)	35 (33)
Cerebrovascular accident (%)	2 (3)	15 (9)	3 (14)	16 (15)
CKD (%)	11 (14)	131 (37)	18 (50)	14 (13)
Carpal tunnel syndrome (%)	0 (0)	6 (2)	6 (17)	41 (38)
AF (%)	1 (1)	92 (30)	10 (42)	48 (60)
First Degree heart block (%)	17 (21)	58 (22)	2 (10)	23 (66)
Left Axis Deviation (%)	17 (21)	58 (17)	7 (21)	32 (30)
Right Axis Deviation (%)	1 (1)	1 (1)	0 (0)	13 (12)
LBBB (%)	6 (7)	29 (8)	1 (3)	12 (11)
RBBB (%)	3 (4)	35 (10)	5 (15)	11 (10)
Deceleration time (msec)	239 (209, 272)	212 (165, 274)	197 (162, 253)	178 (145, 221)
Average E/E’	9 (8, 11)	17 (13, 23)	23 (21, 38)	16 (13, 21)
RV wall thickness (cm)	0.4 (0.3, 0.4)	0.4 (0.4, 0.6)	0.6 (0.4, 0.7)	0.8 (0.7, 1.0)

RV S' (m/s)	0.12 (0.11, 0.14)	0.11 (0.09, 0.13)	0.11 (0.10, 0.13)	0.09 (0.07, 0.12)
RV GLS	-23.6 ± 6.8	-17.5 ± 8.1	-17.2 ± 9.3	-14.7 ± 6.1
PASP (mmHg)	N/A	40 (27, 50)	44 (18, 51)	40 (33, 46)
AV peak velocity (m/s)		4.2 (3.9, 4.6)	3.9 (3.2, 4.6)	
AV peak gradient (mmHg)		70 (59, 84)	63 (43, 84)	
AV mean gradient (mmHg)		43 (34, 52)	39 (28, 48)	
AVAi (cm2/m2)		0.4 (0.3, 0.5)	0.4 (0.3, 0.4)	

Table 5: Normally distributed continuous data are presented as mean ± standard deviation and skewed continuous data as median (interquartile range). Categorical data are presented as frequencies (percentages). RV- right ventricular, TAPSE- tricuspid annular planar systolic excursion, PASP- pulmonary artery systolic pressure, CKD- chronic kidney disease, AF- atrial fibrillation, LBBB- left bundle branch, block, RBBB- right bundle branch block, AV- Aortic valve, AVAi- aortic valve area indexed,

4.3.2. Impact on myocardium stress

Patients with AS-ATTR have higher NT-proBNP (2844; 95% CI (1745, 4635)ng/dL) than older age controls (127; 95% CI (100, 162)ng/dL; P<0.001) and AS (1294; 95% CI (1077, 1554)ng/dL; P=0.002) and similar to ATTR (3272; 95% CI (2552, 4197)ng/dL; p=0.63). These results are consistent with the doubly robust analysis (table 6 and 7).

4.3.3. Impact of myocardial structure

LVMi in AS-ATTR was greater than in older age controls, similar to AS and lower than ATTR. Doubly robust analysis demonstrated no significant difference between groups except between older age controls and AS-ATTR. However, confidence intervals are wide. (table 6 and 7).

4.3.4. Impact of myocardial function

GLS and TAPSE in AS-ATTR was impaired and similar to AS and ATTR. All three patient cohorts had worse function compared to older age controls. However, MCF in AS-ATTR was worse compared to AS and better compared to ATTR, with older age controls demonstrating the best MCF. E/A ratio in AS-ATTR (restrictive diastology) was worse than AS and older age controls and similar to ATTR These results are consistent with the doubly robust analysis except for GLS where confidence intervals for older age controls are wide and for E/A ratio where comparison with AS demonstrates a trend towards significance (p=0.069) (table 6 and 7).

4.3.5. Impact on myocardial damage

hsTnT in AS-ATTR was higher than AS and older age controls and similar to ATTR These results are consistent with the doubly robust analysis (table 6 and 7).

4.3.6. Systemic impact of ATTR

Carpal tunnel syndrome in AS-ATTR was more frequent compared to AS and similar to ATTR. These results are inconsistent with the doubly robust analysis, however, overall numbers of carpal tunnel syndrome are small limiting statistical power (table 6 and 7).

Myocardial factor	Diagnosis	Marginal geometric mean	95% Confidence Interval	P value (versus AS-ATTR)
NT-proBNP	AS-ATTR	2844	(1745, 4635)	NR
	AS	**1294**	**(1077, 1554)**	**0.002**
	ATTR	3272	(2552, 4197)	0.63
	Control	**127**	**(100, 162)**	**<0.001**
LVMi	AS-ATTR	139	(112, 167)	NR
	AS	120	(109, 130)	0.179
	ATTR	**180**	**(167, 194)**	**0.013**
	Control	**92**	**(79, 106)**	**0.003**
MCF	AS-ATTR	0.17	(0.13, 0.22)	NR
	AS	**0.3**	**(0.27, 0.33)**	**0.001**
	ATTR	**0.1**	**(0.09, 0.11)**	**<0.001**
	Control	**0.27**	**(0.24, 0.30)**	**0.017**
GLS	AS-ATTR	-15.1	(-21.6, -8.5)	NR
	AS	-14.8	(-16.5, -13.1)	0.576

	ATTR	-12.2	(-13.5, -10.8)	0.215
	Control	**-19.5**	**(-20.7, -18.2)**	**0.002**
TAPSE	AS-ATTR	1.5	(1.1, 2.0)	NR
	AS	1.9	(1.8, 2.0)	0.332
	ATTR	1.5	(1.4, 1.6)	0.156
	Control	**2.4**	**(2.3, 2.5)**	**<0.001**
TnT	AS-ATTR	50	(30, 83)	NR
	AS	**22**	**(19, 25)**	**<0.001**
	ATTR	49	(43, 56)	0.529
	Control	**12**	**(10, 13)**	**<0.001**
E/A ratio	AS-ATTR	3.3	(0.9, 5.7)	NR
	AS	**1.1**	**(0.9, 1.3)**	**<0.001**
	ATTR	2.3	(1.9, 2.8)	0.272
	Control	**0.7**	**(0.7, 0.8)**	**<0.001**
Carpal tunnel syndrome	AS-ATTR	1.3	(1.1, 1.6)	NR
	AS	**1**	**(1.0, 1.0)**	**0.001**
	ATTR	1.3	(1.2, 1.4)	0.864
	Control	n/a	n/a	n/a

Table 6: Comparison of AS-ATTR to older age controls, AS and ATTR using regression analysis. NT-proBNP- N terminal pro brain natriuretic peptide, hsTnT- high sensitivity Troponin T, LVMi- left ventricular mass index, MCF- myocardial contraction fraction, GLS- global longitudinal strain, TAPSE- tricuspid annular planar systolic excursion.

Variable	Group comparisons (AS-ATTR vs ..)	Coefficient	95 % Confidence interval		P value
			Upper limit	Lower limit	
NT-proBNP	**Elderly control**	**-3.21**	**-3.97**	**-2.46**	**<0.001**
	AS	**-0.83**	**-1.54**	**-0.11**	**0.023**
	ATTR	0.20	-0.51	0.90	0.587
LVMi	**Elderly control**	**-56.57**	**-96.75**	**-16.39**	**0.006**
	AS	-32.64	-67.58	2.31	0.067
	ATTR	26.22	-12.55	64.99	0.185
MCF	**Elderly control**	**0.10**	**0.04**	**0.16**	**0.001**
	AS	**0.13**	**0.07**	**0.19**	**<0.001**
	ATTR	**-0.11**	**-0.16**	**-0.05**	**<0.001**
GLS	Elderly control	-4.41	-11.0	2.23	0.193
	AS	0.27	-6.44	6.98	0.937
	ATTR	2.89	-3.78	9.56	0.396
TAPSE	**Elderly control**	**0.31**	**0.13**	**0.48**	**0.001**
	AS	0.14	-0.03	0.32	0.112
	ATTR	-0.02	-0.20	0.16	0.845
hsTnT	**Elderly control**	**-1.44**	**-1.96**	**-0.91**	**<0.001**
	AS	**-0.82**	**-1.35**	**-0.30**	**0.002**
	ATTR	-0.02	-0.54	0.51	0.948
E/A ratio	**Elderly control**	**-2.58**	**-4.97**	**-0.19**	**0.034**
	AS	-2.22	-4.62	0.17	0.069
	ATTR	-0.99	-3.42	1.43	0.421
Carpal tunnel syndrome	AS	-0.12	-0.39	0.15	0.373
	ATTR	0.06	-0.24	0.35	0.694

Table 7: A doubly robust analysis (using augmented inverse probability weighted regression analysis) was carried out for each end-point. This lends support to the main regression analysis presented in the study. NT-proBNP- N terminal pro brain natriuretic peptide, hsTnT- high sensitivity Troponin T, LVMi- left ventricular mass index, MCF- myocardial contraction fraction, GLS- global longitudinal strain, TAPSE- tricuspid annular planar systolic excursion.

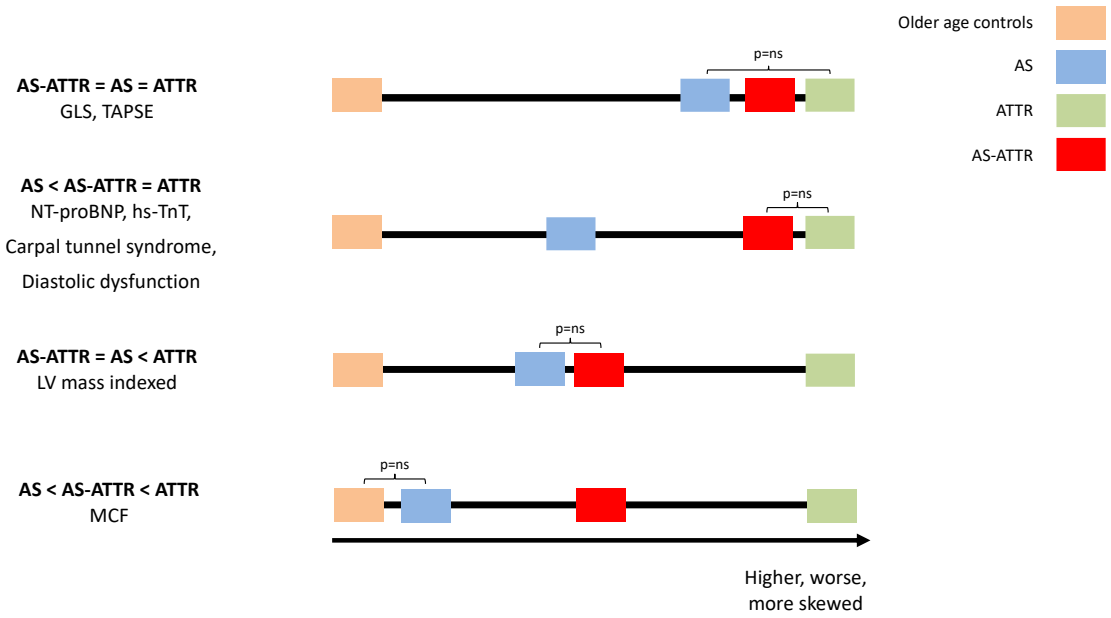


Figure 29: Summary of characterization of AS-ATTR. AS-ATTR compared to AS, ATTR and older age controls (not drawn to scale). For some parameters (GLS, TAPSE), AS-ATTR was similar to AS and ATTR, whilst for others it was similar to ATTR and higher than AS (cardiac biomarkers, carpal tunnel syndrome and diastolic dysfunction). AS-ATTR was similar to AS and less than ATTR for LV mass indexed and in between AS and ATTR for MCF. NT-proBNP- N terminal pro- brain natriuretic peptide, hsTnT- high sensitivity Troponin T, LV- left ventricular, LVEF- left ventricular ejection fraction, TAPSE- tricuspid annular plane systolic excursion. Adapted from my publication [311].

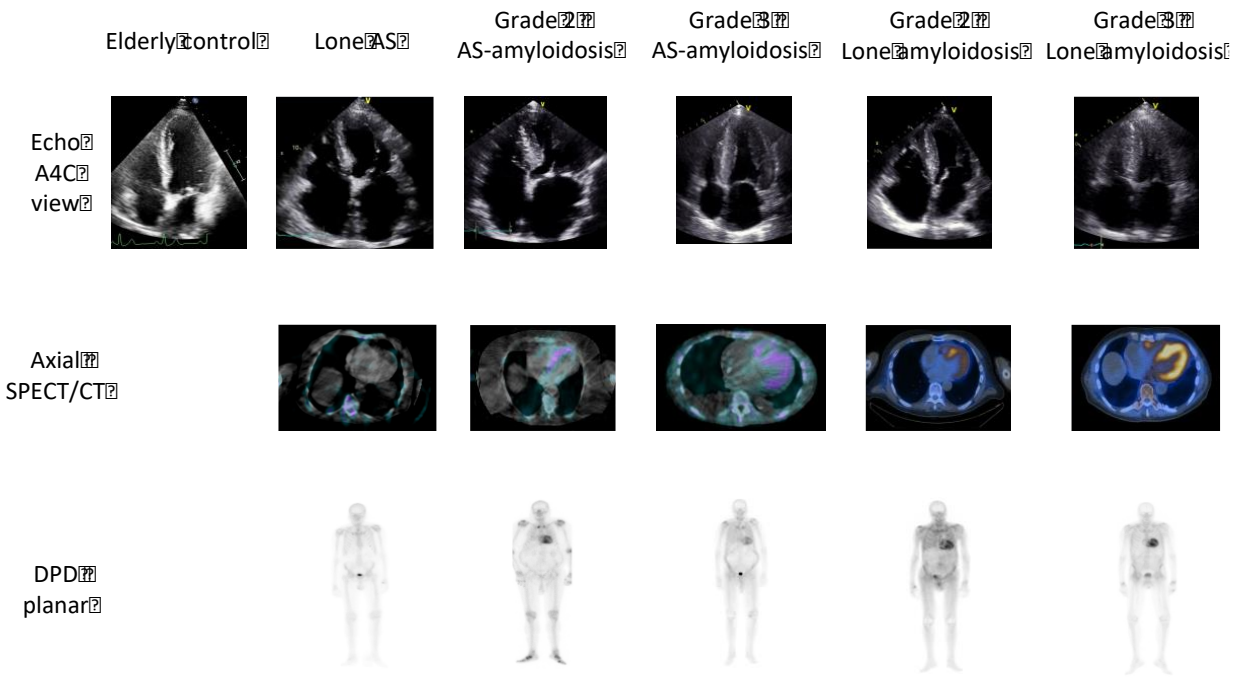


Figure 30: Multi-modality characterisation of AS-amyloidosis. Echocardiographic and DPD (axial SPECT/CT and planar) images of patients from all four cohorts: elderly control, lone AS, AS-amyloidosis and lone amyloidosis. Echocardiography shows an apical four chamber (A4C) view. Single photon emission computed tomography/ computed tomography (SPECT/CT) shows coronal slices at the level of the heart showing radioisotope uptake superimposed on a CT image. Planar images show cardiac radioisotope uptake relative to bony uptake. Adapted from my publication [311].

4.4. Hypotheses B: Grade 1 vs Grade 2/3

4.4.1. Study population

52 patients with AS-ATTR were identified from two prospectively recruited cohorts; 16 had Perugini grade 1 amyloid and 33 had Perugini grade 2 and 3 had Perugini grade 3 amyloid. Patients with grade 2 and 3 were grouped together for this analysis (table 8).

Grade 1: n=16; age 86 (83, 89); 63% male

Grade 2/3: n=36; age 88 (85, 92); 61% male

4.4.2. Comorbidities, electrocardiography and cardiac biomarkers

Both groups had a similar prevalence of comorbidities and conduction abnormalities. Both NT-proBNP and high sensitivity troponin T were almost twice as high in patients

with Grade 2/3 compared to grade 1 AS-ATTR (table 8).

4.4.3. Cardiac structure and function

Structurally the LV was similar between both groups, with the exception of LV mass indexed which demonstrated a trend towards being higher in grade 2/3 (122 ± 55 vs 92 ± 51g/m^2; p=0.093). LVEF was similar between both cohorts, however, there was a trend towards MCF being lower in grade 2/3 (0.21 (0.17, 0.41) vs 0.38 (0.28, 1.37); p=0.061). Stroke volume indexed was lower in grade 2/3 compared to grade 1, (32 (26, 42) vs 40 (37, 85)cm; p= 0.045). Diastology was significantly worse in grade 2/3 compared to grade 1. Right ventricular wall thickness was similar between both groups and only TAPSE demonstrated a trend towards worse function in grade 2/3 vs grade 1 (1.9 (1.5, 2.1) vs 2.3 (1.8, 2.5)cm; p=0.058), (table 8).

4.4.4. Aortic stenosis severity

Compared to grade 1 patients, Grade 2/3 demonstrated lower transvalvular velocities and gradients, although AVA was similar (table 8).

Variable	**Grade 1 (n=16)**	**Grade 2/3 (n=36)**	**P value**
Demographics			
Age (years)	86 (83, 89)	88 (85, 92)	0.194
Gender (% male)	63	61	0.924
Comorbidities			
Ischemic heart disease (%)	50	39	0.454
Diabetes Mellitus (%)	19	17	0.855
Hypertension (%)	69	78	0.488
CKD (%)	38	50	0.404
Carpal tunnel syndrome (%)	13	17	0.701
AF (%)	42	42	1.000
Electrocardiography			
LBBB (%)	7	3	0.544
RBBB (%)	20	15	0.644
Low voltage in limb leads (%)	0	9	0.242
Voltage/mass ratio	0.05 (0.04, 0.29)	0.07 (0.03, 0.19)	0.247
Cardiac biomarkers			
NT-ProBNP (ng/L)	**2732 (850, 3700)**	**4149 (1449, 6459)**	**0.023**

hsTnT (ng/L)	**23 (18, 31)**	**56 (33, 100)**	**<0.001**
Left ventricular remodelling and function			
Inferolateral wall thickness (cm)	1.3 (0.9, 1.4)	1.3 (1.1, 1.5)	0.317
Anteroseptal wall thickness (cm)	1.3 (1.3, 1.5)	1.5 (1.3, 1.8)	0.186
Indexed LV mass (g/m^2)	92 ± 51	122 ± 55	0.093
Stroke Volume indexed (ml/m2)	**40 (37, 85)**	**32 (26, 42)**	**0.045**
LVEF (%)	58 ± 19	55 ± 11	0.526
MCF	0.38 (0.28, 1.37)	0.21 (0.17, 0.41)	0.061
GLS (%)	-15.4 ± 5.1	-14.1 ± 5.6	0.513
Relative apical sparing	1.4 ± 0.5	1.4 ± 0.7	0.883
Lateral S' (m/s)	0.06 (0.05, 0.07)	0.05 (0.04, 0.07)	0.534
Septal S' (m/s)	0.05 (0.05, 0.06)	0.04 (0.03, 0.06)	0.21
E/A	**0.7 (0.7, 0.8)**	**1.1 (0.8, 2.8)**	**0.025**
Deceleration time (msec)	**315 ± 94**	**216 ± 69**	**<0.001**
Lateral E/E'	12.6 (11.0, 26.0)	18.3 (12.4, 22.2)	0.458
Septal E/E'	14.7 (13.3, 22.9)	24.6 (20.6, 35.8)	0.054
Right ventricular remodelling and function			
RV wall thickness (cm)	0.4 ± 0.2	0.6 ± 0.2	0.133
TAPSE (cm)	2.3 (1.8, 2.5)	1.9 (1.5, 2.1)	0.058
RV S' (m/s)	0.12 ± 0.03	0.11 ± 0.02	0.686
RV GLS (%)	-16.8 ± 8.6	-17.2 ± 9.3	0.918
Aortic valve parameters			
AV peak velocity (m/s)	**4.5 ± 0.7**	**3.9 ± 0.8**	**0.018**
AV peak gradient (mmHg)	**83 ± 24**	**64 ± 24**	**0.021**
AV mean gradient (mmHg)	48 ± 15	40 ± 17	0.123
AVA (cm^2)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.989

Table 8: Characteristics of patients with AS-ATTR, comparing Perugini grade 1 to Perugini grade 2/3.

4.5. Results for hypotheses C: The right ventricle is adversely affected in AS-ATTR and demonstrates key features that can be used to screen AS patients for possible AS-ATTR

In order to ascertain whether the RV could be used to discriminate between AS and AS-ATTR, we compared all patients in all 4 cohorts.

4.5.1. Right ventricular remodelling and function

Right ventricular (RV) structure and function was worse in all three cohorts compared to older age controls. RV wall thickness in AS-ATTR was similar to AS and thinner than ATTR. Whilst RV function and PASP were similar between AS-ATTR and both AS and ATTR.

RV DPD radiotracer uptake was assessed in 19 of 36 AS-amyloidosis patients (where SPECT was available) with RV uptake seen in 18 patients (table 9).

Variable	Older age controls (n=81)	AS (n=359)	AS-ATTR (n=36)	ATTR (n=107)	P value
RV wall thickness (cm)	**0.4 (0.3, 0.4) *†‡**	**0.4 (0.4, 0.6) ‖**	**0.6 (0.4, 0.7) #**	**0.8 (0.7, 1.0)**	**<0.005**
RV S' (m/s)	**0.12 (0.11, 0.14) *‡**	**0.11 (0.09, 0.13)**	**0.11 (0.10, 0.13)**	**0.09 (0.07, 0.12)**	**<0.005**
RV GLS	**-23.6 ± 6.8 *†‡**	**-18.5 ± 8.1 ‖**	**-17.2 ± 8.1 ‖#**	**-14.7 ± 6.1**	**<0.005**
PASP (mmHg)	N/A	40 (27, 50)	44 (18, 51)	40 (33, 46)	0.530

Table 9: RV remodelling and function in AS-ATTR. P values represent statistical significance across all four groups. Pair-wise comparisons are represented by symbols below:

* p<0.05, Old age control vs AS

† p<0.05, Old age vs AS-ATTR

‡ Old age vs ATTR

‖ p<0.05, AS vs ATTR

# p<0.05, AS-ATTR vs ATTR

4.6. Results for hypotheses D: Regional characterisation of AS-ATTR

34 patients with AS-ATTR were included in this study. Structural and functional data was quantified where possible; GLS (n=27), ECV (n=20) and SUV (n=26). 14 patients had all three variables.

The AS population was obtained from the ATTRact AS cohort, 70 patients with AS had both ECV quantification by CT and GLS analysis. 3 patients with focally elevated ECV due to beam hardening artefact secondary to a cardiac device lead were excluded from this study. 2 had focally elevated ECV due to previous myocardial infarction and were excluded, which left a total of 65 patients with AS for this study.

4.6.1. Baseline characteristics

34 patients with AS-ATTR, age 89 ± 5 years, 71% male with Perugini grade 1 (n=10), grade 2 (n=22) and grade 3 (n=2) were included. Table 10 shows the baseline characteristics of the study cohort.

Variable	**Value (n=34)**
Demographics	
Age (years)	89 ± 5
Male sex (n) %	(24) 71
Hypertension (n) %	(23) 68
Previous stroke (n) %	(3) 9
Coronary artery disease (n) %	(12) 35
Diabetes Mellitus (n) %	(6) 18
Cardiac biomarkers	
Troponin (ng/L)	42 (25, 87)
NT proBNP (ng/L)	3702 (1286, 5626)
Echocardiography	
LVEF (%)	53 ± 12
Stroke volume indexed (ml/m^2)	33 ± 10
Advanced imaging analysis	
GLS (%)	-14.0 ± 5.5
ECV fraction (%)	39.7 ± 7.7
SUV	3.4 ± 1.8

Table 10: Baseline characteristics of all patients in this study.

4.6.2. Apical sparing in AS-ATTR

Figure 31 demonstrates higher basal compared to apical values for all four metrics (GLS, ECV fraction, SUV and indexed LV mass) (p<0.001 for all). An apex to base gradient was demonstrated with GLS; apex vs mid vs base was -21.3 (-26.6, -15.1) vs -11.7 (-15.1, -9.4) vs -10.2 (-14.6, -7.5) %; p<0.001. The mean apex to base ratio derived using GLS was 2.2 ± 1.0.

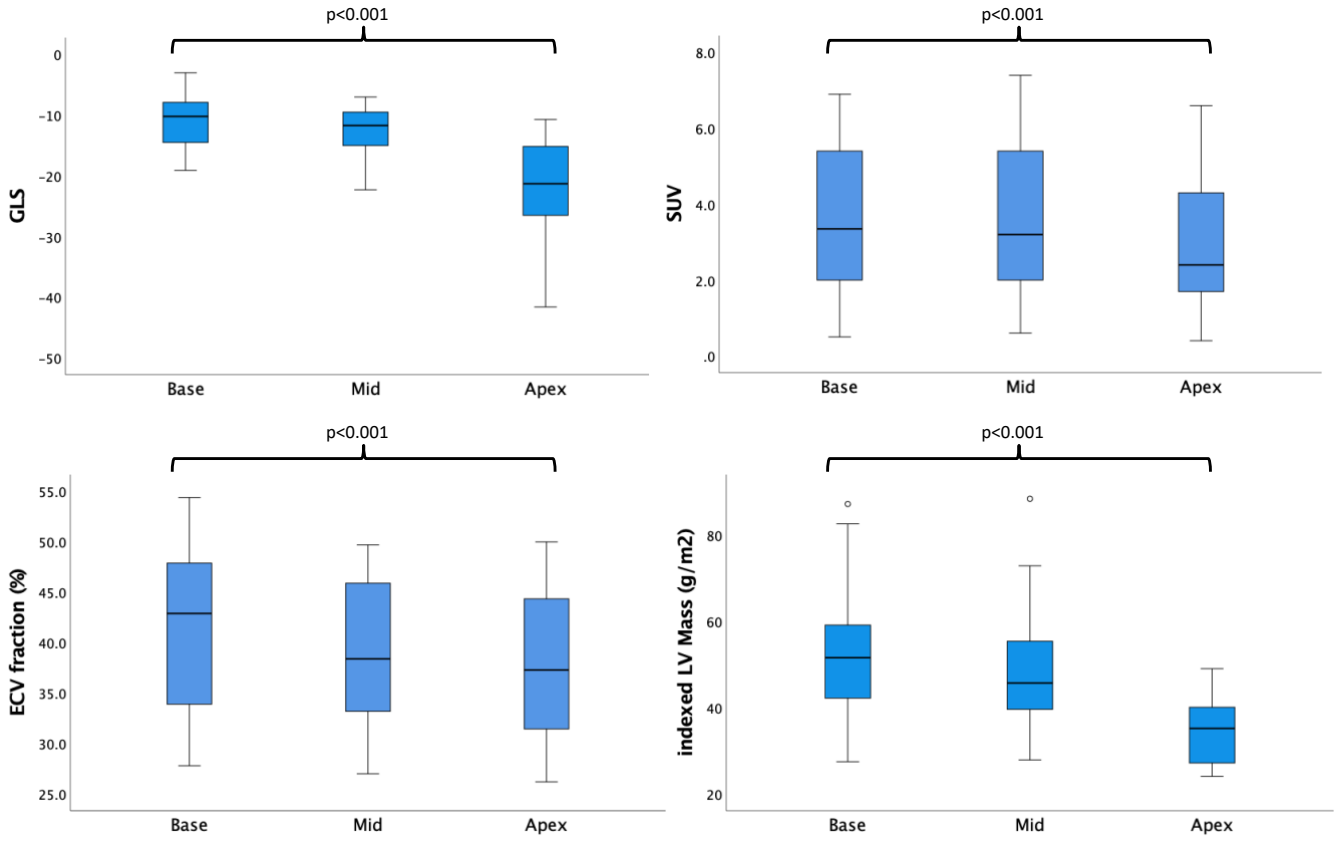


Figure 31: Regional values of GLS, ECV fraction, SUV and indexed LV mass. Basal values are significantly higher than apical values

4.6.3. Correlation between amyloid metrics and GLS

Figure 32 demonstrates a moderate and weak correlation between GLS and both ECV fraction and SUV respectively. No significant correlation was observed between the GLS derived apex to base ratio and that derived from ECV fraction or SUV.

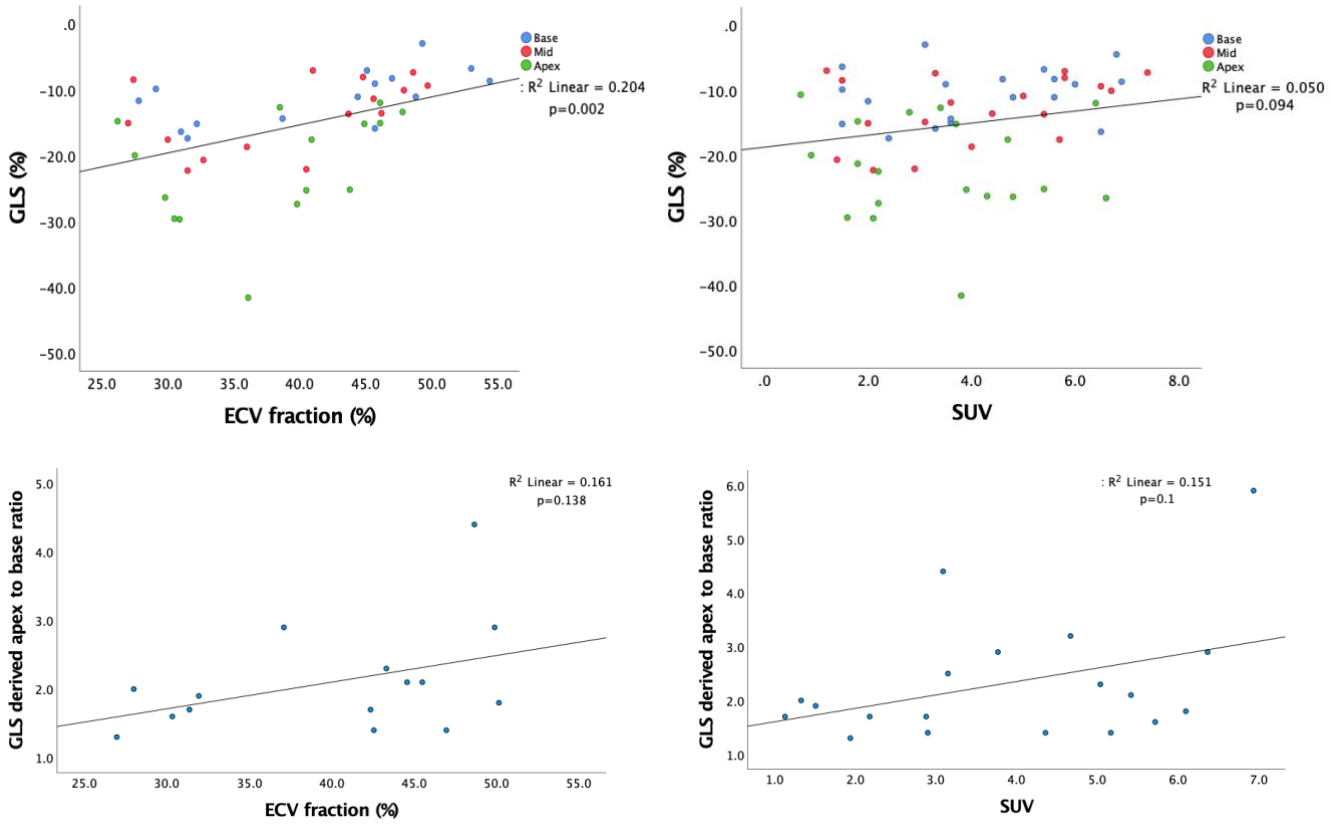


Figure 32: Correlation between GLS and amyloid metrics among patients with AS-ATTR.

4.6.4. Regionality in AS and comparison to AS-ATTR

Baseline characteristics were similar between AS and AS-ATTR (table 11).

Variable	AS (n=65)	AS-ATTR (n=34)	P value
Age (years)	87 ± 5	89 ± 5	0.069
AV mean gradient (mmHg)	**42 (35, 48)**	**38 (26, 48)**	**0.038**
AVA (cm)	0.6 (0.5, 0.8)	0.7 (0.6, 0.9)	0.184
Hypertension (%)	53 (80)	23 (68)	0.16
Diabetes (%)	20 (30)	6 (18)	0.172
Previous MI/PCI/CABG (%)	19 (29)	12 (35)	0.505
Previous stroke (%)	6 (9)	3 (9)	0.965

Table 11: Baseline characteristics of AS vs AS-ATTR.

The GLS-based apex to base ratio was higher with AS-ATTR compared to AS, 2.87 ± 2.24 vs 1.90 ± 1.30; p=0.011. ECV fraction was significantly higher in AS-ATTR compared to AS: (39.9 (32.5, 46.6) vs 29.0 (27.6, 30.9); p<0.001, whereas ECV fraction-based apex to base ratio was similar between both diseases. A weak correlation was found between GLS and ECV fraction. (Table 12, figure 33 and 34).

Imaging parameter	AS-ATTR (n=20)	AS (n=65)	P value
ECV fraction (%)	**39.9 (32.5, 46.6)**	**29.0 (27.6, 30.9)**	**<0.001**
ECV fraction Apex to Base ratio	0.93 (0.87, 0.97)	0.93 (0.90, 0.96)	0.39

Table 12: comparison of ECV between AS-amyloid and lone AS.

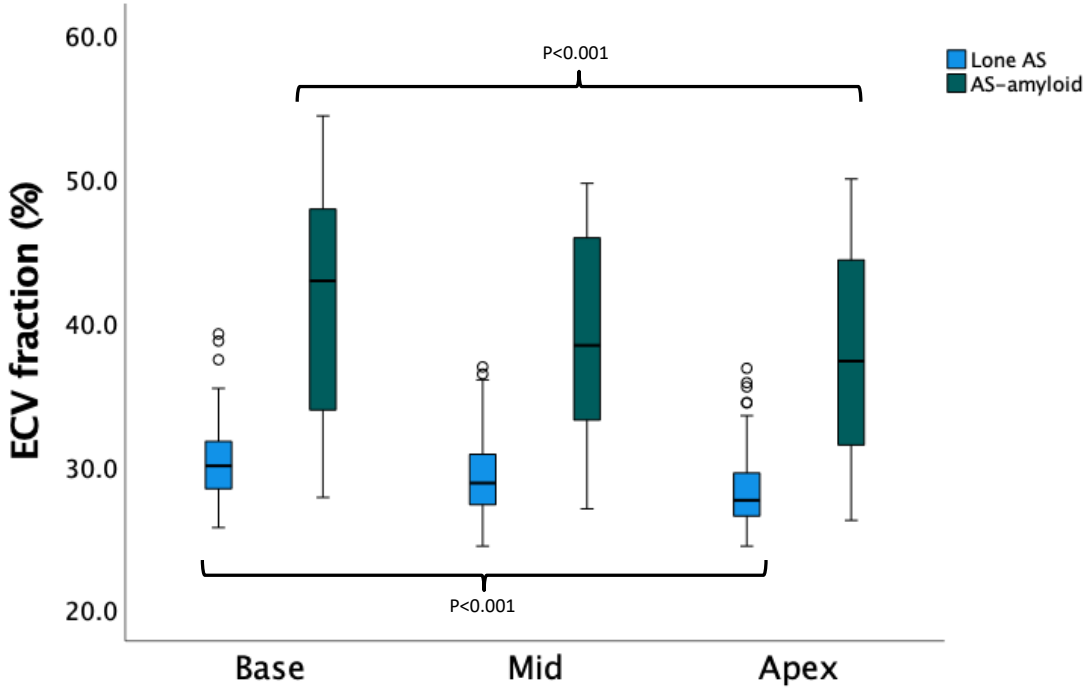


Figure 33: Comparison of regional variation in ECV fraction in both lone AS and AS-amyloid

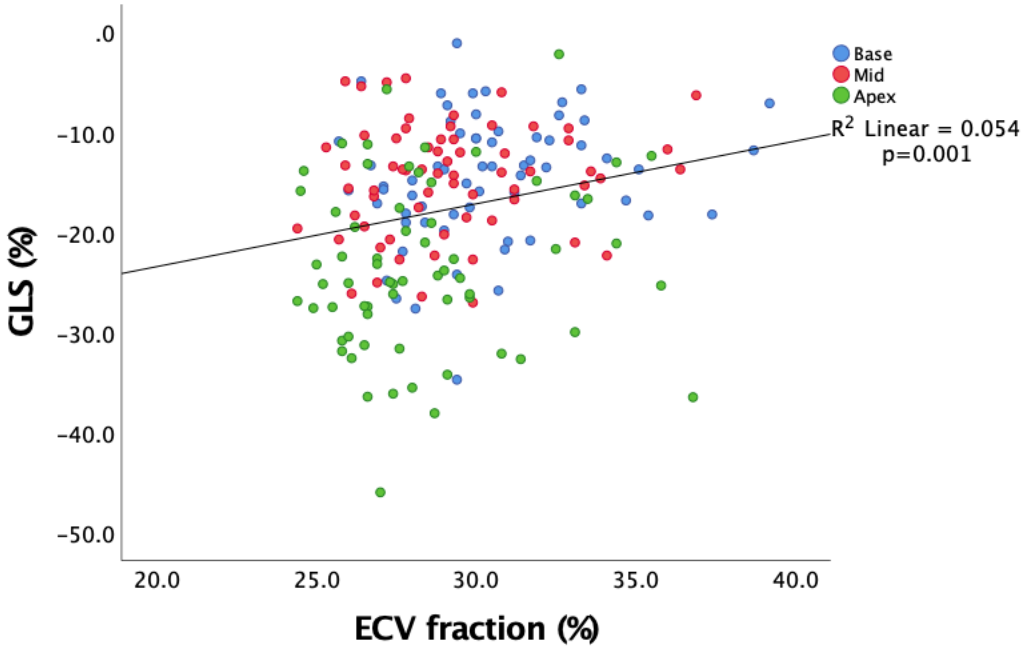


Figure 34: Correlation between ECV fraction and GLS among patients with AS.

4.6.5. Correlation with cardiac Troponin T

Correlation between hsTnT and GLS is shown in figure 35. GLS had a no correlation, whereas the apex to base ratio demonstrated a moderate correlation with hsTnT.

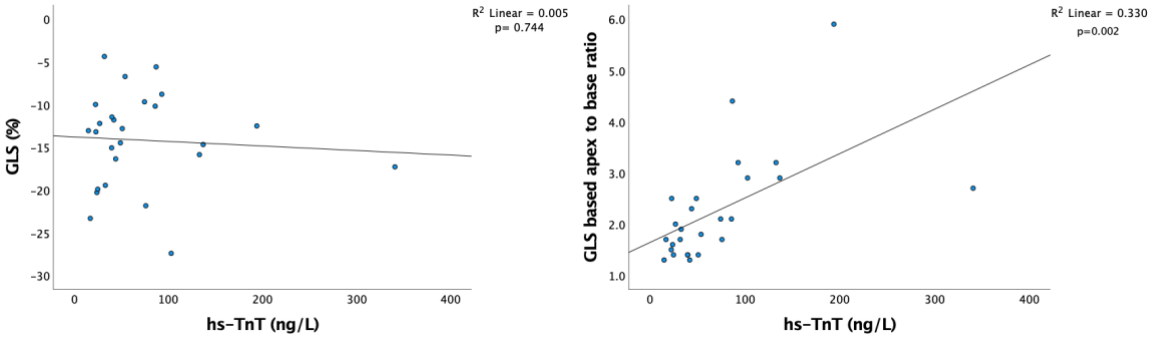


Figure 35: Correlation between GLS and high sensitivity Troponin T

In order to validate these results for the overall study population, I performed the same analysis on 14 patients with a complete set of all 3 variables and obtained similar results (tables 13 and 14).

Variable	Apex	Base	P value
GLS (%)	-22.6 (-28.0, -14.5)	-11.1 (-15.4, -8.6)	0.001
ECV fraction (%)	39.2 (30.3, 44.1)	45.1 (31.4, 48.9)	0.001
SUV	3.6 (2.0, 4.7)	4.2 (2.3, 5.7)	0.01
LVMi (g/m^2)	35.2 (27.4, 39.1)	52.8 (46.7, 58.6)	0.002

Table 13: Comparison of Apex to Base using different imaging parameters demonstrates that the base is adversely affect more than the apex. This was performed in 14 patients with all three imaging parameters.

Correlation between GLS and …	R^2	P value
ECV fraction	**0.193**	**0.004**
SUV	**0.1**	**0.041**

Table 14: Correlation between GLS and ECV fraction and SUV in 14 AS-ATTR patients with all three imaging parameters.

4.7. Discussion

Using a multi-centre, multi-cohort approach of over 500 patients, I characterized AS-ATTR by comparing the phenotype to that of AS, ATTR and age and ethnicity-matched controls.

Six main conclusions can be drawn:

- Firstly, despite an equivalent amyloid infiltration bone scintigraphy grade of ATTR, myocardial remodelling (LVMi) in AS-ATTR is similar to AS and less than ATTR, suggesting a lower amyloid burden in AS-ATTR patients, with the possibility of early detection.
- Secondly, the impact of dual pathology on the clinical phenotype is increased myocardial stress and damage with NT-proBNP and hsTnT levels similar to patients with ATTR.
- Thirdly, systolic longitudinal function is impaired in AS-ATTR but similar to the AS and ATTR phenotype.
- Fourthly, diastology in AS-ATTR is restrictive and closely resembles ATTR.

- Fifthly, grade 1 AS-ATTR does appear to be a milder version compared to grade 2/3 with lower cardiac biomarkers, slightly better function with some parameters (SVi) and diastology but equivalent amyloid burden (LVMi).
- Lastly, RV involvement is common in AS-ATTR (+ve DPD) albeit without affecting the structure or function, suggesting that the amyloid component is commonly biventricular and supporting the hypotheses of earlier detection.
- AS-ATTR demonstrates an apical sparing pattern using GLS, amyloid deposition and extracellular fraction. Changes in amyloid burden and fibrosis do track GLS, albeit weak to moderately. Greater apical sparing defined by GLS is associated with more myocyte death.

Table 15 summarises some of the findings described below. AS-ATTR poses several challenges, from diagnostics- screening patients with AS for coexisting amyloid to management- timing (either pre or post- aortic valve replacement) and mode of aortic valve interventions (either surgical aortic valve replacement or TAVI) and amyloid-targeted therapy. This makes understanding the relative impact of each contributing pathology very important.

DPD grades are indicative of the distribution of amyloid in the heart relative to other organ systems. Despite comparing patients with only Perugini grade 2 (majority of patients) and 3 and adjusting for several covariates, AS-ATTR had a lower amyloid burden (estimated using LVMi) compared to ATTR. The most plausible reason for this is that the amyloid in AS-ATTR, here discovered by screening, was simply an earlier phase of amyloid compared to ATTR, which was derived from a national referral cohort. Despite the lower amyloid burden, the dual impact of AS-related afterload and ATTR-related infiltration may be sufficient to drive certain markers of myocardial remodelling to resemble those of ATTR.

Myocardial marker	AS-ATTR vs AS	AS-ATTR vs ATTR
NT-proBNP	Worse	Similar
hsTnT	Worse	Similar
LVMi	Similar	lower
MCF	Worse	Better
GLS	Similar	Similar
TAPSE	Similar	Similar
E/A	Worse	Similar
Carpal Tunnel Syndrome	More frequent	Similar

Table 15: Summary of comparison of AS-ATTR with AS and ATTR. NT-proBNP- N terminal pro brain natriuretic peptide, hsTnT- high sensitivity Troponin T, LVMi- left ventricular mass index, MCF- myocardial contraction fraction, GLS- global longitudinal strain, TAPSE- tricuspid annular planar systolic excursion.

Both NT-proBNP and hsTnT have demonstrated prognostic value in patients with AS [312], [313] and ATTR [314], [315]. In AS-ATTR, the double hit to the myocardium from AS-related afterload and amyloid infiltration significantly increases both biomarkers. However, despite this increase, mortality is similar between AS and AS-ATTR post-TAVI [316], [317], suggesting that the AS component of AS-ATTR is the dominant pathology in AS-ATTR. This calls for an evaluation of the biomarkers' prognostic role in AS-ATTR but supports their diagnostic value in discriminating AS-ATTR from AS [316].

Assessment of LV systolic function using left ventricular ejection fraction in patients with cardiac remodelling can be misleading as changes in ventricular capacitance are not accounted for. GLS is a more sensitive marker of LV function and was found to be similar between AS-ATTR and AS and ATTR, indicating that longitudinal deformation is unaffected by dual pathology. However, when indexing stroke volume to the amount of myocardium using MCF, there is a clear difference between all four cohorts with AS-ATTR demonstrating better function than ATTR but worse function than older age controls and AS. This indicates the impact of amyloid in AS-ATTR alters ventricular geometry and reduces function without significantly increasing LVMi. The amyloid component of AS-ATTR also contributes to worse diastolic function compared to AS, resulting in a restrictive physiology- similar to ATTR. This

is expected given the infiltrative nature of amyloid and how it disrupts the extracellular matrix architecture.

Our study differed from previous descriptions of AS-ATTR, which likely reflects differences in sample selection, study methodology and ascertainment, here exclusively by prospective screening. There are similarities between our data and others on the description of AS-ATTR compared to AS: worse diastolic function and MCF. However, our study has demonstrated similar GLS and LVMi, higher cardiac biomarkers and more carpal tunnel syndrome in AS-ATTR compared to AS [159], [160].

Our findings have important clinical implications. The similarities in cardiac function, biomarkers and carpal tunnel syndrome between AS-ATTR and ATTR suggest that the amyloid component in AS-ATTR plays a key role in the phenotype. And given that the amyloid burden may be lower in AS-ATTR, the phenotype may be more amenable to treatment than previously thought. Although speculative- amyloid stabilizing drugs such as Tafamidis, may have a greater benefit when treating amyloid at an earlier stage than at later stages when the amyloid burden and impact is greater. Therefore, studies evaluating the effect of amyloid-targeted therapy are needed for AS-ATTR [318]. Treating AS-ATTR only with aortic valve replacement would neglect a significant part of phenotype. The subtle differences between AS-ATTR and AS call for a high index of suspicion and screening pathways to identify AS-ATTR in patients with AS. AS-ATTR affects the elderly, where quality of life and symptomatic relief are just as important as mortality benefit; future studies need to consider these outcomes when trialling interventions for AS-ATTR.

By comparing grade 1 AS-ATTR to grade 2/3, I confirmed the general consensus that grade 1 ATTR is a milder version compared to grade 2/3. However, it may still be clinically relevant. The presence of elevated biomarkers and changes in remodelling and function compared to known normal values suggests that grade 1 AS-ATTR is not benign. Supporting this is evidence from patients with ATTR, where no difference in mortality was observed between patients with Perugini grade 1, 2 and 3 [299]. This also alludes to the utility of Perugini grading. As I have demonstrated, the amyloid burden in AS-ATTR seems to be lower than ATTR, despite a similar Perugini grading. So whilst bone scintigraphy is diagnostically a very valuable investigation, the Perugini grading is less beneficial. Other quantitative

methods, such as heart to contralateral ratio described in the introduction may hold more important prognostic value [297].

The presence of RV involvement on DPD scintigraphy indicates that amyloid deposition is biventricular. I have simply classified it as a binary variable and there may be a role for better quantification of RV involvement. The presence of RV involvement is less useful compared to its absence. AS is predominantly a left sided myocardial disease, although RV involvement does occur [300]. If RV involvement was uncommon in AS-ATTR it may support the hypotheses of a biological interaction between AS and ATTR.

The possible pathophysiological mechanisms that result in apical sparing include a predilection for increased amyloid deposition, myocyte death/fibrosis and less diversity of myocyte and matrix orientation at the base compared to the apex [308]. In this study, I have evaluated the former two processes in AS-ATTR. The results demonstrate that amyloid burden does weakly correlate with reduced GLS, lending support to the hypotheses that amyloid deposition results in reduced GLS. However, this does not prove causation nor is it the sole mechanism. The apical sparing pattern is also observed in lone AS [174], [319] and basal unlike apical GLS does demonstrate an age-related reduction, suggesting alternative mechanisms [320]. Bravo et al, demonstrated that amyloid mass rather than the proportion of amyloid deposition is responsible for apical sparing in patients with light chain (AL) amyloidosis. Although our metrics of amyloid burden, radionucleotide tracer (DPD vs ^{18}F- Florbetapir) and population (AS-ATTR vs AL amyloidosis) differed from Bravo et al, there are similarities as well. Our data shows that the absolute amount (ECV fraction) demonstrates an apical sparing pattern [321].

I also assessed the relationship between GLS-defined apical sparing and hsTnT- which has prognostic value [312], [314], [322], [323]. The results demonstrate a moderate correlation between GLS-defined apex to base ratio and hsTnT. Although not confirmatory, the association with hsTnT supports the hypotheses that there is increased myocyte death with more apical sparing. This is complementary to a study that demonstrated higher relative apical sparing independently predicts mortality in patients with both AL and transthyretin amyloidosis [304]. Although the same group reported that lack of an apex to base gradient defined using PYP scintigraphy affects prognosis [306], which is contrary to my data showing increasing prognostic

biomarker with higher apex to base ratios and their previous data discussed above [304].

Lastly, we evaluated the association of fibrosis with apical sparing. The extracellular space of patients with AS contains fibrosis, vasculature and proteins but is devoid of amyloid. Accordingly, ECV fraction is used as a marker of fibrosis in AS, with important prognostic implications [76]. GLS and ECV fraction had a weak correlation, and both demonstrated an apical sparing pattern in AS suggesting that increasing burden of fibrosis is associated (albeit weakly) with lower GLS. By comparing AS to AS-ATTR we demonstrated marginally more GLS defined apical sparing with AS-ATTR compared to AS which could be explained by the additional amyloid component.

4.7.1. Limitations of characterisation of AS-ATTR

Ascertainment bias remains in this study due to the different recruitment strategies for each cohort. Although I matched across cohorts using regression and augmented inverse probability weighting, some differences may persist. Despite a relatively high prevalence of coexisting amyloid in patients with AS, the number of patients in this study with AS-ATTR is low; a multi-cohort approach was therefore used to overcome this. Diastolic function was only assessed with one parameter: E/A ratio and further studies need to provide a more detailed analysis of diastology. Pacemaker rates were not compared due to the impact of TAVI on pacemaker need. Lastly, the older age cohort did not have bone scintigraphy, so some occult amyloid may have been missed- I minimized this by selecting participants without a history of heart failure and given their normal echocardiographic appearance and biomarker levels- ATTR within this cohort was deemed unlikely. This is a cross-sectional study at a single-time point and further longitudinal studies are needed.

Although this represents the largest dataset (n=34) evaluating regional differences in AS-amyloid, only 14 patients had all three parameters measured. I accounted for this in two ways: firstly by analysing 2 parameters at a time, increasing the number of patients compared and by reanalysing our data in those 14 patients, obtaining similar results to the full study (tables 13 and 14). Partial voluming effects are well known and we accounted for this by co-registration of SPECT data with CT and ignoring the apical segment for both SUV and ECV.

5. Results: Presentation and outcomes of AS-CAD with TAVI

This chapter is based on the following publication:

***Patel KP**, Rathod K, Akhtar M, Jones DA, Ozkor M, Kennon S, Mathur A, Pugliese F, Mullen MJ, Baumbach A. Diagnostic challenges between acute decompensated aortic stenosis and myocardial infarction. Cardiovascular Revascularisation Medicine. 2022*

I was involved in the genesis, data collection, statistical analysis, writing, editing and manuscript creation.

5.1. Background

Studies remain divided on the significance of coexistent CAD and on the benefit of pre-procedural coronary revascularization among patients undergoing TAVI. Some demonstrate a prognostic benefit [200], [235] whilst others do not [197]–[199], [201], [202]. Studies have showed that stratifying CAD by severity can identify patients at higher risk of mortality [324], [325]. Recently, the first randomized controlled trial of PCI vs medical therapy in TAVI patients demonstrated no benefit of PCI and a higher bleeding rate [326]. The combination of these discrepant findings, one negative trial and increasing adoption of TAVI calls for more data to determine what type of CAD needs revascularization and what can be managed medically. Guidelines recommend PCI pre-TAVI for left main stem (LMS) stenosis >50% or proximal coronary artery >70% stenosis [104]. These recommendations are derived from non-AS patients. Both classifications confer an increased risk of an adverse event based on the concept of subjecting a larger area of myocardium at risk. LMS and multivessel CAD has demonstrated prognostic impact and consequently revascularization is recommended on prognostic ground for these patients [216].
For this PhD, I want to go back to the drawing board and identify which cohort of patients are at the highest risk of major adverse cardiovascular events because of CAD and therefore have the most to gain from intensive treatment- be it with medical therapy or revascularization. Therefore, the aim of this study was to assess the prognostic impact of CAD in a large population of TAVI patients, majority of who have not had any revascularization. This allows a natural history study of CAD in a TAVI population.
Coronary revascularization has a greater benefit among patients with acute coronary syndromes than stable coronary artery. Yet diagnostic and management pathways

for these patients are not established. Patients with often present with signs and symptoms suggestive of a myocardial infarction- chest pain and dyspnoea. Subsequently, they are treated for a presumed type 1 non-ST elevation myocardial infarction (NSTEMI) with medical therapy and invasive coronary angiography (ICA) with a view to having PCI. Anecdotally, many do not have a plaque event requiring PCI or even have obstructive CAD and instead AS is responsible for their presentation, warranting TAVI. Cardiac remodelling associated with AS leads to a mismatch between myocardial oxygen demand and supply, increasing the susceptibility to myocardial ischemia and a type 2 NSTEMI [327], [328]. Differentiating between a type 1 and 2 NSTEMI or ADAS at presentation is important as only the former benefits from PCI, dual antiplatelet therapy upfront and medical secondary prevention. Several case reports of myocardial infarction in patients with AS, illustrate the difficulty in differentiating between epicardial coronary obstruction and AS related type 2 NSTEMI [329]–[332]. Among patients with AS, guidelines for the diagnosis and management of a type 1 NSTEMI and studies on the utility of common diagnostic metrics are non-existent.

For my PhD, I want to examine the diagnostic accuracy of commonly used metrics- cardiac chest pain, elevated troponin T (TnT) and ischemic signs on an ECG, for determining a type 1 NSTEMI and obstructive CAD among patients with AS presenting with suggestive signs and symptoms, hypothesizing that majority of patients did not have a type 1 NSTEMI.

5.2. Specific methodology for outcomes of AS-CAD

5.2.1. Study population

Using prospectively collected data from the Barts Structural Interventional Registry, I included all TAVI patients between January 2015 and July 2020 into this study. The study population (n=1902) was divided into 3 cohorts; those without significant CAD (n=1269), single vessel CAD (n=257) and multi vessel CAD (n=376) of which 101 patients had LMS CAD.

5.2.2. TAVI procedure

All patients had pre-TAVI cardiac computed tomography (CCT) for procedural planning and echocardiography to evaluate cardiac structure and function and AS severity. Patients were then discussed at a multi-disciplinary team (MDT) meeting,

where the imaging was reviewed, and all subsequent management decisions were made. Coronary anatomy and disease severity were assessed using CCT. If this was inconclusive, revealed stenosis felt to be significant or it was felt that the patient's symptoms could be attributed to CAD, patients went on to have invasive coronary angiography. Given the lack of data regarding revascularization in TAVI, the departmental policy is to largely manage asymptomatic CAD without revascularization, prior to TAVI. PCI at BHC is performed on the basis of patient symptoms and CAD stenosis severity, location and complexity. The decision for revascularization and further functional assessment is made by the MDT. All procedures were performed at BHC, by experienced structural cardiac interventionists using standard implant techniques. The choice of TAVI valve was at the discretion of the treating cardiologist. Post-procedure, patients had aortography and echocardiography to assess the function of the TAVI valve.

5.2.3. Study definitions and end-points

Significant CAD was defined as a stenosis >50% in a major epicardial coronary artery, defined by either cardiac computed tomography or invasive coronary angiography performed pre-TAVI. Multivessel CAD was defined as either 2 or more major epicardial vessels with a stenosis >50% or left main stem stenosis >50%. Patients with previous revascularization were categorized according to the status of their native coronary artery disease at the time of cardiac computed tomography or invasive coronary angiography. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction <50%. Frailty was assessed using the Rockwood clinical frailty score. Here I report the prevalence of patients with a score >5. The primary study end-point was all-cause mortality. Procedural complications were defined according to the VARC-2 criteria [333].

5.2.4. Statistical analysis

Data are presented as median (interquartile range) for parametric data and number (percentage) for categorical data. The Kruskall-Wallis test was used to compare non-parametric data across all 3 cohorts with pair-wise comparisons performed between 2 cohorts. The Chi Square test was used to compare categorical data. Kaplan-Meier curves were drawn to compare the time to death between the cohorts. Cox regression analysis was performed to identify significant predictors of all-cause

mortality at baseline. Covariates included in the model were decided a-priori based on their prognostic importance in other studies [151], [334] and included:

a) age
b) Comorbidities: renal function, pulmonary disease, previous stroke, left ventricular systolic dysfunction and frailty
c) CAD, which was considered according to location (LMS vs non-LMS) and extent (single vs multivessel) in different models

A 2-sided p value <0.05 was considered to be statistically significant. All analysis was performed using SPSS statistical software (V26, IBM, Chicago, IL).

5.3. Specific methodology for acute presentation of AS-CAD

This study was a retrospective observational study at a single centre, evaluating patients with severe AS who present with acute cardiac symptoms.

5.3.1. Study definitions and end-points

Patients with AS who presented acutely with angina (Canadian Cardiovascular Society Class 3/4), dyspnoea (NYHA 4) or syncope were included. The diagnostic ability of high-sensitivity Troponin T (TnT), ischemic ECG and angina were evaluated for the end-point of a type 1 NSTEMI (culprit lesion requiring PCI). TnT thresholds were set according to guideline 'rule-in' cut-offs (5-fold higher than the upper limit of normal). Ischemic ECG was defined as either ST depression, T wave inversion/flattening or Q waves [335].

5.3.2. TAVI and PCI procedure

All patients were discussed at an MDT meeting to evaluate patients' symptoms, clinical data, echo and CT findings. Patients felt to have an acute coronary event had dual antiplatelet agents and went on to have ICA and if needed PCI. All patients also had a TAVI during their index admission as it was felt that AS was severe, and their symptoms could also be attributed to AS. Local ethical approval was obtained for this study and the need for informed consent waived.

Data collection and procedures

Coronary assessment was performed during patients' acute admission. All patients had a computed tomography angiogram and coronary angiogram (CTCA) as part of

their diagnostic work-up for a TAVI. Patients with inconclusive findings or obstructive disease on CTCA had an invasive coronary angiogram (ICA). CAD was defined according to luminal stenosis for both CTCA and ICA: none- no visible stenosis, mild <50% stenosis, moderate for 50-70% stenosis and severe>70% stenosis in any part of the coronary tree. The primary endpoint was a type 1 NSTEMI defined by the presence of a coronary thrombus or >90% stenosis on ICA. The latter was included in the definition as coronary thrombus can resolve with antiplatelet therapy and can be challenging to visualize on ICA. The secondary endpoint was obstructive CAD defined as a stenosis>70% on ICA.

Data on comorbidities, investigations and procedural details were collected prospectively on a local database. Details regarding the diagnostic metrics being studied were obtained retrospectively through patients' medical records. Chronic kidney disease was defined as an estimated glomerular filtration rate<60ml/min/1.73m^2. Frailty was defined as a Rockwood clinical frailty score>5 [336].

The diagnostic accuracy of Troponin T (TnT), ischemic ECG and angina were evaluated for the endpoint of a type 1 NSTEMI. TnT thresholds were set according to guideline 'rule-in' cut-offs (5-fold higher than the upper limit of normal) [335]. Ischemic ECG was defined as either ST depression, T wave inversion/flattening or new Q waves [335].

Statistical analysis

Baseline characteristics of patients are presented as median (interquartile range) for continuous, non-parametric data and percentages for frequencies. Two analyses were carried out for each endpoint- the first on all patients (n=273), the second included patients with all three diagnostic metrics available (n=133). Area under the receiver operating characteristic (ROC) curve analysis, sensitive, specificity, positive predictive value and negative predictive values were calculated for each metric individually and in combination. Ethical approval was obtained for this study and the need for informed consent waived.

5.4. Results of outcomes of AS-CAD with TAVI

5.4.1. Baseline characteristics

1902 patients were included in this study, age 84 (79-88) years, 51% male, recruited between January 2015 and July 2020. The study population was divided into three cohorts: without significant CAD (n=1269), single vessel CAD (n=257) and multi vessel CAD (n=376). Patient characteristics at baseline are shown in table 4. Compared to patients without CAD, those with CAD were of similar age, had a higher prevalence of males and lower mean aortic valve gradients. They also had a higher prevalence of comorbidities (diabetes, hypertension, stroke, left ventricular systolic dysfunction) and a higher logistic Euroscore (table 16). Prior PCI unrelated to the TAVI was performed in 248 (13%) patients. PCI was performed as a staged procedure prior to TAVI in 30 (1.6%) patients.

Variable		**All patients (n=1902)**		**No Significant CAD (n=1269)**	**Single vessel CAD (n=257)**	**Multi vessel CAD (n=376)**	**P value**
Age (years)		84 (79-88)		84 (79- 88)	84 (80- 87)	83 (78- 87)	0.453
Sex (% male)		**51**		**44**	**52**	**73**	**<0.001**
AS severity							
Mean aortic valve gradient (mmHg)		**42 (35-52)**		**43 (35- 53) ***	**41 (34- 52)**	**41 (33- 49)**	**0.001**
Aortic valve area (cm^2)		0.7 (0.6-0.8)		0.7 (0.6- 0.8)	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.064
Comorbidities							
Logistic Euroscore (%)		**12.8 (8.1-21.2)**		**12.1 (7.8-20.2) ***	**12.5 (8.0-19.5) †**	**16.5 (9.5-27.5)**	**<0.001**
eGFR (ml/min/1.73m^2)		57 (43-70)		57 (44- 70)	57 (44- 72)	56.5 (43-69)	0.578
Diabetes (%)		**439 (23.1)**		**251 (19.8)**	**66 (25.7)**	**122 (32.4)**	**<0.001**
Hypertension (%)		**1321 (69.5)**		**825 (65.0)**	**189 (73.5)**	**307 (81.6)**	**<0.001**
Previous stroke (%)		**254 (13.4)**		**151 (11.9)**	**40 (15.6)**	**63 (16.8)**	**0.028**
Left ventricular ejection fraction (%)	**>50%**	**1393 (73.2)**		**968 (76.8)**	**186 (72.4)**	**239 (63.6)**	**<0.001**
	30-50%	**344 (18.1)**		**193 (15.3)**	**53 (20.6)**	**98 (26.1)**	
	<30%	**156 (8.2)**		**99 (7.9)**	**18 (7.0)**	**39 (10.4)**	
Frailty>5 (%)		231 (12.1)		159 (13.0)	27 (10.7)	45 (12.2)	0.585
Pulmonary disease (%)		399 (21)		253 (19.9)	61 (23.7)	85 (22.6)	0.271
Coronary artery disease							

Number of non-LMS vessels >50% stenosis (%)	**1 (%)**	**272 (14.3)**	**0 (0)**	**257 (100)**	**15 (4.0)**	**<0.001**
	2 (%)	**186 (9.8)**	**0 (0)**	**0 (0)**	**186 (49.5)**	
	3 (%)	**166 (8.7)**	**0 (0)**	**0 (0)**	**166 (44.1)**	
LMS >50% stenosis (%)		**101 (5.3)**	**0 (0)**	**0 (0)**	**101 (26.9)**	**<0.001**
Previous MI (%)		**266 (14)**	**109 (8.6)**	**45 (17.5)**	**112 (29.8)**	**<0.001**
Symptoms						
CCS angina class	**0 (%)**	**1526 (80.3)**	**1079 (85.0)**	**190 (73.9)**	**257 (68.4)**	**<0.001**
	1 (%)	**120 (6.3)**	**73 (5.8)**	**18 (7.0)**	**29 (7.7)**	
	2 (%)	**169 (8.9)**	**82 (6.5)**	**31 (12.1)**	**56 (14.9)**	
	3 (%)	**78 (4.1)**	**33 (2.6)**	**14 (5.4)**	**31 (8.2)**	
	4 (%)	**9 (0.5)**	**2 (0.2)**	**4 (1.6)**	**3 (0.8)**	
NYHA	**1 (%)**	**54 (3.2)**	**43 (3.9)**	**3 (1.2)**	**8 (2.2)**	**<0.001**
	2 (%)	**535 (31.7)**	**350 (32.1)**	**80 (31.5)**	**105 (29.1)**	
	3 (%)	**979 (57.9)**	**619 (56.7)**	**156 (61.4)**	**204 (56.5)**	
	4 (%)	**122 (7.2)**	**64 (5.9)**	**15 (5.9)**	**43 (11.9)**	

Table 16: Baseline characteristics of patients. eGFR- estimated glomerular filtration rate, LVEF- left ventricular ejection fraction, LMS- left main stem, MI- myocardial infarction, CCS Canadian cardiovascular society, NYHA- New York Heart Association, CAD- coronary artery disease.

5.4.2. TAVI procedure

Compared to patients with no significant/single vessel CAD, those with multi vessel CAD had a higher use of general anaesthesia and non-transfemoral route access. Majority of the valves used were balloon expandable valves (table 17).

Procedural details		**No significant/single vessel CAD (n=1526)**	**Multi vessel CAD (n=376)**	**P value**
General anaesthesia (%)		**76 (5)**	**30 (8)**	**0.019**
Non-transfemoral route (%)		**36 (2.4)**	**21 (5.6)**	**0.002**
Valve type	**balloon expandable (%)**	**1138 (75.4)**	**289 (77.5)**	**0.003**
	self-expandable (%)	**306 (20.3)**	**55 (14.7)**	

	mechanically expandable/other (%)	**66 (4.4)**	**29 (7.8)**	

Table 17: TAVI procedural details. CAD- coronary artery disease.

5.4.3. Procedural complications

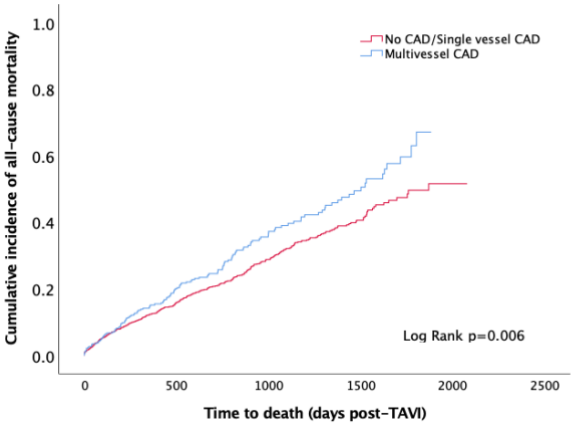
Table 18 shows a higher rate of further valve intervention required in the multi vessel CAD cohort compared to the no significant/single vessel CAD cohort (2.9 vs 1.1%; p=0.013). There were no other differences in procedural complications including death between both cohorts.

Variable	No significant CAD/single vessel CAD (n=1526)	Multi vessel CAD (n=376)	P value
Further valve intervention (%)	**17 (1.1)**	**11 (2.9)**	**0.013**
Cardiac tamponade (%)	4 (0.9)	1 (0.3)	0.441
Bail out PCI (%)	8 (0.5)	2 (0.5)	1
Permanent pacemaker implantation (%)	134 (8.8)	45 (12)	0.058
Stroke (%)	33 (2.2)	9 (2.4)	0.785
Vascular access complication (%)	97 (6.4)	23 (6.1)	0.213
New renal replacement therapy (%)	6 (0.4)	2 (0.5)	0.661
In-hospital mortality (%)	26 (1.7)	9 (2.4)	0.391

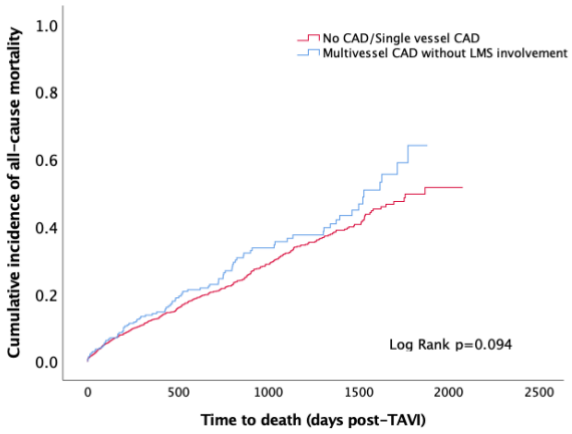
Table 18: TAVI procedural complications. PCI- percutaneous coronary intervention, CAD- coronary artery disease.

5.4.4. Impact of coronary artery disease on all-cause mortality

In-hospital mortality was similar between patients without CAD/single vessel CAD vs multivessel CAD (1.7 vs 2.4%; p=0.391 respectively). Median follow-up for the study population was 1.9 (0.9-3.1) years post-TAVI. At which point, all-cause mortality was significantly greater in the multivessel CAD cohort than those with no significant CAD or single vessel CAD (Log rank test, p=0.006). After exclusion of patients with LMS involvement (n=101), mortality was no longer different between the two cohorts (Log rank test, p=0.094), (Figure 36).



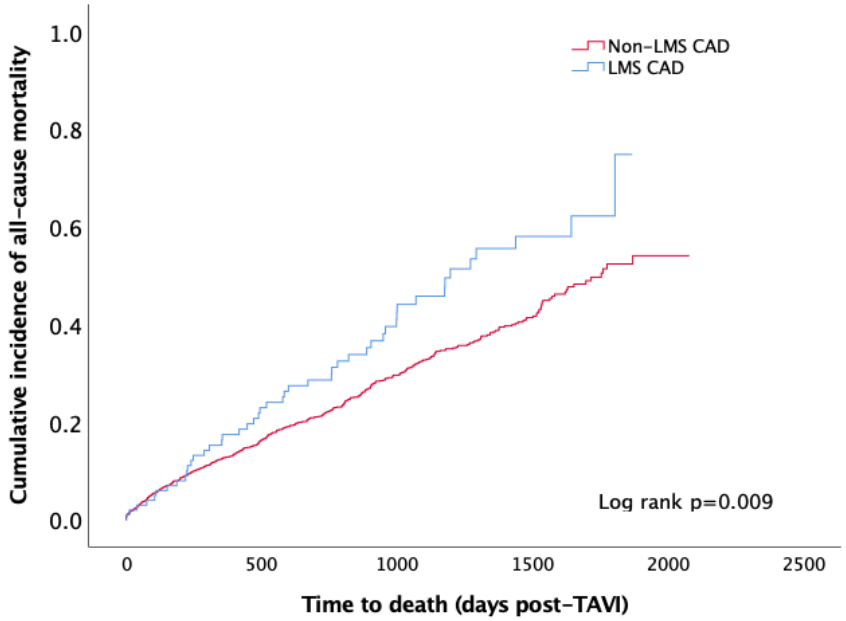
	Day 0	1 Year	2 Years	3 years	4 Years	5 Years
No CAD/single vessel CAD	1526	1092	699	400	173	34
Multi vessel CAD	376	264	186	99	51	7



	Day 0	1 Year	2 Years	3 years	4 Years	5 Years
No CAD/single vessel CAD	1526	1092	699	400	173	34
Multi vessel CAD without LMS involvement	275	188	131	68	35	5

Figure 36: Kaplan Meier analysis demonstrating a significantly higher mortality with MV disease compared to no CAD/single vessel CAD (left image) and no significant difference in mortality between MV disease without LMS involvement and no CAD/single vessel CAD (right image).

Stratifying patients according to LMS involvement (LMS cohort vs the rest of the study population (non-LMS cohort)), mortality was significantly higher in patients with LMS involvement (Log rank test, p=0.009), (figure 37).



	Day 0	1 Year	2 Years	3 years	4 Years	5 Years
Non-LMS CAD	1801	1280	830	468	208	39
LMS CAD	101	76	55	31	16	2

Figure 37: Significant difference in mortality between LMS and non-LMS disease.

5.4.5. Predictors of mortality

The presence of significant CAD as an undifferentiated group did not impact on all-cause mortality (HR 1.069; 95% CI: 0.894-1.277; p=0.465) . With CAD stratified according to number of coronary arteries involved, multivessel CAD was a significant predictor of mortality (HR 1.254; 95% CI: 1.023-1.537; p=0.029). Whereas single vessel CAD was not (HR 0.823; 95% CI:0.631-1.074; p=0.151) (table 19).

Variables	Hazards ratio	95% CI for HR		P value
		Lower	Upper	
Age	**1.013**	**1**	**1.025**	**0.048**
Renal function (eGFR)	**0.993**	**0.989**	**0.997**	**0.001**
Pulmonary disease	1.147	0.93	1.414	0.2
Previous stroke	1.169	0.928	1.474	0.185
Left ventricular systolic dysfunction	**1.287**	**1.068**	**1.552**	**0.008**
Frailty	**1.806**	**1.465**	**2.226**	**<0.001**
Single vessel CAD	0.823	0.631	1.074	0.151
Multi vessel CAD	**1.254**	**1.023**	**1.537**	**0.029**

Table 19: Cox regression analysis with coronary artery disease defined according to the number of coronary arteries involved. eGFR- estimated glomerular filtration rate, CAD- coronary artery disease.

Among patients without LMS involvement, multivessel CAD (n=275) no longer remained an independent predictor of mortality (HR 1.19; 95% CI: 0.94-1.51; p=0.142) whilst LMS CAD did (HR 1.57; 95% CI:1.16-2.14; p=0.004) (table 20).

Variables	Hazards ratio	95% CI of HR		P value
		Lower	Upper	
Age	**1.013**	**1.001**	**1.026**	**0.037**
Renal function	**0.993**	**0.989**	**0.997**	**0.001**
Pulmonary disease	1.156	0.937	1.426	0.175
Previous stroke	1.162	0.922	1.465	0.203
Frailty	**1.82**	**1.477**	**2.243**	**<0.001**
Left ventricular systolic dysfunction	**1.284**	**1.065**	**1.549**	**0.009**
Multivessel CAD without LMS	1.191	0.943	1.505	0.142
LMS CAD	**1.574**	**1.159**	**2.139**	**0.004**

Table 20: Predictors of all- cause mortality including patients with multi vessel CAD without LMS involvement and LMS CAD. LMS- left main stem, CAD- coronary artery disease

30 patients had staged/hybrid PCI in our population. I excluded these patients and repeated the analysis in patients without hybrid/staged PCI (n=1807) to assess outcomes in non-revascularized patients. LMS disease remained prognostically significant (HR 1.55 (1.14-2.10); p=0.005). In order to assess the impact on angina on all-cause mortality, a regression model was created with the addition of multi vessel CAD and CCS>1. This variable was not a significant predictor of mortality (HR 0.846; 95% CI: 0.553-1.296; p=0.443).

5.4.6. Impact of CAD on mid vs long-term mortality.

At 1 year post-TAVI, LMS CAD did not predict all-cause mortality (HR 1.201; 95% CI: 0.881-1.637; p=0.247), whereas after 1 year post-TAVI, LMS CAD was an independent predictor of all-cause mortality (table 21).

	All-cause mortality at 1 year					**All-cause mortality after 1 year**			
Variables	**Hazards ratio**	**95% CI of HR**		**P value**		**Hazards ratio**	**95% CI of HR**		**P value**
		Lower	**Upper**				**Lower**	**Upper**	
Age	1.006	0.988	1.025	0.488		**1.02**	**1.002**	**1.037**	**0.025**
Renal function	**0.99**	**0.984**	**0.997**	**0.005**		0.995	0.989	1.000	0.061
Pulmonary disease	1.083	0.781	1.503	0.633		1.231	0.936	1.618	0.137
Previous stroke	1.052	0.726	1.524	0.79		1.239	0.92	1.668	0.158
Frailty	**1.707**	**1.229**	**2.370**	**0.001**		**1.904**	**1.451**	**2.498**	**<0.001**
Left ventricular systolic dysfunction	**1.353**	**1.021**	**1.794**	**0.035**		1.266	0.988	1.621	0.062
LMS CAD	1.324	0.804	2.18	0.27		**1.687**	**1.151**	**2.472**	**0.007**

Table 21: Predictors of all-cause mortality at 1 year and after 1 year post-TAVI. LMS- left main stem, CAD- coronary artery disease

5.5. Results of acute presentation of AS-CAD

5.5.1. Baseline characteristics and presentation

Between April 2015 and October 2019, 273 patients with severe AS had acute presentations: age 84 (79-88) years, male sex 53%, aortic valve area 0.6 (0.5-0.8)

cm^2, left ventricular ejection fraction 55 (35-60)%. Angina was present in 30% and ischemic ECG changes in 25%. 133 patients (49%) had a TnT tested, of which 124 patients (93%) had elevated levels and 68 patients (51%) had TnT values above the 5-fold cut-off. Table 22 highlights the baseline characteristics of the study population.

Demographics	
Age (years)	84 (79-88)
Male sex	(144) 53%
Comorbidities	
Logistic Euroscore	14 (9-26)
Diabetes Mellitus	73 (27%)
Chronic Kidney Disease	170 (62%)
Dialysis	5 (2%)
Previous myocardial infarction	43 (16%)
Previous percutaneous coronary intervention	36 (13%)
Pulmonary disease	55 (20%)
Hypertension	201 (73%)
High Cholesterol	21 (8%)
Frailty	47 (17%)
Echocardiography	
Left ventricular internal diameter (cm)	4.8 (4.3-5.3)
Interventricular septum (cm)	1.2 (1.0-1.4)
Left ventricular posterior wall (cm)	1.1 (0.9-1.3)
Left ventricular ejection fraction (%)	55 (35-60)
E/A ratio	0.9 (0.7-1.6)
Deceleration time (ms)	220 (154-287)
Left atrial area (cm^2)	25.8 (21.0-30.2)
Tricuspid annular planar systolic excursion (cm)	1.8 (1.5-2.2)
Pulmonary artery systolic pressure (mmHg)	39 (30-48)
AV peak velocity (m/s)	4.1 (3.6-4.6)
AV mean gradient (mmHg)	41 (32-52)
AV area (cm^2)	0.6 (0.5-0.8)

Table 22: baseline characteristics of the study population. Data is presented as median (IQR) or number (%). AV- aortic valve.

5.5.2. Type 1 NSTEMI

85 patients (31%) had an ICA before having a CTCA as the treating clinical team felt the presenting diagnosis was a type 1 NSTEMI ICAs were performed, of which 17

patients (6.2%) had a type 1 NSTEMI. Figure 38 illustrates the tests and their frequencies. Of the 17 patients with a type 1 NSTEMI who had PCI, 4 required PCI to 2 vessels and 13 to a single vessel. 2 patients required PCI to a vein graft supplying the right coronary artery and 1 patient required the use of laser atherectomy. 8 vessels had PCI to a proximal artery and 11 vessels had PCI to a non-proximal artery.

Patients without obstructive CAD went onto have a TAVI with the primary diagnosis of their acute admission identified as acute decompensated aortic stenosis.

The area under the ROC curve (AUC) for a type 1 NSTEMI, for 5-fold TnT cut-off, ischemic ECG and angina was 0.622, 0.563 and 0.689 respectively. All 3 variables demonstrated good negative predictive values, but weak positive predictive values (table 23). Specificity increased with increasing number of negative diagnostic metrics, whilst sensitivity and positive predictive value reduced with increasing number of positive diagnostic metrics (table 23). There was no significant difference in all-cause mortality at 1 year post-TAVI between patients with and without a type 1 NSTEMI (18 vs 19% respectively; p=0.589).

Diagnostic variable	True positives	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>5-fold Troponin T cut-off	8/17	73%	50%	12%	95%
Ischemic ECG	6/17	38%	73%	9%	94%
Angina	11/17	65%	72%	13%	97%
Any 1 metric	4/17	50%	57%	4%	97%
Any 2 metrics	6/17	43%	86%	15%	96%
All 3 metrics	3/17	18%	95%	19%	95%

Table 23: Diagnostic accuracy for a type 1 NSTEMI, defined as a coronary thrombus or >90% stenosis on coronary angiography. The last 3 rows denote to the diagnostic accuracy if any number of metrics were either positive or negative.

Among 133 patients with all 3 diagnostic metrics available, the diagnostic ability of each metric is demonstrated in table 24. This secondary analysis demonstrated similar results to that in the overall study population.

Diagnostic variable	True positives	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>5-fold Troponin T cut-off	8/11	73%	50%	12%	95%
Ischemic ECG	5/11	45%	67%	12%	93%
Angina	9/11	81%	56%	14%	97%
Any 1 metric	3/11	-	33%	5%	-
Any 2 metrics	5/11	63%	72%	14%	96%
All 3 metrics	3/11	27%	89%	19%	93%

Table 24: Diagnostic accuracy for a type 1 NSTEMI in 133 patients with all three diagnostic metrics available. The last 3 rows denote to the diagnostic accuracy if any number of metrics were either positive or negative. Two values could not be reported with any 1 metric due to lack of numbers.

5.5.3. Obstructive coronary artery disease

107 (39.2%) patients had obstructive CAD diagnosed by a combination of ICA and CTCA. Of these, 17 patients underwent PCI prior to TAVI. Table 25 provides further details regarding the degree of obstruction in each coronary artery. The area under the ROC curve (AUC) for obstructive CAD, for 5-fold TnT cut-off, ischemic ECG and angina was 0.617, 0.570 and 0.645 respectively. The diagnostic ability of each metric is shown in Table 26. Specificity increased with increasing number of negative diagnostic metrics, whilst sensitivity reduced.

Coronary artery	None	Mild stenosis	Moderate stenosis	Severe stenosis
Left main stem	203 (74%)	49 (18%)	9 (3%)	12 (4%)
Left anterior descending	139 (51%)	64 (23%)	23 (8%)	47 (17%)
Left Circumflex	151 (55%)	66 (24%)	19 (7%)	37 (14%)
Right coronary	149 (55%)	57 (21%)	13 (5%)	54 (20%)

Table 25: Degree of stenosis in each coronary artery defined as none: no visible stenosis, mild: <50%, moderate: 50-70% and severe: >70%

Diagnostic variable	True positives	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>5-fold Troponin T cut-off	36/107	64%	57%	52%	69%
Ischemic ECG	34/107	34%	77%	49%	63%
Angina	44/107	41%	77%	53%	67%
Any 1 metric	35/107	48%	60%	38%	69%
Any 2 metrics	23/107	24%	89%	58%	66%
All 3 metrics	11/107	10%	97%	69%	63%

Table 26: Diagnostic accuracy for obstructive CAD, defined as a coronary stenosis>70% on coronary angiography. The last 3 rows denote to the diagnostic accuracy if any number of metrics were either positive or negative.

Among 133 patients with all 3 diagnostic metrics available, the diagnostic ability of each metric is demonstrated in table 27. This secondary analysis demonstrated similar results to that in the overall study population.

Diagnostic variable	True positives	Sensitivity	Specificity	Positive predictive value	Negative predictive value
>5-fold Troponin T cut-off	36/56	64%	57%	52%	69%
Ischemic ECG	23/56	42%	72%	53%	62%
Angina	36/56	64%	65%	57%	71%
Any 1 metric	18/56	78%	36%	33%	81%
Any 2 metrics	22/56	49%	81%	61%	72%
All 3 metrics	11/56	20%	94%	69%	62%

Table 27: Diagnostic accuracy for obstructive CAD among 133 with all three diagnostic metrics available. Obstructive CAD is defined as a coronary stenosis>70% on coronary angiography. The last 3 rows denote to the diagnostic accuracy if any number of metrics were either positive or negative.

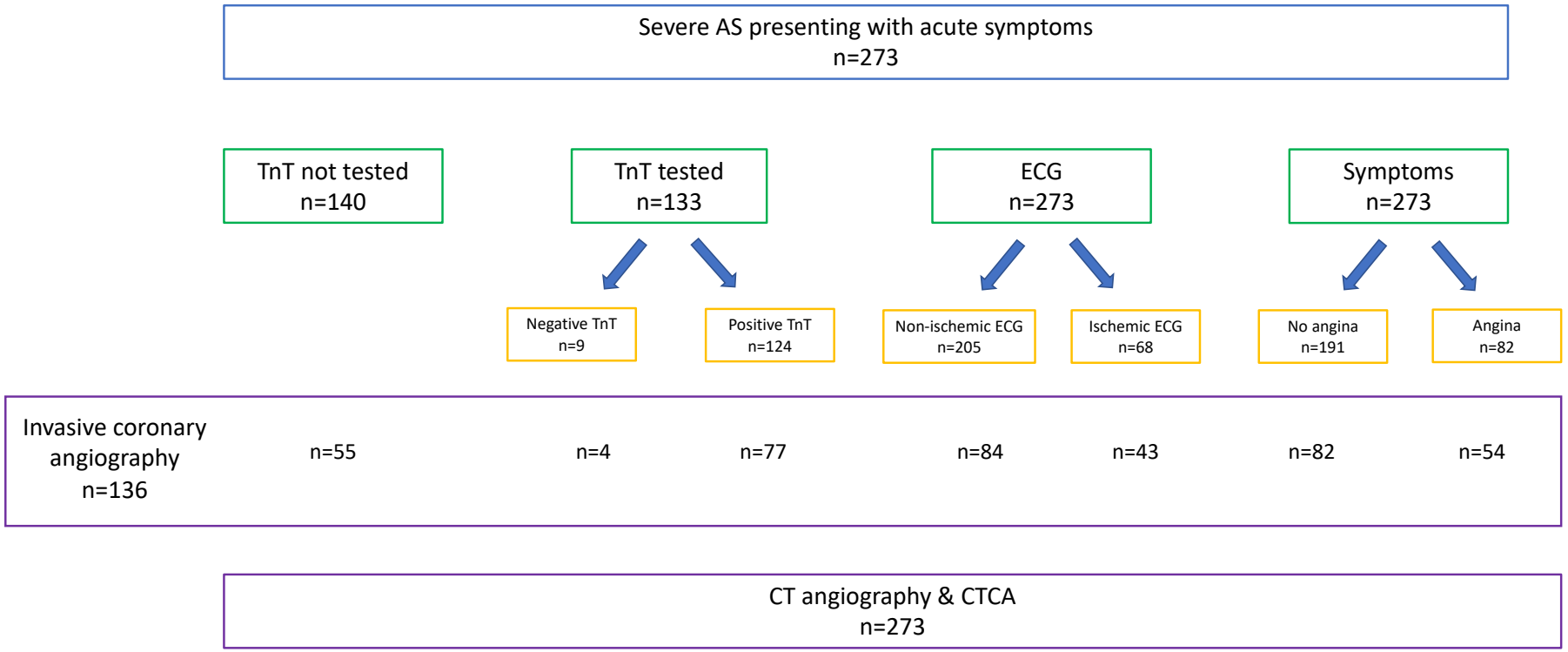


Figure 38: diagnostic tests and procedures for the study population

5.6. Discussion for outcomes of AS-CAD with TAVI

I sought to assess the prognostic impact of largely non-revascularized coronary artery disease after stratification by location (LMS or not) and extent (single vessel vs multivessel), in a large elderly population undergoing contemporary TAVI. This study demonstrated three key findings; firstly, multi vessel CAD did not affect short-term mortality, enabling TAVI to be performed safely. Secondly, long-term mortality was not affected by either single vessel or multivessel CAD without LMS involvement. Only CAD involving the LMS independently increased all-cause mortality. Thirdly, this prognostic impact occurs after the first year post-TAVI and not before. The clinical and research implications of this study deserve further consideration. In the short-term, among TAVI patients with CAD, revascularisation is not needed to reduce mortality. Revascularization of single vessel CAD on prognostic grounds is unlikely to yield much benefit and medical management alone maybe a reasonable option. Prospective studies evaluating the prognostic role of revascularization need to focus on patients with LMS CAD.

5.6.1. Prognostic impact of coronary artery disease in TAVI

Concern exists over the procedural safety of TAVI in the presence of CAD. My study demonstrated similar mortality and procedural complications between patients with and without multivessel CAD. However, I did not collect data on ventricular arrhythmias or myocardial injury using cardiac biomarkers. The latter has been shown to affect mortality [239].

There is heterogeneity in the literature regarding the definition of significant CAD. Defining significant CAD by angiographic stenosis, whilst crude and subjective, is easy to perform, widely used and forms the basis of guidelines [123]. Based on my definition and stratification of CAD, I have demonstrated the prognostic value of this simple parameter.

Several studies have demonstrated that CAD does not affect 30 day [200], [202], [234], [337], 1 year [338] or longer term mortality, post-TAVI [199], [202]. My data supports this- if dichotomized using a binary definition of CAD (i.e. present or absent). However, CAD is a heterogenous disease and its impact is determined by the severity of the disease, both in terms of anatomical distribution and physiological influences [339]–[341]. Multivessel and LMS CAD are both surrogates for a larger area of myocardium at risk. My findings show that a larger myocardial territory at risk

does confer a higher mortality risk. Although I demonstrated that non-LMS multivessel CAD does not affect mortality, a more detailed categorization may identify subgroups that do have a higher mortality and therefore may benefit from revascularization, e.g. stenosis in a proximal left anterior descending and proximal dominant right coronary artery.

Previous studies have evaluated the impact of CAD based on its severity using the SYNTAX score among TAVI populations. The general consensus is that patients with a higher SYNTAX score have a higher mortality. Its prognostic value has been proven at 30 days, 1 year [324] and at a median of 1.9 years [325]. Outcomes are primarily driven by cardiovascular mortality [236]. One study demonstrated that having a Syntax score ≤10 doesn't confer any additional risk compared to no CAD [338]. These studies support my finding that mortality is linked to the amount of myocardium at risk. Contrarily, Paradis et al, showed that neither the presence nor the severity of CAD based on the SYNTAX score determined outcomes at 30 days or 1 year post-TAVI. This study did use a high rate of transapical access (52%), had relatively low numbers and limited follow up, potentially accounting for the discrepancy in findings. Similarly, stratifying patients according to the Duke Myocardial Jeopardy Score (DMJS), did not identify patients at higher risk of mortality at 30 days, 1 or 2 years post-TAVI [202], [234]. However, limited follow-up, low study numbers and overall low DMJS may have accounted for the lack of effect observed. These discrepant results of these studies emphasize the importance of identifying a cohort of patients with CAD who are at an increased risk of adverse outcomes before attempting to target this cohort for revascularization.

5.6.2. Revascularization in TAVI patients

The question of revascularization with percutaneous coronary intervention for prognostic benefit among TAVI patients remains unanswered. Several studies have demonstrated no survival benefit from revascularization [197], [198], [202], some have suggested worse outcomes [342] whilst others have determined that it is safe and feasible [343]. A large retrospective registry has demonstrated the safety and feasibility of PCI of LMS CAD in TAVI patients. Mortality at 1 year was similar between those who had PCI of the LMS and matched controls who did not have LMS disease (9.4% vs. 10.2%, p = 0.83) [269]. However, these findings warrant

prospective, randomized studies with longer follow up (over a year) evaluating PCI in such patients. The first non-inferiority, randomized control trial (ACTIVATION study) assessing pre-TAVI PCI in patients with coronary stenosis >70%, reported no difference in mortality and hospitalization between the PCI and the no PCI group at 1 year: 41.5 vs 44.0%; p=0.067 respectively. Majority of patients had CCS≤2, PCI was not physiologically guided, bare metal stents were used and the study may have been underpowered [344], [345]. The ISCHEMIA trial demonstrated among patients without severe AS, that PCI based on the presence of moderate to severe ischemia does not improve mortality [203]. My data supports this finding among patients with AS. I showed that the presence of angina (a surrogate for ischemia) does not influence mortality among patients with multi vessel CAD. My findings suggest that further studies evaluating the prognostic benefits of PCI in TAVI patients need to focus on patients with LMS disease, where the most benefit is likely to be found. In addition the role of PCI-guided by physiology and PCI in those with left ventricular systolic dysfunction caused by CAD needs to be explored.

5.6.3. Limitations

This was a single centre, observational study and as such is prone to uncontrolled confounders and biases. 3.5% of patients were excluded from the Cox regression analysis because of missing data. Others and I have showed that patients with CAD have a higher prevalence of comorbidities [202]. Despite performing a multivariable analysis, there will be some prognostic factors that have not been considered. Non-transfemoral access and the use of general anaesthesia was higher among patients with multivessel CAD, which could have influenced my findings. Functional evaluation of CAD and medications were not collected for this study. My definition of significant CAD is based on both CCT or invasive coronary angiography. Although I recognize the potential for overestimating coronary stenosis with CCT [346], my data represents real world data where a trend towards selective rather than routine angiography pre-TAVI is being increasingly considered. Few patients had PCI as a staged/hybrid procedure prior to TAVI (n=30, 1.6%). This study did not capture PCI post-TAVI. This limits an evaluation of the prognostic benefit of PCI among this population. However, it provides a unique population with native, largely non-revascularized CAD to the natural history of CAD in patients with AS. Lastly these

results are applicable to a high-risk population and therefore may not apply to lower risk cohorts.

5.7. Discussion for acute presentation of AS-CAD

This study has several important findings; firstly, acute presentations among AS patients are predominantly due to cardiac decompensation related to AS rather than a type 1 NSTEMI. Secondly, angina, ischemic ECG and positive TnT (including that >5-fold upper limit of normal) are common among patients with AS and often not associated with a type 1 NSTEMI. Thirdly, the negative predictive value of any diagnostic variable and the specificity of all 3 variables combined is high for a type 1 NSTEMI. Fourthly, only a minority of patients required PCI, resulting in unnecessary pre-procedural dual antiplatelet therapy. Lastly, the diagnostic accuracy of each metric was poor (AUC<0.7) for diagnosing a type 1 NSTEMI or obstructive CAD.

5.7.1. Acute decompensated AS is more common than type 1 NSTEMI among severe AS

Acute decompensated AS is common and accounts for 7-23% of all TAVI [249], [250], [281]. Despite TAVI being safe and effective in these patients, they remain at high risk of mortality: 5.3% at 30 days and 15.3% at 1 year post-TAVI and morbidity [249]. The incidence of acute presentations among patients with severe AS is increasing [347], [348]. The COVID-19 pandemic has resulted in a delay in elective aortic valve replacements for many patients which, although speculative, may be contributing to an increase in acute presentations. Therefore, refining investigation and management pathways for these patients is essential to improve resource allocation and potentially improve patient outcomes [349].

5.7.2. Importance of differentiating between ADAS and a type 1 NSTEMI

There are important clinical implications of these findings. Outcomes for a type 1 NSTEMI or acute decompensated aortic stenosis are likely to be time sensitive [349], [350]. Differentiating between the two presentations is important as only a type 1 NSTEMI benefits from pre-procedural dual antiplatelet therapy. Patients without a type 1 NSTEMI and with acute decompensated aortic stenosis may not require ICA, especially if their CTCA can be adequately interpreted and obstructed CAD excluded. Therefore, a timely diagnosis obtained using only necessary investigations

is key to facilitating early treatment, optimizing resource allocation and reducing unnecessary risk to patients.

These findings also have research implications, as many TAVI trials frequently exclude patients with a recent MI, the definition of which is often based on elevated TnT levels, which as we have demonstrated does not necessarily indicate a type 1 MI.

5.7.3. High negative predictive value: PCI required infrequently

All 3 metrics individually and in combination demonstrated high negative predictive values. Similarly, in combination, all 3 demonstrated high specificity. This suggests that negative results may reassuringly rule out a type 1 NSTEMI, allowing clinicians to focus on treating AS.

5.7.4. Angina, ischemic ECG changes and TnT not specific for a type 1 NSTEMI or obstructive CAD

The challenge arises with positive results which are very common in AS. In this circumstance, no metric individually nor in combination can accurately differentiate between a type 1 NSTEMI and acute decompensated AS, indicating a need to identify alternative pre-angiographic criteria to guide management for these patients.

Obstructive CAD is common in patients with AS [328]. We presented data on obstructive CAD as guidelines recommend PCI in TAVI patients with proximal coronary stenosis >70% based on a level of evidence C. Over a third of our study patients fulfilled this criterion in at least one part of their coronary anatomy. All 3 metrics demonstrated weak diagnostic accuracy for obstructive CAD (AUC<0.7). However, in combination, all 3 showed good specificity. For both endpoints, using only a subset of our study population with complete diagnostic data, demonstrated similar results to those seen in the whole study population.

5.7.5. Future directions

Given that all patients undergoing a TAVI have a CTCA, this could provide a screening tool to identify obstructive CAD, which can then trigger specific treatment pathways involving ICA ± PCI (figure 39). However, the potential of both increasing the number of ICA referrals and the lower diagnostic accuracy of CTCA in heavily calcified coronary arteries needs to be considered. Echocardiography may provide

an alternative screening tool. Studies have established the diagnostic utility of 2D echocardiography [351], [352] and strain imaging [353] to diagnose a type 1 NSTEMI (in patients without AS) by identifying regional wall motion abnormalities. This needs to be evaluated in prospective studies among patients with AS.

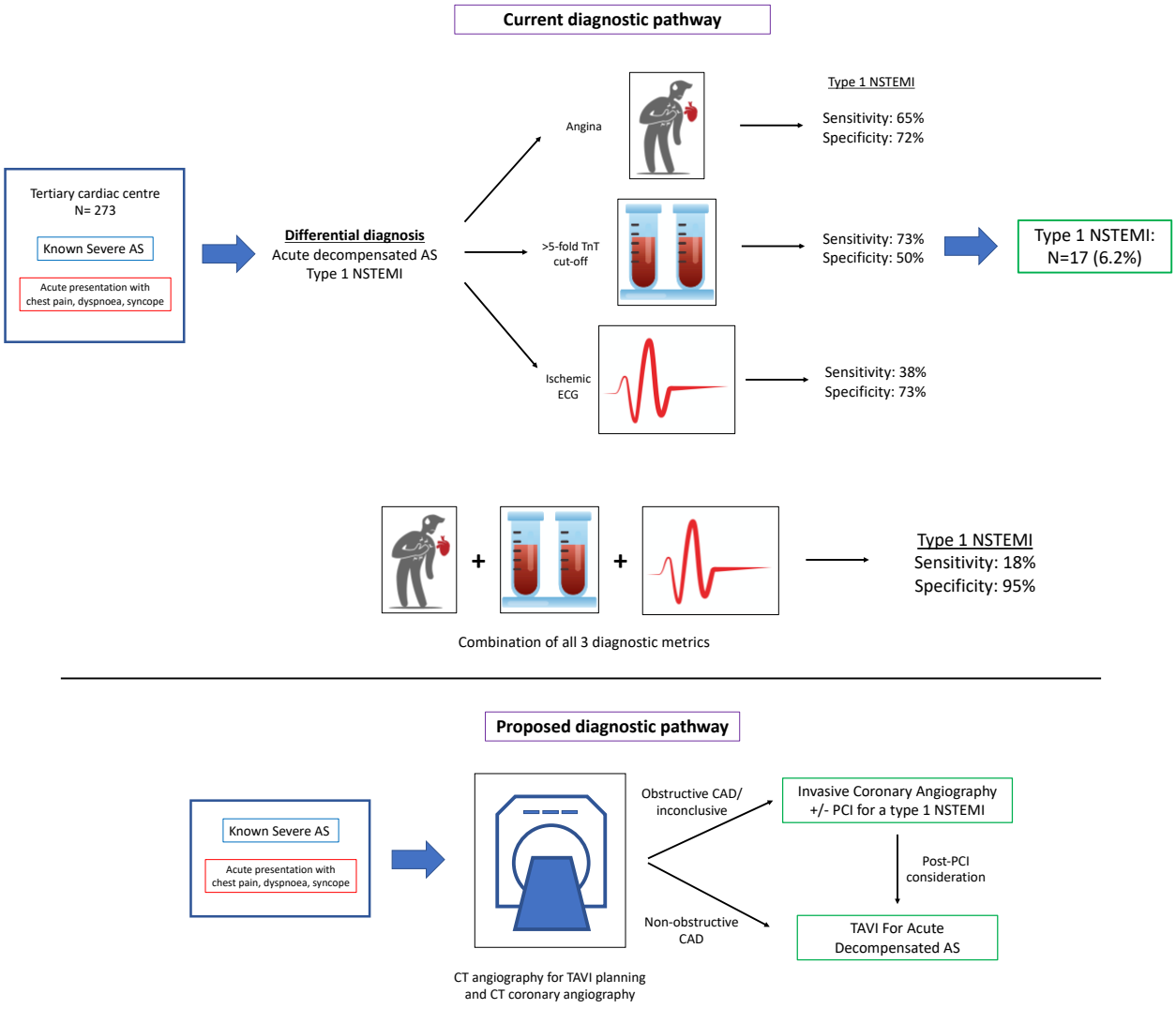


Figure 39: Summary of findings- diagnostic accuracy of 3 commonly used metrics for a type 1 NSTEMI and a proposed diagnostic pathway to screen patients who may benefit from ICA for a potential type 1 NSTEMI

5.7.6. Limitations

This study is limited by its retrospective, observational nature and should be considered hypothesis generating. Larger multicenter studies are required to validate our findings. Decisions regarding investigations and management of patients were

left to the clinical team caring for the patient. TnT was only assessed in half the study population. Similarly, only half the study population underwent ICA, reflecting our local practice. However, all patients had their coronaries evaluated with CTCA. Although the diagnostic accuracy of CTCA is inferior to ICA, if there was a suggestion of obstructive disease or the CTCA was inconclusive, patients did go on to have an ICA. We only assessed a single TnT value at the time of admission. Future studies need to evaluate the degree of TnT fluctuation in such analysis. These findings should be interpreted keeping in mind the specific study population involved, which is elderly and at high surgical risk. Additionally, we only included patients undergoing TAVI and not those who were treated medically or who underwent surgical aortic valve replacement, creating a selection bias. Therefore, these findings may not apply to all AS populations.

6. Results: Risk stratification and outcomes of ADAS

This chapter is based on the following publications:

***Patel KP**, Badiani S, Ganeshalingam A, Vijayakumar M, Thornton G, Mathur A, Kennon S, Bhattacharyya S, Baumbach A, Moon JC, Tribel TA, Lloyd G. Characterisation of acute decompensated aortic stenosis and its impact on mortality. American Heart Journal, 2022.*

***Patel KP**, Broyd C, Chehab O, Jerrum M, Queenan H, Bedford K, Barakat F, Kennon S, Ozkor M, Mathur A, Mullen MJ. Transcatheter aortic valve implantation in acute decompensated aortic stenosis. Catheterisations and Cardiovascular Interventions. 2019*

***Patel KP**, Chahal A, Mullen MJ, Rathod K, Baumbach, A, lloyd G, Treibel TA, Awad, WI, Ricci F, Khanji M. Acute decompensated aortic stenosis: State of the art review. Current Problems in Cardiology, 2022*

I was involved in the genesis, data collection, statistical analysis, writing, editing and manuscript creation.

6.1. Background

Once severe AS develops, surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) are the only treatments that provide both symptomatic and prognostic benefits [2–4]. Current guidelines indicate intervention for symptomatic patients, with a few recommendations for asymptomatic patients [18]. This often results in a watch and wait strategy employed by clinicians, until such time that a patient meets guideline-defined criteria for intervention. Consequently, a significant proportion of patients (7.3% to 21%) present acutely with a combination of pulmonary oedema, heart failure, angina at rest or on minimal exertion, syncope or sudden death [250], [281]. Despite advances in our understanding of the natural history of AS, identification of novel prognostic markers [76] and development of risk stratification tools [355], many patients with AS continue to present with acute decompensation. The ideal management of this patient cohort is unclear. The risk of definitive SAVR or TAVI is often perceived to be high with less certain outcomes and therefore patients in many centres are routinely only offered a temporising balloon aortic valvuloplasty (BAV) [356] or medical therapy [357]. Patients who respond well to initial treatment may be later offered a more definitive SAVR/TAVI.

Symptoms in AS are associated with changes in myocardial structure and function [358]. Additionally, greater degrees of myocardial and valvular dysfunction are associated with worse outcomes according to a validated staging classification.[355] This suggests a key role played by the myocardium in patients with ADAS.

The aim of this PhD with regards to ADAS, was 2 fold:

1) To assess the safety and efficacy of TAVI in ADAS
2) To identify whether myocardial and non-aortic valvular damage/dysfunction, including the recently developed echo staging classification can predict short and mid-term mortality for ADAS patients.

The methodology for these aims was based on retrospective analysis of the same study population over two different time periods. The first aim used a population referred between 2015-2018 and the second aim used a population referred between 2015-2019.

6.2. Specific methodology for safety and efficacy of TAVI in ADAS

This was a retrospective, single-centre, observational study of patients with severe AS treated as Barts Heart Centre (BHC) between 01 May 2015 and 31 January 2018.

6.2.1. Study population

Patients were referred from the local region, with a population approximating 6 million.

Patients with a type 1 non-ST elevation myocardial infarction or a ST elevation myocardial infarction were excluded. It is our departmental policy that ADAS patients are admitted and treated urgently with a TAVI. The ADAS cohort was compared to patients with severe AS who had an elective TAVI (non-ADAS)).

6.2.2. Pre-procedural evaluation

All patients had transthoracic echocardiography to assess cardiac and valvular structure and function and a gated cardiac CT scan to assess valvular calcification, geometry, size and vascular access route. Patients were discussed at a multi-disciplinary heart team meeting to review the diagnosis and decide on the most appropriate management.

6.2.3. TAVI procedure

All TAVIs were performed by experienced cardiologists following standard implant techniques. The choice of valve technology and type of anaesthetic were at the discretion of the medical team.

6.2.4. Post-procedural management

Post implant, an aortogram and echocardiography were performed to assess valve position, coronary perfusion, aortic regurgitation and pericardial effusion. Depending on the level of care required patients were either treated in an intensive care unit, a coronary care unit or a general cardiology ward or a combination of the these. When medically fit they were discharged. If their recovery was protracted or they required additional social support, they were transferred to another hospital or rehabilitation centre.

6.2.5. Definitions and end-points

ADAS was defined as an unplanned acute admission to hospital with symptoms (dyspnoea (NYHA 4), syncope, angina (CCS 3/4)) that developed or deteriorated within a week prior to admission and were secondary to severe AS. These patients were felt to require intervention during their index admission. Critically unwell patients were defined as having any of the following: ventricular tachycardia, aborted sudden death, ventricular fibrillation or requiring preoperative cardiac massage, intra-aortic balloon pump, mechanical ventilation, inotropic support or acute renal failure (anuria or oliguria <10ml/hr).

Primary endpoints were procedural (48 hours post-TAVI) and 30-day mortality and hospital length of stay (LOS). The latter was calculated from admission to hospital (the earliest of either admission to BHC or a local general hospital) to discharge from hospital (the latest of either discharge from BHC or a local general hospital).

Secondary endpoints included 1-year mortality, rates of post-procedural acute kidney injury (AKI), stroke, new renal replacement therapy, permanent pacemaker implantation (PPI), vascular complications, procedural failure, moderate to severe paravalvular leak (PVL) and further valve intervention as defined by the VARC II criteria [333].

6.2.6. Data collection and statistical analysis

All patient data was prospectively collected on a local database from the point of referral to follow up. Mortality data was obtained by linkage to NHS Spine.
Data are presented as mean ± standard deviation, number (percentages), or medians (interquartile range). Inter-group comparisons were made using χ^2 test or Fisher's exact test as appropriate, for categorical data, and Mann Whitney U-tests for continuous data. Cox and linear regression analysis were used to identify significant determinants for 30-day mortality and length of stay respectively. Data were analysed using Stata (version 13.0, StataCorp, College Station, Texas, USA) and a two-sided p value < 0.05 was considered statistically significant.

6.3. Specific methodology for pre-procedural prognostic factors for ADAS

This was a retrospective, observational study carried out at a single cardiac centre. Myocardial and valvular structure and function were evaluated using pre-TAVI echocardiograms.

6.3.1. Study population

Patients with a type 1 non-ST elevation myocardial infarction or a ST elevation myocardial infarction were excluded. ADAS was defined as either dyspnoea at rest (NYHA 4), angina on minimal exertion or at rest (CCS 3/4) or syncope. It is our departmental policy that ADAS patients are admitted and treated urgently with a TAVI. Patients presenting with ADAS who received a TAVI (ADAS cohort) between 2015 and 2019 were included in this study. Out of a cohort of 300 ADAS patients, 6 were excluded due to a lack of data. Frailty was defined as a Rockwood clinical frailty score >5 [336]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60ml/min/1.73m^2. Multivessel coronary artery disease (CAD) was defined as more than 1 epicardial coronary artery >50% stenosis or left main stem stenosis >50% stenosis.

6.3.2. Echocardiography and analysis

All patients had pre-TAVI echocardiography that was performed by British Society of Echocardiography accredited physiologists according to the British Echocardiographic Society guidelines [359]. Cardiac parameters were measured using EchoPAC software (GE Healthcare, Wauwatosa, WI, USA). Echocardiographic data was used to categorise patients depending on the degree of extra-valvular

involvement described in a previously validated staging classification [355]. Additional criteria were added in order to be more inclusive. These additional criteria are considered to indicate a similar severity to the already validated criteria used in the staging classification [355]; for stage 1- E/A ratio >2 and deceleration time <150ms, for stage 2- left atrial (LA) diameter >4.3cm and LA area >20cm^2. Stage 4 was defined as tricuspid annular planar systolic excursion (TAPSE) <17cm or right ventricular S' <9.5cm/s. This staging classification is illustrated in table 28. As the cohort populations were smaller than the original derivation and validation study, in addition to the original 5 stage classification, As the study population was smaller than the original derivation and validation study [355], in addition to the original 5 stage classification, we classified patients as either having greater than stage 2 or less than or equal to stage 2.. Relative wall thickness was defined as (interventricular septal wall thickness + inferolateral wall thickness)/LV systolic diameter in diastole. LVEF was determined using either Simpson's biplane method or estimated visually if the Simpsons biplane method was not possible. Transaortic valve flow rate was calculated according to a formula which has been validated elsewhere [360]:

$$\text{Flow rate} = AVA \times ([MG + \sqrt{(MG^2 + 32 \times MG \times Vmax^2)}] / [16 \times Vmax])$$

Stages	0	1	2	3	4
Criteria	No cardiac damage	LV damage	LA or mitral damage	Pulmonary vasculature or tricuspid damage	RV damage
Original echo criteria		Increased LV mass indexed >115g/m^2 (male) >95g/m^2 (female)	Indexed LA volume>34ml/m^2	Systolic pulmonary hypertension> 59mmHg	Moderate-severe RV dysfunction
		E/e'>14	Moderate-severe mitral regurgitation	Moderate-severe tricuspid regurgitation	
		LVEF<50%	Atrial fibrillation		
Additional echo criteria		E/A>2 Deceleration time<150ms	LA diameter >4.3cm LA area>20cm^2		

Table 28: Echo staging system and number of patients in each cohort. LV- left ventricle, LA- left atrium, RV- right ventricle, LVEF- left ventricular ejection fraction

6.3.3. Transcatheter aortic valve implantation (TAVI)

Each patient was discussed at a multi-disciplinary team meeting for suitability of TAVI. All patients had pre-TAVI cardiac computed tomography in order to plan the procedure. Prosthetic valve size and type was left to the discretion of the operator.

6.3.4. Statistical analysis

Data is presented as either mean ± standard deviation if parametric or median (interquartile range) if non-parametric or number (percentage) for frequencies. The prognostic value of echocardiographic variables was evaluated using univariate Cox regression analysis for mortality at 2.4 ± 1.4 years post-TAVI. Variables that were significant were included into a multivariable Cox regression model which included

known clinical prognostic factors. These clinical were decided a priori: chronic kidney disease (CKD- estimated glomerular filtration rate (eGFR)<60ml/min/1.73m^2), any chronic pulmonary disease, previous stroke, atrial fibrillation (AF), multivessel coronary artery disease (CAD) and frailty. The outcome was all-cause mortality at and >1 year post-TAVI.

Ethical approval was obtained for this study from the Health Research Authority and Health and Care Research Wales (REC reference: 21/NW/0182). The need for informed consent was waived given the retrospective nature of the study.

6.4. Results for safety and efficacy of TAVI in ADAS

Figure 40 shows the treatment pathway of patients with severe symptomatic AS referred to BHC. Of the 1383 patients referred, 175 presented with ADAS. Within this group, 5 patients had a BAV followed by an elective TAVI and 1 had a BAV followed by a TAVI during the index admission. In total, 893 patients had a TAVI with 723 (81.0%) treated electively and 170 (19.0%) treated during their index admission.

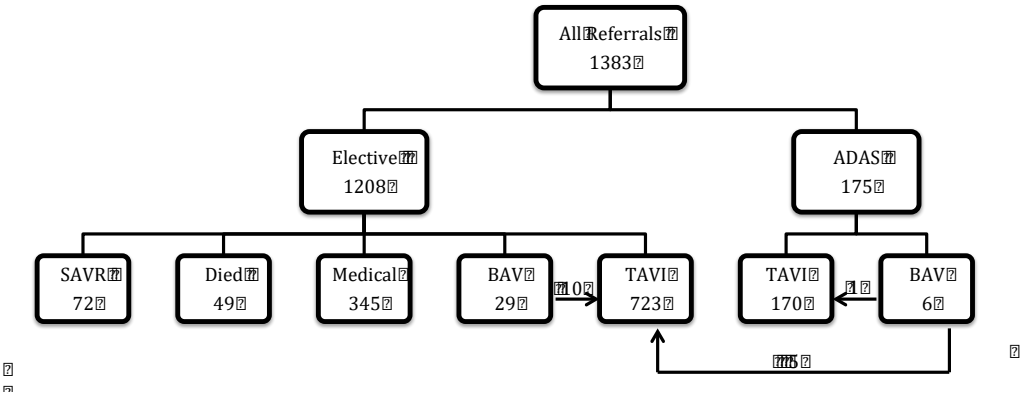


Figure 40: Patient pathways of all patients referred to the BHC. The two TAVI groups were included in this study.

6.4.1. Baseline characteristics

Table 29 shows the baseline characteristics of patients. Compared to the non-ADAS cohort, the ADAS cohort had a higher prevalence of classical low-flow low-gradient AS, previous myocardial infarction, renal failure and critically unwell patients. However, there were fewer patients with diabetes, a smoking history and neurological diseases in the ADAS cohort. Patients with ADAS were more

symptomatic with a higher prevalence of Canadian Cardiovascular Society angina grading scale >2 and New York Heart Association >2. Echocardiography data demonstrated higher pulmonary artery systolic pressures and prevalence of left ventricular systolic dysfunction and smaller aortic valve areas.

Variable	ADAS (n=170)	Non-ADAS (n=723)	p value
Age (years)	83.1 ± 7.6	82.9 ± 7.3	0.8
Male	88 (51.8%)	362 (50.1%)	0.7
Logistic Euroscore	23.2 (1.82-91.88)	19.9 (1.41-70.43)	0.11
Critical Pre-Op status	**14 (8.2%)**	**0 (0%)**	**<0.001**
Angina CCS > 2	**18 (10.6%)**	**28 (3.9%)**	**0.009**
NYHA > 2	**124 (73.0%)**	**432 (59.8%)**	**<0.001**
Smoking history	**57 (33.5%)**	**330 (45.6%)**	**0.014**
Diabetes	**27 (15.9%)**	**175 (24.2%)**	**0.02**
eGFR (ml/min/1.73m^2)	**52.2 ± 23.0**	**58.8 ± 28.1**	**0.0006**
Dialysis	2 (1.2%)	17 (2.4%)	0.27
Previous MI	**38 (22.4%)**	**96 (13.3%)**	**0.003**
Previous PCI	29 (17.1%)	103 (14.2%)	0.322
Previous CABG	15 (8.8%)	102 (14.1%)	0.066
Previous valve Surgery	5 (2.9%)	28 (3.9%)	0.562
Hypertension	122 (71.8%)	540 (74.7%)	0.433
Pulmonary disease	35 (20.6%)	170 (23.5%)	0.415
Liver disease	3 (1.8%)	11 (1.5%)	0.737
Neurological disease	**17 (10.0%)**	**126 (17.4%)**	**0.017**
PASP (mmHg)	**45.90 ± 13.5**	**40.50 ± 15.1**	**0.0002**
AV MG (mmHg)	45.07 ± 18.4	44.16 ± 14.2	0.78
AV PG (mmHg)	73.90 ± 26.9	74.31 ± 22.9	0.3223
AVA (cm^2)	**0.65 ± 0.2**	**0.70 ± 0.2**	**0.0027**
Severe LVSD	**30 (17.6%)**	**29 (4.0%)**	**<0.001**
Classical LFLG AS	**44 (25.9%)**	**78 (10.8%)**	**0.0001**
Paradoxical LFLG AS	22 (12.9%)	135 (18.7%)	0.093

Table 29: Comparison of baseline characteristics of patients in the ADAS and non-ADAS cohort.

6.4.2. Presentation data

Data on the known history of the 170 ADAS patients was evaluated; 30 (17.6%) were new presentations without a prior diagnosis of AS. By contrast, 95 (55.9%) were known to have either moderate or severe AS; whilst 2 (1.2%) were known to have mild AS. Of these patients with a previous history of AS, 22 had progression of their disease without their medical team's knowledge, 42 were awaiting a TAVI, 12 were because of patient related delays and 21 were due to other reasons, including new cancer diagnosis, awaiting SAVR and inadequate information. No data was available for 43 patients (25.3%).

6.4.3. Implantation data

Vascular access was similar between both groups; non-transfemoral access used in 6 patients (3.5%) vs 20 patients (2.8%); p=0.37 in ADAS vs non-ADAS cohorts respectively. Majority of patients had a Sapien 3 valve implanted- 84.1% of the ADAS cohort and 78.6% of the non-ADAS cohort (Table 30).

Access site	**ADAS (n=170)**	**Non-ADAS (n=723)**
Transfemoral	164	703
Transapical	6	12
Subclavian	0	2
Axillary	0	6
Valve type		
CoreValve Evolut	13	65
CoreValve	1	1
Acurate Neo	2	4
Sapien 3	143	568
Sapien XT	0	6
Lotus	11	65
Lotus edge	0	1
Direct Flow	0	13

Table 30: Procedural data showing access site and valve type

6.4.4. Procedural mortality and outcomes

Procedural mortality (within 48 hours post-TAVI) was similar between the ADAS and non-ADAS cohorts (1.2% vs. 0.7%; p=0.624) respectively. However, at 30 days, all-cause mortality was higher in the ADAS cohort (5.3% vs. 1.1%; p=0.002). This was maintained up to 1 year (15.3% vs. 8.4%; p=0.009). However, as figure 41 illustrates, the Kaplan-Meier curves appear to run parallel to each other 6 months post-TAVI.

Although several factors were found to be significant predictors for 30 day mortality on univariate analysis (table 31), multivariable analysis demonstrated (table 32) acute kidney injury (AKI), further valve intervention, liver disease and ADAS to be statistically significant. At 1 year, AKI was the only predictor of mortality on multivariable linear regression analysis (HR 1.28; 95% CI 1.09-1.51, p=0.003). AKI post-TAVI was higher in the ADAS cohort (11.8%. vs. 6.5%, p=0.02). There was a trend towards greater use of general anaesthesia (GA) among the ADAS cohort (5.3% vs. 2.6%; p=0.07). Other complications were similar between both cohorts (table 33).

Univariate analysis				
Variable	**HR**	**95% Confidence interval**		**P value**
		Lower limit	**Upper limit**	
Demographics				
Age (years)	1.00	1.00	1.00	0.369
Male sex	1.01	0.99	1.03	0.443
Comorbidities				
eGFR (ml/min/1.73m^2)	1.00	1.00	1.00	0.715
Previous PCI	1.00	0.98	1.03	0.74
Previous MI	1.01	0.99	1.04	0.321
Hypertension	1.00	0.98	1.02	0.737
Lung disease	1.01	0.99	1.03	0.523
Neurological disease	0.99	0.96	1.01	0.251
Smoking	0.99	0.97	1.00	0.091
Liver disease	**1.13**	**1.06**	**1.22**	**0.001**
Logistic Euroscore	1.00	1.00	1.00	0.738
Diabetes	0.99	0.97	1.02	0.621
Clinical presentation				
Critical pre-operative status	1.12	1.05	1.20	0.001
Acute kidney injury	**1.04**	**1.01**	**1.08**	**0.011**
ADAS	**1.04**	**1.02**	**1.07**	**<0.001**
CCS class	1.00	0.99	1.01	0.438
NYHA	1.01	0.99	1.02	0.222
Echocardiography				
PASP (mmHg)	1.00	1.00	1.00	0.441
AV mean gradient (mmHg)	1.00	1.00	1.00	0.165
Peak gradient (mmHg)	1.00	1.00	1.00	0.147
Aortic valve area (cm^2)	1.00	1.00	1.00	0.805
Severe left ventricular systolic dysfunction	1.01	0.99	1.03	0.241
Procedural details				
Further valve intervention	**1.26**	**1.17**	**1.36**	**<0.001**
Conversion to GA	**1.18**	**1.12**	**1.24**	**<0.001**
Vascular complications	1.03	1.00	1.05	0.052
Cardiac tamponade	**1.51**	**1.37**	**1.67**	**<0.001**
Bleeding	1.01	0.99	1.03	0.182
Discharge MG (mmHg)	1.00	1.00	1.00	0.244
Discharge Aortic Regurgitation	**0.99**	**0.98**	**1.00**	**0.046**

Table 31: Univariate regression analysis for all-cause mortality at 30 days in all TAVI patients

Variable	Multivariable analysis			
	HR	95% CI: lower limit	95% CI: upper limit	p value
Conversion to GA	1.03	0.99	1.07	0.169
Cardiac tamponade,	0.92	0.83	1.01	0.085
Aortic Regurgitation	0.99	0.98	1.00	0.053
Vascular complications	1.00	0.98	1.02	0.744
Acute kidney injury	**1.05**	**1.03**	**1.08**	**<0.001**
Further valve intervention	**1.13**	**1.06**	**1.21**	**<0.001**
Liver disease	**1.08**	**1.02**	**1.13**	**0.005**
ADAS	**1.02**	**1.00**	**1.03**	**0.022**

Table 32: Multivariable regression analysis for all-cause mortality at 30 days in all TAVI patients

Procedural complications	ADAS (n=170)	Non-ADAS (n=723)	p value
Conversion to general anaesthetic	**9 (5.3%)**	**19 (2.6%)**	**0.07**
Further valve intervention	3 (1.8%)	9 (1.2%)	0.71
Vascular access site complication	9 (5.3%)	34 (4.7%)	0.75
Cardiac tamponade	2 (1.2%)	5 (0.7%)	0.62
Stroke	2 (1.2%)	22 (3.0%)	0.29
Acute kidney injury	**20 (11.8%)**	**47 (6.5%)**	**0.02**
Renal replacement therapy	1 (0.6%)	3 (0.4%)	0.57
Permanent pacemaker implantation	17 (10%)	80 (11.1%)	0.69

Table 33: Procedural complications between non-ADAS and ADAS cohorts

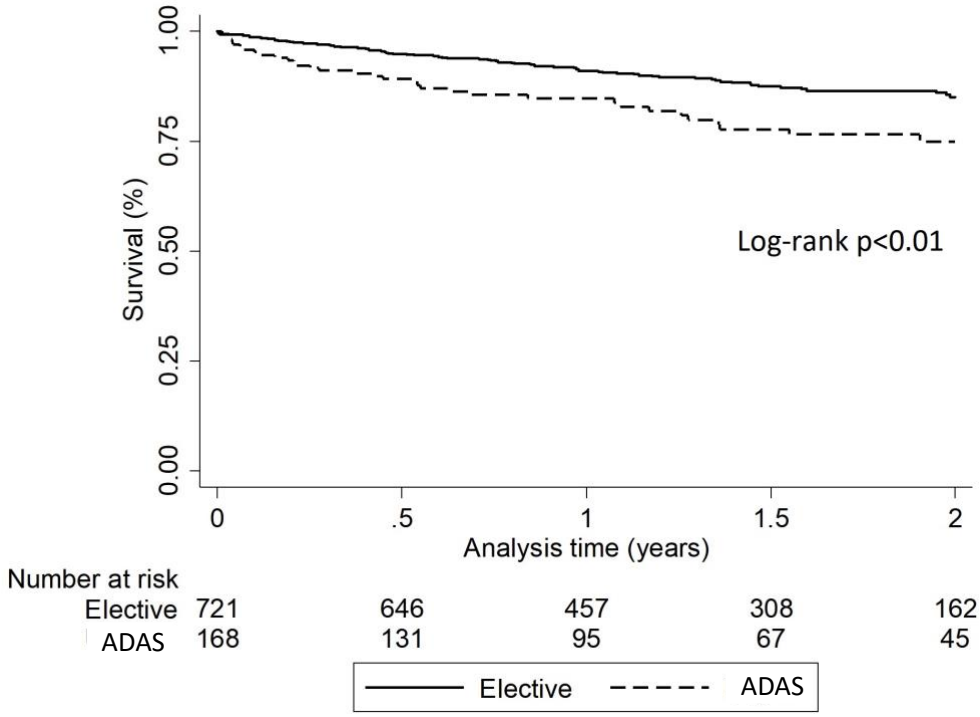


Figure 41: Kaplan-Meier curves demonstrate an initial divergence in mortality with subsequent (>6 months) parallel progression

6.4.5. Length of stay (LOS)

LOS was greater for the ADAS cohort compared to the non-ADAS cohort (31.9 ± 20.7 days vs. 6.1 ± 6.5 days; p<0.001). Among the ADAS group, the mean delay from hospital admission to TAVI was 25.0 ± 18.6 days, with 23.2 ± 16.7 days between admission at a local hospital to admission at BHC. During this time patients were treated medically, had their cardiac investigations and were discussed at an MDT meeting. The average time from admission at BHC to having a TAVI was 7.0 ± 8.4 days. Post-TAVI, patients in the ADAS cohort were less likely to be discharged home compared to the non-ADAS cohort (percentage discharged home 73.5% vs. 88%; p<0.01). Univariate analysis identified several predictors of LOS (table 34). However, multivariable logistic regression analysis (table 35) revealed ADAS, and dialysis were the only independent predictors of LOS.

Univariate analysis

Variable	Odds Ratio	95% Confidence Interval		P value
		Upper limit	Lower limit	
Demographics				
Age (years)	1.00	0.97	1.03	0.93
Male sex	0.76	0.48	1.18	0.22
Clinical comorbidities				
Euroscore	1.00	0.98	1.02	0.92
Smoking	1.15	0.75	1.75	0.52
Diabetes	0.78	0.47	1.29	0.33
Neurological disease	0.82	0.46	1.45	0.49
eGFR (ml/min/1.73m^2)	1.00	0.99	1.01	0.53
On dialysis	**0.29**	**0.10**	**0.81**	**0.02**
Previous PCI	1.37	0.69	2.72	0.37
Previous MI	1.00	0.54	1.86	1.00
Liver disease	0.63	0.14	2.88	0.55
Hypertension	1.35	0.84	2.19	0.22
Lung disease	0.98	0.58	1.66	0.94
Clinical presentation				
Critical pre-operative status	**0.29**	**0.10**	**0.81**	**0.02**
NYHA class	**0.68**	**0.47**	**0.97**	**0.03**
ADAS	**0.55**	**0.34**	**0.91**	**0.02**
Echocardiography				
PA systolic pressure (mmHg)	0.99	0.97	1.01	0.21
Aortic valve PG (mmHg)	1.02	1.00	1.03	0.06
Aortic valve MG (mmHg)	1.01	1.00	1.02	0.09
Aortic valve area (cm^2)	0.72	0.25	2.07	0.55
Severe LVSD	0.85	0.60	1.22	0.39
Procedural factors				
Vascular access complications	0.73	0.43	1.23	0.24
Life threatening bleeding	0.92	0.59	1.42	0.70
Acute kidney injury	0.58	0.28	1.18	0.13

Conversion to General anaesthesia	0.47	0.18	1.28	0.14
Further valve intervention	0.53	0.11	2.44	0.41
Cardiac tamponade	0.26	0.05	1.37	0.11
Discharge peak gradient (mmHg)	0.99	0.96	1.02	0.44
Discharge aortic regurgitation	0.89	0.60	1.32	0.58

Table 34: Univariate regression analysis for length of stay

Multivariable analysis				
Variable	**Odds Ratio**	**95% confidence interval**		**P value**
		Lower limit	**Upper limit**	
On dialysis	**0.26**	**0.08**	**0.84**	**0.02**
ADAS	**0.55**	**0.31**	**0.97**	**0.04**

Table 35: Multivariable regression analysis for length of stay

6.5. Results for pre-procedural prognostic factors for ADAS

292 ADAS patients were included in this study and followed up for an average of 2.4 ± 1.4 years.

6.5.1. Baseline characteristics

Demographics and clinical comorbidities were comparable between both cohorts (table 36). The prevalence of echo stage >2 was 51.7%.

Variable	**ADAS (n=292)**
Age (years)	84 (79, 88)
Men	54.1%
Clinical parameters	
Diabetes mellitus	26.4%
Chronic kidney disease	59.4%
Pulmonary disease	20.2%
Previous stroke	13.3%
Hypertension	73.3%

Multivessel CAD	24.5%
Frailty (CFS>5)	17.9%
Logistic Euroscore	14 (9, 26)
Echocardiographic parameters	
LV internal dimension in diastole (cm)	4.7 (4.3, 5.3)
LV internal dimension in systole (cm)	3.4 (2.9, 4.2)
Interventricular septum thickness (cm)	1.2 (1.0, 1.4)
LV inferolateral wall thickness (cm)	1.1 (0.9, 1.3)
Eccentricity index	1.08 (1.00, 1.18)
relative wall thickness	0.49 (0.40, 0.58)
LVEF (%)	55 (35, 60)
Lateral S' (m/s)	0.06 (0.04, 0.07)
Septal S' (m/s)	0.05 (0.04, 0.06)
LV mass index (g/m2)	115 (94, 138)
E/A ratio	0.9 (0.7, 1.5)
average E/e'	18.7 (13.5, 24.0)
Lateral E/e'	15.0 (11.1, 21.4)
Septal E/e'	20.8 (14.9, 27.3)
Left atrial area (cm^2)	25 (21, 29)
TAPSE (cm)	1.8 (1.4, 2.1)
Pulmonary artery systolic pressure (mmHg)	38 (29, 51)
Moderate or severe MR	17.7%
AV peak velocity (m/s)	4.1 (3.6, 4.6)
AV mean gradient (mmHg)	41 (32, 53)
AV area (cm^2)	0.6 (0.5, 0.8)
Flow rate (ml/s)	144 (116, 179)
Classical LFLG AS	24.1%
Paradoxical LFLG AS	19.1%
Echocardiographic staging classification*	
Echocardiographic Stage >2	150 (51.7%)
Stage 0	11 (3.9%)
Stage 1	14 (4.9%)
Stage 2	115 (39.3%)
Stage 3	22 (7.7%)
Stage 4	128 (44.2%)

Table 36: Baseline characteristics of study population. *7 patients did not have sufficient data to enable categorisation into a particular echo stage. CAD- coronary artery disease, LV- left ventricle, AV aortic valve, echocardiographic stage >2, CFS-

clinical frailty score, LVEF- left ventricular ejection fraction, TAPSE- tricuspid annular planar systolic excursion, LFLG- low flow low gradient, MR- mitral regurgitation, AS- aortic stenosis

6.5.2. Prognostic impact of echocardiographic and clinical parameters for the study population

Univariate analysis performed on echo parameters demonstrated an association with all-cause mortality for LV mass indexed (HR: 1.160, 95% CI: 1.027-1.310; p=0.017) and >Stage 2 echo class (HR: 1.498, 95% CI: 1.009-2.222; p=0.045) (table 37).

Variable		Univariate analysis			
			95% Confidence Interval		
		Odds ratio	Lower limit	Upper limit	p value
LV internal diameter in diastole		1.204	0.935	1.551	0.150
Eccentricity index		1.055	0.412	2.701	0.911
Relative wall thickness		0.810	0.253	2.597	0.723
LV mass indexed (per 20g increase)		**1.160**	**1.027**	**1.310**	**0.017**
LV ejection fraction		1.001	0.988	1.013	0.933
E/A ratio		0.903	0.691	1.181	0.457
Average E/E’		1.018	0.995	1.042	0.121
AV mean gradient		0.989	0.978	1.000	0.053
AV Vmax		0.844	0.661	1.077	0.172
AV flow rate		1.000	0.998	1.002	0.933
Echo stage	1	1.621	0.313	8.393	0.565
	2	1.520	0.365	6.330	0.565
	3	3.023	0.675	13.532	0.148
	4	2.101	0.510	8.655	0.304
Echo stage> 2		**1.498**	**1.009**	**2.222**	**0.045**

Table 37: Univariate cox regression analysis of echocardiographic variables for all-cause mortality at 2.4 ± 1.4 years among patients with ADAS**.** LV- left ventricle. V max- peak transvalvular velocity, AV- aortic valve

There were 59 deaths at 1 year post-TAVI. Therefore 6 variables were included in the multivariable Cox regression models (table 38). Echo class >stage 2 was the only predictor of mortality at 1 year (HR: 1.85, 95% CI: 1.01-3.39; 95% CI: 0.045).

	Multivariable analysis			
Variable	**Hazards ratio**	**95% Confidence Interval**		**p value**
		Lower	**Upper**	
> Stage 2	**1.853**	**1.013**	**3.387**	**0.045**
CKD	1.109	0.621	1.981	0.726
pulmonary disease	1.195	0.594	2.406	0.618
Previous stroke	0.968	0.425	2.206	0.939
AF	0.973	0.501	1.89	0.935
Frailty	1.687	0.89	3.198	0.109

Table 38: Multivariable cox regression analysis for all-cause mortality at 1 year post-TAVI in patients with ADAS. CKD- chronic kidney disease, AF- atrial fibrillation

A second model was created with clinical factors and echo class >stage 2 for all-cause mortality at a mean follow-up of 2.4 ± 1.4 years (table 39). There was no multicollinearity between variables. Frailty remained the only variable independently associated with mortality (HR 1.667, 95% CI: 1.045-2.659; p=0.032). Echo class >Stage 2 and other clinical variables were not associated with mortality (table 39).

	Multivariable analysis			
Variable	**Hazards ratio**	**95% Confidence Interval**		**p value**
		Lower	**Upper**	
> Stage 2	1.443	0.934	2.229	0.098
CKD	1.267	0.822	1.954	0.284
pulmonary disease	1.05	0.626	1.762	0.852
Previous stroke	1.207	0.68	2.144	0.521
AF	1.387	0.852	2.258	0.188
Multivessel CAD	1.179	0.747	1.862	0.479
Frailty	**1.667**	**1.045**	**2.659**	**0.032**

Table 39: Multivariable cox regression analysis for all-cause mortality for patients in the ADAS cohort at a mean follow-up of 2.4, SD 1.4 years. CKD- chronic kidney disease, CAD- coronary artery disease, AF- atrial fibrillation

6.6. Discussion of safety and efficacy of TAVI in ADAS

This retrospective, observational study revealed three important findings: firstly, TAVI is safe and effective in ADAS with procedural outcomes similar to that of elective patients. Secondly, ADAS patients have worse physiological features at baseline, longer hospital stays and higher mortality at both 30 days and one year. Lastly, majority of patients with ADAS were previously known to have AS prior to decompensation.

The optimum management for patients with ADAS is unknown. Due to the perceived risks and logistical challenges of SAVR or TAVI in the acute setting, many clinicians opt for temporising measures with BAV [356] or medical therapy [357]. However, these strategies result in poor outcomes for many patients. Medical therapy has limited value in symptomatic AS, whilst BAV may not sufficiently relieve AS [361] and only marginally reduces the risk of recurrent ADAS [250]. Furthermore, 30-day mortality is higher following BAV, ranging between 11.6% and 47%, compared to those reported for TAVI in this study [362]–[365]. Subsequently performing an elective TAVI in patients with a prior BAV results in a high 30-day mortality of 15.6% [284]. Alternatively, TAVI provides definitive treatment of AS in a single procedure and this study supports its use as a first-line alternative to BAV in patients presenting with ADAS.

This study showed that despite their worse physiological status at presentation, there was no significant difference in procedural mortality (at 48 hours post-TAVI) or complications between ADAS and non-ADAS cohorts. Therefore, TAVI can be safely undertaken in patients with ADAS.

However, 30-day mortality was still higher among ADAS patients, despite TAVI. This reflects the increased comorbidity and reduced physiological reserve at referral, including poorer left ventricular systolic and renal function. ADAS patients had increased rates of AKI, which demonstrated an independent association with mortality. Other determinants of 30 day mortality were further valve intervention, ADAS and liver disease. It is important to note that the overall number of patients requiring further valve intervention or who had liver disease at baseline were small in this study. Thus, caution needs to be exercised when interpreting these two predictors. ADAS seems to affect short- rather than mid-term mortality. This is illustrated by the Kaplan Meier survival curves (figure 44) which show an initial divergence between the ADAS and non-ADAS cohorts, followed by a parallel decline

in survival. This is also supported by the multivariable analysis that identified ADAS as a significant predictor of mortality at 30 days but not at 1 year.

These results are consistent with those from the TVT registry [250]. However, mortality rates were higher in the TVT registry. Differences in the study population with more comorbidities, procedural techniques- higher use of general anaesthesia and transapical access and experience that encompasses earlier versions of TAVI technology are likely to account for this. TAVI can also be used among patients presenting with ADAS and cardiogenic shock, with acceptable procedural and 30-day outcomes [366].

Patients with ADAS had lengthier hospital admissions due to their acutely unwell state and need for more intensive treatment. This will have a significant bearing on resources and cost.

This study also identified that majority (57.1%) of patients with ADAS were known to have some degree of AS prior to their decompensation. This is similar to previous reports [281]. Two main reasons can account for this: variability in the progression of AS and the development of symptoms among patients with asymptomatic AS, reflecting failure of the 'watchful wait' strategy.

This data has identified two important challenges for clinical practice. Firstly, there needs to an emphasis on early diagnosis and treatment of AS before patients decompensate. Secondly, pathways for rapid assessment and treatment for those who do decompensate, similar to those for acute coronary syndromes, need to be evaluated [367]. This will reduce the time patients with ADAS spend with outflow tract obstruction, haemodynamic disturbances and pressure and volume overload. Although speculative, this could potentially improve prognostic outcomes, reduce hospital length of stay and costs.

6.6.1. Limitations

This is a single-centre, observational, retrospective study which makes it liable to uncontrolled confounders and biases. There was no BAV group to compare with, limiting any conclusions drawn regarding BAV as a first-line strategy in ADAS. This study included a small number of patients with liver disease, further valve intervention and dialysis. Although these parameters were identified as significant determinants of the study outcomes on multivariable analysis, the results need to be interpreted with caution. This study did not have a control group of medically treated

patients. So although I have demonstrated that TAVI is equally safe and effective in ADAS as it is in non-ADAS, I cannot make a comparison to medical treatment. Anecdotally and our understanding from non-ADAS inoperable AS patients treated medically suggest very poor outcomes in this cohort [151]. Further work with a larger number of patients will be needed to verify the significance of these parameters.

6.7. Discussion for pre-procedural prognostic factors in ADAS

This study assessed cardiac and clinical parameters, including an echo-based AS staging classification for the risk stratification of ADAS. It demonstrates two key findings: firstly, echo class >stage 2 independently predicted mortality at 1 year post-TAVI. Secondly, neither echo nor clinical parameters, with the exception of frailty, predicted mortality from TAVI in the mid-term. This has important clinical implications for patients with ADAS.

Prior studies, including ours, have identified procedural (non-transfemoral access, further valve intervention and cardiopulmonary bypass) and clinical factors (oxygen-dependant lung disease, immunosuppression, liver disease, acute kidney injury, atrial fibrillation and mitral stenosis) as important prognostic indicators among ADAS [249], [250], [348]. Frailty was not assessed in these studies. Our finding that only frailty was an independent prognostic marker (1.7 fold higher risk of mortality) at mid-term follow-up is of paramount importance as more than 1 in 6 ADAS patients were frail in our population. Studies in stable TAVI patients have identified frailty as an important short-term predictor of mortality [368]. However, in ADAS patients, the degree of cardiac damage/dysfunction appears to be the predominant driver of outcomes, with echo staging classification> 2 independently predicting mortality in the short term. This supports the integration of frailty and the echo staging classification (albeit for different time points) into risk stratification and decision making for ADAS. Several studies have demonstrated the prognostic importance of the echo staging classification in AS [369], [370] with greater degrees of dysfunction associated with an increase in the risk of mortality among various populations: symptomatic severe AS treated with aortic valve replacement [300], [355], asymptomatic moderate to severe AS [371] and moderate AS [372]. A limitation of this staging classification is its binary nature, where dysfunction is either present or not, rather than considered as a continuous parameter. For example, we demonstrated the unadjusted incremental prognostic significance of LV mass

indexed. However, the staging classification would categorise all such patients as stage 1, regardless of the severity of LV mass indexed.

The absence of a mid-term impact of echocardiographically characterised cardiac structure and function and short-term impact of clinical parameters on mortality in ADAS is unexpected and important. Several reasons may account for these findings. Firstly, although speculative, mortality in the short term may be primarily driven by cardiovascular causes. This may explain why in these acutely unwell patients, adverse myocardial and valvular changes impact mortality early. Survivors may potentially benefit from reverse remodelling and improved function thereby diminishing the impact of pre-TAVI adverse myocardial structure and function in the mid-term [373]. Secondly, in this elderly, high-risk population, with multiple comorbidities, non-cardiovascular causes may drive mortality in the mid-term, accounting for conditions such as frailty (and possibly other comorbidities not studied) having a greater impact on mortality than the heart. Thirdly, we identified myocardial structural and functional characteristics using echocardiography. The role of focal and diffuse fibrosis determined using cardiac magnetic resonance imaging and more subtle changes in function using strain imaging need to be evaluated.

Centres and clinicians differ in their approach to treating ADAS. Some prefer a period of medical stabilisation before undergoing aortic valve replacement electively. Whilst others, including us, treat ADAS with TAVI during their acute illness (21.1 ± 16.3 days from admission). The optimal approach is yet unknown, although a retrospective study has demonstrated a higher unadjusted mortality rate in AS patients with acute heart failure if treated with TAVI >60hours after presentation compared to ≤60 hours (40 vs 16%; log-rank p=0.022) [349].

6.7.1. Limitations

The retrospective, observational nature of this study does subject it to bias. The results of this study should also be interpreted with the study population in mind, which was high-risk and elderly. Therefore, the results may not be applicable to lower risk populations. Certain factors of myocardial structure and function were not evaluated in this study- deformation and fibrosis, which deserve evaluation in future studies. 6 patients were excluded due a lack of data. Out of 292 patients included in this study, 7 did not have sufficient data to accurately classify them into an echocardiographic stage.

7. General discussion, conclusions and clinical implications

The myocardium is the end-tissue target for many diseases affecting the heart. Afterload from AS drives myocardial remodelling that is both heterogenous and often unpredictable. Building on this substrate are the additional insults imposed by comorbidities, whether it is ischemia driven by CAD or infiltration as a result of ATTR. I have demonstrated that the combined pathological phenotype influences the myocardium's structure and function and consequently the patient's outcomes.

TAVI has been established as the predominant mode for aortic valve replacement. Improvements in technology, better techniques and greater experience are constantly improving outcomes. Additional therapies may also facilitate this improvement. However, targeting these therapies to patients who need it is crucial. This PhD brings us a step closer towards achieving this.

This thesis has established that AS-ATTR is a mixed phenotype which is worse than AS but is not the summation or even potentiation of the two insults (afterload and infiltration). It likely reflects an early stage of amyloid infiltration, but the combined insult in a phenotype resembles ATTR. Even after treatment of AS, ATTR-specific therapy is therefore likely to provide benefit. Given the prevalence of AS-ATTR within the TAVI population and the similarities between AS and AS-ATTR using echocardiography, screening pathways are required to identify these patients for consideration of further therapy. CT_{ECV} provides the ideal modality for doing so, as patients routinely have a CT pre-TAVI and our group has demonstrated that CT_{ECV} can act as a good screening tool for AS-ATTR.

Stable CAD does not affect TAVI procedural complications or mortality and therefore it is unlikely to be a prerequisite for TAVI. However, the larger the myocardial territory at risk, the greater the risk of mortality, with LMS disease associated with a 68% increased risk of mortality compared to non-LMS disease, after 1 year post-TAVI. These patients may benefit from additional therapy, whether that is revascularisation or optimum medical therapy. The timing of revascularisation requires further consideration of clinical and procedural factors.

Improving our current diagnostic and management pathways for patients with AS can also help improve outcomes. From this PhD, I have identified a population that warrant further consideration- ADAS.

During an acute presentation in patients with AS, differentiating between a type 1 NSTEMI and ADAS is clinically challenging, and commonly used metrics (TnT, ischaemic ECG and angina), if positive, are not helpful. Alternative pre-angiographic screening is required, and CT or echo may provide the solution by assessing for coronary stenosis and regional wall motion abnormalities respectively and gate keeping subsequent invasive coronary angiography.

Despite TAVI being safe and effective for ADAS patients, mortality remains high, acute kidney injury is common and hospital length of stay is prolonged. Although prediction and prevention of ADAS with timely AVR is key, this requires further research. Risk stratification and optimisation of treatment pathways for ADAS are important. The degree of cardiac damage based on the echo staging classification and frailty in the short and mid-term respectively are the only prognostically important markers I identified in this population. We should integrate these more commonly into risk stratification in order to better inform clinicians and patients. Treatment with TAVI earlier after decompensation in order to reduce the duration of potential haemodynamic compromise, arrhythmias, associated organ damage and hospital length of stay may yield benefits to patients and healthcare provision.

8. Further work

My research work has enabled the development of 4 projects, through the successful application of further funding, collaboration and research fellows. I have developed 2 new clinical diagnostic and management care pathways, setup a multicentre registry and aligned with this: 3 prospective and 1 prospective/retrospective research study.

8.1. AS-Amyloid registry- multicentre, international registry with 250 patients pledged

Dual pathology of AS and ATTR has been increasingly recognized as a common diagnosis in elderly patients undergoing TAVI with reported prevalence of 10-15%. However, there is a significant gap in understanding of the pathophysiological mechanisms, disease interaction, choice of intervention, post intervention drug therapies, and outcomes. Therefore, multicentre registry data is required to fill this gap. We have received pledges from several cardiac centres across the World with an estimated 250 patients with AS-ATTR to be included in the registry. Infrastructure for the registry has been drawn up including a Redcap platform and ethics.

8.1.1. Study aim

Defining stages, best diagnostic and treatment pathways as well as evaluating clinical outcomes of patients with a dual pathology of AS-ATTR.

8.1.2. Data to be collected for the registry

- Demographics
- Clinical characteristics- electrocardiogram findings, symptoms, medical history, medications,
- Laboratory results- Blood, urine and genetics results
- Imaging- bone scans, echocardiograms, magnetic resonance imaging (MRI)
- Treatment- valve intervention, drug therapy
- Outcomes- death, hospitalisation, symptomatic improvement

8.1.3. Methods

We will only collect anonymised data on this registry, with the host centre having the linkable identifiable data. We will work with hospitals/health care facilities across the UK, USA and Europe to gather this data.

8.2. Quantification of ECV in TAVI patients undergoing CT: care pathway implementation for the risk stratification of TAVI patients and the screening of AS-ATTR

Recent drug developments have led to promising advances in therapy for ATTR: Tafamidis [374], AG10 [375], Patisiran [376] and Inotersen [377]. This makes the diagnosis of ATTR very important. The gold standard and most commonly used modality for diagnosing ATTR is bone scintigraphy (DPD, HMDP or PYP scintigraphy) with concomitant blood and urine analysis to rule out a plasma cell dyscrasia. ATTR also increases myocardial ECV, more than any other non-ischaemic cardiomyopathy (due to the extracellular nature of the amyloid deposition) – such increases are detectable using both cardiac MRI and CT [192]. More recently, our group has shown that concomitant ATTR can be detected in patients with severe aortic stenosis at the time of their TAVI work-up CT, with a simple addition to the clinical protocol (AUC 0.87) [196].

Additionally, risk stratification of patients to better inform decisions regarding TAVI has several benefits: from a patient's perspective- in order to avoid a futile, invasive procedure; from a healthcare perspective- to ensure cost-effectiveness and appropriate resource utilisation and finally from a procedural perspective to maximise efficacy. Our study (Scully et al, in press JACC Imaging) has shown that ECV_{CT} is an independent predictor of mortality among TAVI patients with higher ECV values pertaining a higher risk of death. By calculating the ECV using CT we can add substantially to the discussions surrounding the optimum treatment pathway for our patients.

8.2.1. Study proposal

Patients over the age of 75 years undergoing a CT angiogram for TAVI planning will have an ECV dataset added to their protocol. This will involve an additional pre-contrast and 3 minutes post-contrast dataset. Using dedicated software the ECV will be calculated. Patients with a high ECV will have a clinically indicated DPD scan to look for ATTR. Depending on the result patients will get a referral to either

haematology (to rule out/diagnose AL amyloidosis), cardiomyopathy (to treat ATTR) or their referring cardiologist (for continuing management).

In the absence of ATTR, ECV will also inform treating clinicians about the amount of myocardial fibrosis, which has known prognostic implications in patients with AS [33], [76].

8.2.2. Clinical benefit

Identification of ECV_{CT} will provide 2 clinical benefits:

1) Risk stratification based on the prediction of mortality
2) Trigger a diagnostic pathway to identify ATTR or AL amyloidosis that would benefit from further treatment

8.2.3. Trial of ECV by CT

We have clinically implemented a CT protocol to enable the measurement of ECV in 22 patients who had CT angiography for TAVI planning in 2021. No adverse events were recorded in any of the patients. ECV was calculated in all patients except 2- where the late scan failed to transfer onto an external hard drive used to store and process the data. The quality of the ECV obtained was adequate compared to previous ECV obtained using a research protocol. CT_{ECV} is now routinely obtained in all patients undergoing CT angiography for TAVI planning. We are now performing CT_{ECV} in all patients undergoing CT angiography for TAVI planning.

8.3. Evaluation of CT-FFR in patients undergoing TAVI—Multicentre, observational study to identify optimum cut-offs for prognostic impact and angina

Current guidelines, based on a level of evidence C, recommend concomitant revascularization in patients undergoing TAVI, with an angiographically defined coronary stenosis of >50% or 70% [154], [378]. However, pivotal studies have demonstrated that visually-identified coronary stenoses are not always functionally significant [379]. Angiographically-guided revascularization results in worse outcomes compared to fractional flow reserve (FFR)-guided revascularization [380]. AS introduces specific challenges to the use of FFR, due to changes in coronary haemodynamics and myocardial remodelling (see section 1.7.1.2.). First, the effect of adenosine in patients with AS is often blunted, calling into question whether true FFR values can be obtained in patients with AS [217]. Secondly, there is uncertainty

about the change in hyperaemic microvascular resistance pre- and post-TAVR and hence FFR, with studies showing discrepant results. Some studies demonstrate a reduction [81], [138], [142], [218], some an increase [219], [220], and others minor to non-significant changes in post-TAVR FFR compared to pre-TAVR FFR values [220]–[223]. This indicates that a FFR based prognostic cut-off is likely to be different in patients with AS compared to non-AS patients.

Performing invasive FFR, pre-TAVI, in patients considered to have significant CAD is not feasible in all patients from an economic and healthcare provision perspective. It is also associated with procedural risks, requires dual antiplatelet therapy- potentially increasing the risk of bleeding. Many TAVI patients are elderly and frail, further dissuading cardiologists from performed invasive FFR. Computed tomography (CT) offers a viable, safer, potentially cost-effective and reliable alternative. All TAVI patients already undergo CT for procedural planning making the integration of CT-FFR easy. By optimizing image quality, CT-FFR can be performed in patients with CAD. This can then be used to guide management strategies.

However, thus far, only one study has evaluated CT-FFR among TAVI patients. CAST-FFR was a single centre, prospective study that successfully demonstrated the safety, feasibility, and diagnostic accuracy of CT-FFR. On comparison with invasive FFR it demonstrated a sensitivity, specificity, positive predictive value, negative predictive value of 73.9%, 78.4%, 68.0%, 82.9% respectively and a diagnostic accuracy of 76.7% [215]. Because of changes in coronary haemodynamics and questions regarding the reliability of invasive FFR (described above), we now need to address the translational aspect of CT-FFR by assessing the optimum prognostic cut-off related to outcomes in patients undergoing TAVI.

Revascularisation is also commonly used to reduce angina. However, in the setting of AS, angina is a poor discriminator of pathology (CAD vs AS). CT FFR may provide guidance regarding which coronary lesions contribute to angina and therefore may benefit from revascularisation compared to which lesions are not the predominant factor causing angina and where valve replacement may itself reduce angina.

8.3.1. Study endpoints

8.3.1.1. Primary endpoint

- Major adverse cardiovascular events (MACE)- composite of Revascularization, Myocardial infarction, and cardiovascular death

- Angina post-TAVI graded using CCS and compared to pre-TAVI

8.3.1.2. Secondary endpoints

- All-cause mortality
- Cardiovascular death
- Type 1 myocardial infarction
- Coronary revascularization for chronic coronary syndrome
- Safety endpoints: allergic reaction to contrast or CT medications, decrease in systolic blood pressure with CT medications requiring fluid resuscitation
- Proportion of CT scans of insufficient quality for CT-FFR analysis
- Myocardial damage defined as high-sensitivity Troponin T>3x upper limit of normal

8.4. ASTRID-AS- A novel management strategy for ADAS involving 22 hospitals

Several studies including mine have demonstrated the safety and efficacy of TAVI in ADAS. However, short and mid-term outcomes continue to remain poor [249], [250]. A better management strategy is needed. Studies in acute heart failure have highlighted the prognostic benefits of early and rapid treatment. The REALITY-AHF study was a prospective, multicentre, observational study assessing the association between time from presentation to diuretic administration and in-hospital mortality among 1291 patients with acute heart failure. Earlier treatment was associated with reduced in-hospital mortality compared to late treatment (OR 0.39; 95% CI: 0.20 to 0.76) [381]. This temporal benefit of treatment in acute heart failure has been demonstrated using vasodilators and diuretics in the ADHERE studies [382], [383]. Debry *et al* performed balloon aortic valvuloplasty (BAV) in patients with ADAS and cardiogenic shock, demonstrating a significant increase in mortality or recurrent cardiogenic shock if BAV was delayed by more than 48 hours from initiation of inotropes (90% vs. 59%; p=0.01 [364]. A similar study evaluating the role of BAV in ADAS patients with cardiogenic shock, demonstrated that a delay >48 hours from onset of cardiogenic shock to BAV was the only predictor of mortality [384]. Although these studies have the inherent issue of bias, include uncontrolled confounders and represent the extreme end of a spectrum of ADAS, they do demonstrate a signal indicating improved outcomes associated with quicker treatment for ADAS.

8.4.1. Study aims

I want to test the hypotheses that rapid treatment of ADAS using TAVI, can reduce morbidity, mortality and hospital length of stay. To this effect I am conducting a single centre, open-label, cohort study based on the implementation of a clinical pathway to expedite the investigations and treatment of ADAS.

8.4.2. Conventional pathway

Patients presenting with ADAS are admitted at their local hospital, investigated and treated medically. After demonstrating clinical improvement in symptoms and signs of decompensation, patients are referred to BHC. Based on a waiting list, patients will be admitted to BHC, and any pending investigations carried out. All patients are discussed at a multi-disciplinary team meeting (once weekly) and if TAVI is deemed favourable, allocated a procedural slot within a few days. The time from admission to TAVI in this pathway is currently 25.0 ± 18.6 days.

8.4.3. ASTRID-AS pathway

Patients presenting with ADAS are admitted at their local hospital, with investigations and treatment commenced. Patients are referred to BHC as soon as a diagnosis of ADAS is made. The ASessment and TReatment In Decompensated Aortic Stenosis (ASTRID-AS) pathway aims to investigate and treat a patient with ADAS within 5 days of receiving the referral (figure 42).

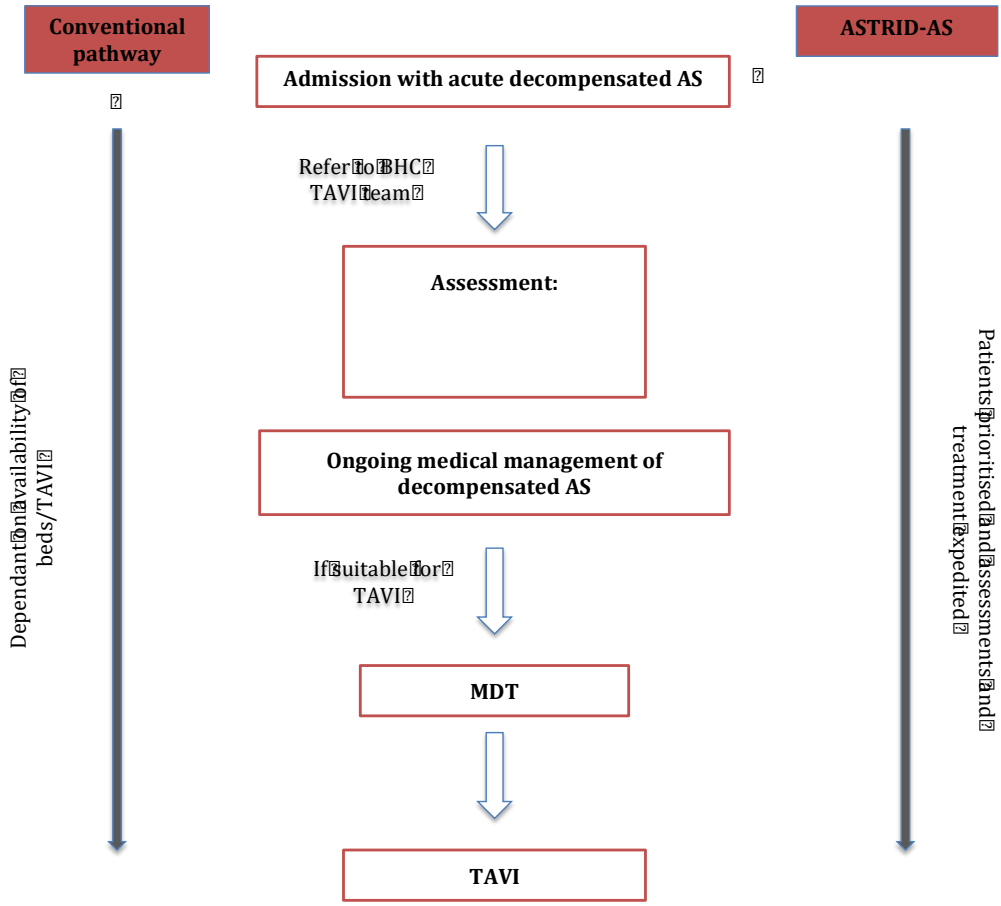


Figure 42: ASTRID-AS vs the conventional pathway for treating ADAS patients with TAVI.

8.4.4. <u>End-points</u>

- Primary end-point of 30 day mortality and AKI.
- Secondary end-points of procedural mortality (at 48 hours post-TAVI), 30-day mortality, 1 year mortality, VARC2 associated procedural complications, acute kidney injury and hospital length of stay.
- Cost-effective analysis.
- Symptomatic improvement and effect on quality of life

9. References

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10. Appendix

10.1. Studies on valvular heart disease and coronary artery disease published or in press

1. **Patel KP,** Mukhopadhyay S, et al. Rapid assessment and treatment in acute decompensated aortic stenosis (ASTRID-AS)- a pilot study. In press. European Heart Journal Quality of Care and Clinical Outcomes. 2022
2. **Patel KP**, Chahal A, Mullen MJ, Rathod K, Baumbach, A, lloyd G, Treibel TA, Awad, WI, Ricci F, Khanji M. Acute decompensated aortic stenosis: State of the art review. Current Problems in Cardiology, 2022
3. **Patel KP,** Rathod K, Akhtar M, Jones DA, Ozkor M, Kennon S, Mathur A, Pugliese F, Mullen MJ, Baumbach A. Diagnostic challenges between acute decompensated aortic stenosis and myocardial infacrtion. *Cardiovascular Revascularisation Medicine. 2022*
4. **Patel KP**, Badiani S, Ganeshalingam A, Vijayakumar M, Thornton G, Mathur A, Kennon S, Bhattacharyya S, Baumbach A, Moon JC, Tribel TA, Lloyd G. Characterisation of acute decompensated aortic stenosis and its impact on mortality. *American Heart Journal*. 2022
5. **Patel KP,** Vandermolen S, Menezes L, Moon JC, Pugliese F, Treibel TA. Cardiac computed tomography : application in valvular heart disease. *Frontiers Cardiovascular Imaging*. 2022.
6. Seraphim A, Dowsing B, Rathod K, Shiwani H, **Patel KP**, Zaman S, Razvi Y, Patel R, Xue Hui, Jones DA, Fontana M, Cole G, Uppal R, Davies R, Moon JC, Kellman P, Manisty C. Quantitative myocardial perfusion predicts outcomes in patients with prior surgical revascularisation. JACC.
7. **Patel KP** et al. Outcomes of the novel Supreme drug-eluting stent in complex coronary lesions: A PIONEER III substudy. *JSCAI. 2022*
8. **Patel KP** et al. Futility in Transcatheter aortic valve replacement: A search for clarity. *Interventional Cardiology Reviews. 2022*
9. **Patel KP** et al. Early pacemaker implantation for transcatheter aortic valve implantation is safe and effective. *Pacing and Clinical Electrophysiology. 2021;1-8*
10. **Patel KP** et al. Coronary revascularisation in patients undergoing aortic valve replacement for severe aortic stenosis. *JACC CVInterventions. 2021; Vol 14,No 19.*
11. **Patel KP** et al. Impact of afterload and infiltration on coexisting aortic stenosis and transthyretin amyloidosis. *Heart, 2021.*
12. Bhuva AN, Moralee R, Brunker T, Lascelles K, Cash L, **Patel KP**, et al. Evidence to support magnetic resonance conditional labelling of all pacemaker and defibrillator leads in patients with cardiac implantable electronic devices. *Eur Heart J 2021.*
13. Broyd C, Pugliese F, **Patel KP**. Development of a novel CT-derived measure of cardiovascular health: the CT aortic stiffness index (CTASI). *Clinical research in Cardiology, 2021*
14. Akhtar M, Shafi A, Khanna V, Mukhopadhyay S, **Patel KP**, Ozkor M, Baumbach A, Mathur A, Kennon S, Awad W, Mullen M. The management of severe aortic stenosis during the COVID-19 pandemic: an observational study comparing TAVI and SAVR. EHJ, Volume 42, Issue supplement 1, October 2021
15. Sarathy K, **Patel K**, et al. Large bore access closure device strategies. *Structural Heart. 2020*

16. Nitsche C, Scully P, **Patel K**, et al. Prevalence and outcomes of concomitant AS and cardiac amyloidosis. *JACC. Vol 77, No 2. 2020*
17. Treibel T, **Patel K**, Cavacante J. ECV in CT. *JACC Cardiovascular imaging. 2020*
18. Chasapi A, Karogiannis N, Zidros S, **Patel K**, et al. Determinants of outcomes in patients with heart failure with reduced ejection fraction and secondary MR. *IJC. 2020*
19. Scully P, **Patel K**, Treibel T, et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *European Heart Journal*, Volume 41, Issue 29, 1 August 2020, Pages 2759–2767, https://doi.org/10.1093/eurheartj/ehaa170
20. Scully P, Morris E, **Patel K**, et al. DPD Quantification in Cardiac Amyloidosis. A Novel Imaging Biomarker. *JACC: Cardiovascular Imaging. Volume 13, Issue 6, June 2020*. DOI: 10.1016/j.jcmg.2020.03.020
21. Scully P, **Patel K** et al. Identifying Cardiac Amyloid in Aortic Stenosis. ECV Quantification by CT in TAVR Patients. *JACC: Cardiovascular Imaging. August 2020*. DOI: 10.1016/j.jcmg.2020.05.029
22. **Patel K** et al. Transcatheter aortic valve implantation in acute decompensated aortic stenosis. *Catheterisations and cardiovascular interventions. Nov 2019*.
23. Bhuva A, Treibel T, Seraphim A, Knott K, Scully P, Augusto J, Torlasco C, Menacho K, **Patel K**, Moon J, Kellman P, Manisty C. Measurement of T1 mapping in patients with cardiac devices: Off-resonance error extends beyond visual artifact but can be quantified and corrected. *Frontiers in Cardiovascular Medicine. 2021.*
24. Bhuva A Treibel T, Marvao A, Biffi C, Dawes T, Doumou G, Bai W, **Patel K**, et al. Sex and regional differences in myocardial plasticity in Aortic Stenosis are revealed by 3D model machine learning. *EHJ CVImaging*
25. Broyd CJ, **Patel K**, Pugliese F, Chehab O, Mathur A, Baumbach A, Ozkor M, Kennon S, Mullen M. Pulse wave velocity can be accurately measured during transcatheter aortic valve implantation and used for post-procedure risk stratification. *J Hypertens. 2019 May 30. doi: 10.1097/*
26. Torii R, Stettler R, Räber L, Zhang YJ, Karanasos A, Dijkstra J, **Patel K**, Crake T, Hamshere S, Garcia-Garcia H, Tenekecioglu E, Ozkor M, Windecker S, Serruys P, Regar E, Mathur A, Bourantas C. Implications of the local hemodynamic forces on the formation and destabilization of neoatherosclerotic lesions. *Int J Cardiol, Dec 2018.* doi:10.1016/j.ijcard.2018.06.065
27. **Patel K**, Tarkin J, Serruys P, Tenekecioglu E, Foin N, Zhang YJ, Crake T, Moon J, Mathur A, Bourantas C. Invasive or non-invasive imaging for detecting high-risk coronary lesions? *Expert Review of Cardiovascular Therapy, 2017;15:3,165-179, doi: 10.1080/14779072.2017.1297231*
28. Honarbakhsh S, Baker V, Kirkby C, **Patel K**, et al. Safety and efficacy of paramedic treatment of regular supraventricular tachycardia: a randomised controlled trial. *Heart 2016;0:1–6 doi:10.1136/heartjnl- 2016-309968*

10.2. Studies under review for publication

29. Esposito G, Kumar N, Pugliese F, Sayers M, Chow AWC, Kennon S, Ozkor M, Mathur A, Baumbach A, Lloyd G, Mullen A, Cook A, Mullen MJ, **Patel KP**. Predictors of post-TAVI conduction abnormalities in patients with bicuspid aortic stenosis. Under review with Open Heart.
30. **Patel KP**, Aziminia N, Boubertakh R, Thornton GD, Eiros R, Moir S, Davies R,

Manisty C, Bhattacharyya S, Lloyd G, Moon JC, Treibel TA. Global longitudinal strain is a more sensitive marker of remdeollign and reverse remodelling than LVEF in patients with aortic stenosis aundergoing aortic valve replacement. Under review by JACC CVImaging

31. **Patel KP**, Vandermolen S, Cooper J, Pugliese F, Ozkor M, Kennon S, Mathur A, Khanji MY Mullen MJ, Baumbach A, Awad WI. Under review by Journal of Cardiac Surgery.

10.3. Publications not related to valvular heart disease or coronary artery disease

32. Gama F., Rosmini S., Bandula S, **Patel KP**, et al. Extracellular Volume Fraction by Computed Tomography Predicts Long-Term Prognosis Among Patients With Cardiac Amyloidosis. JACC Cardiovasc Imaging, 2022
33. Bhuva AN, Moralee R, Brunker T, Lascelles K, Cash L, **Patel KP**, Lowe M, Sekhri N, Alpendurada F, Pennell DJ, Schilling R, Lambiase PD, Chow A, Moon JC, Litt H, Baksi AJ, Manisty CH. Evidence to support magnetic resonance conditional labelling of all pacemaker and defibrillator leads in patients with cardiac implantable electronic devices. *Eur Heart J* 2021
34. Bajaj R, Sinclair HC, **Patel K**, Low B, Pericao A, Manisty C, Guttmann O, Zemrak F, Miller O, Longhi P, Proudfoot A, Lams B, Agarwal S, Marelli-Berg FM, Tiberi S, Cutino-Moguel T, Carr-White G, Mohiddin SA. Delayed-onset myocarditis following COVID-19. Lancet. Respir. Med. 2021. p. e32–e34.
35. Augusto JB, Menacho K, Andiapen M, Bowles R, Burton M, Welch S, Bhuva AN, Seraphim A, Pade C, Joy G, Jensen M, Davies RH, Captur G, Fontana M, Montgomery H, O'Brien B, Hingorani AD, Cutino-Moguel T, McKnight Á, Abbass H, Alfarih M, Alldis Z, Baca GL, Boulter A, Bracken O V, Bullock N, Champion N, Chan C, Couto-Parada X, Dieobi-Anene K, **Patel KP** et al. Healthcare Workers Bioresource: Study outline and baseline characteristics of a prospective healthcare worker cohort to study immune protection and pathogenesis in COVID-19. *Wellcome open Res* 2020;**5**:179.
36. Swadling L., Diniz MO., Schmidt NM., COVIDsortium investigators (including **Patel KP**) et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. Nature 2021. Doi: 10.1038/s41586-021-04186-8.
37. Reynolds CJ., Pade C., Gibbons JM., COVIDsortium investigators (including **Patel KP**) et al. Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose. Science (80-) 2021;372(6549):1418–23. Doi: 10.1126/science.abh1282.
38. Reynolds CJ, Swadling L, Gibbons J, COVIDsortium investigators (including **Patel KP**) et al. Discordant neutralising antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection. Science Immunology, 2020.
39. Gupta RK., Rosenheim J., Bell LC., COVIDsortium investigators (including **Patel KP**) et al. Blood transcriptional biomarkers of acute viral infection for detection of pre-symptomatic SARS-CoV-2 infection: a nested, case-control diagnostic accuracy study. The Lancet Microbe 2021;2(10):e508–17. Doi: https://doi.org/10.1016/S2666-5247(21)00146-4.
40. **Patel K**, Would world-wide vaccination of both males and females against the human papillomavirus be a good investment? *McGill Journal of Medicine : MJM. 2009;12(2):131.*

41. **Patel K**, Robotics: The future of surgery, *Int J Surg. 2008;6(6):441-2, doi: 10.1016/j.ijsu.2008.08.010.*

10.4. Grants

1) British Heart Foundation Clinical Research Training Fellowship. 2019-2021. £253,633.00. Primary applicant. The myocardium in AS-ATTR.
2) Edwards Lifesciences 2019. £127,727.00. Primary applicant. Outcomes in Acute Decompensated Aortic Stenosis.
3) National Institute for Health Research Targeting Research Funding 2020. £39,182.00. Co-applicant. Support research in heart failure.
4) Pfizer Amyloid Fellowship Grant 2021. £68,104.77. Co-applicant. Funding for a fellow (Dr Francisco Gama) to develop CT_{ECV} in TAVI patients.
5) Heart Research UK 2021 (accepted into round 2). £350,000.00. Co-applicant. Development of CT_{ECV} in a multicentre setting.

10.5. Conference presentations

2021 Nayyar D, Hughes RK, Shiwani H, Rosmini S, **Patel KP** et al. Excellent performance of the electrocardiographic QRS-T angle against CMR in identifying left ventricular hypertrophy phenotype cardiomyopathies. SCMR 2021

2021 Vandermolen S, **Patel KP**, Saberwall B, Cooper J, Khanji M, Mullen MJ, Ozkor M, Kennon S, Baumbach A, Awad W. Outcomes of TAVR vs SAVR for patients with LFLG AS. ESC 2021

2021 Saberwal B, **Patel KP**, Scully PR, Klotz E, Seraphim A, Augusto J, Vandermolen S, Knott K, Thornton G, Joy G, Pavitran A, Khanji M, Moon JC, Treibel TA, Pugliese F. Computed tomography vs cardiac MRI derived extracellular volume fraction in a stable new-onset chest pain cohort. ESC 2021

2020 **Patel K,** et al. Characterisation of AS-amyloidosis using a multimodality, multicohort study. Presented at ESC 2020

2019 **Patel K**, et al. Clinical utility of CT angiography over and above procedural planning. To be presented at ICNC 2019.

2019 **Patel K**, et al. Functional assessment of myocardial reverse remodelling after valve replacement in aortic stenosis by CMR tissue tracking. To be presented at EuroCMR 2019

2019 Akhtar M, **Patel K,** et al. Hypereosinophilic carditis (HEC): A CMR-based case series from a quaternary Cardiology Centre. To be presented at EuroCMR 2019.

2019 Scully P, **Patel K**, et al. Cardiac amyloid in the TAVI population: bystander or disease modifier. To be presented at ICNC 2019. Shortlisted for Young investigator award.

2019 Scully P, Morris E, **Patel K,** et al. SUV quantification in DPD scintigraphy. To be presented at ICNC 2019.

2018 Bhuva A, Treibel T, Marvao A, Biffi C, **Patel K,** *et al*. Septal hypertrophy in aortic stenosis and its regression after valve replacement is more plastic in males than females: insights from a machine learning approach, ESC congress, Munich 2018 (poster presentation)

2018 Eiros R, Treibel T, Scully P, Bhuva A, **Patel K** *et al.* Myocardial T2 in Aortic stenosis: compensatory vasodilatation or subacute inflammation? ESC congress, Munich 2018 (poster presentation)

2018 **Patel K**, Chehab O, Barakat M, Jerrum M, Queenan H, Bedford K, Broyd C, Kennon S, Ozkor M, Mathur A, Mullen M. Outcomes in TAVI in patients with acute decompensated aortic stenosis. *ESC congress, Munich 2018 (poster presentation)*

2018 Chehab O, **Patel K,** *et al* Outcomes of transcatheter aortic valve implantation in patients with moderate to severe chronic kidney disease. *Accepted for presentation at London Valves (poster presentation)*

2018 **Patel K** et al. Pieces of a puzzle: case of eosinophilic myocarditis: second prize at *British Cardiovascular Imaging conference, Edinburgh (oral presentation)*

2018 Scully P, Tarkin J, Treibel T, **Patel K**, Westwood M, Moon J, Menezes L. Occasional hoof beats are caused by zebras. *British Cardiovascular Imaging conference, Edinburgh (oral presentation)*

2009 Hooker C, **Patel K,** Wechaleker K, Maenhout A, Rahman L, Underwood R. A clinical and physics evaluation of resolution recovery software used for myocardial perfusion studies. *Current state and future directions of nuclear medicine imaging technology, London. (oral presentation)*

2010 **Patel K,** Noronha S, Sheppard M. Variation in both macroscopic and microscopic features of arrhythmogenic right ventricular cardiomyopathy (ARVC), *Pathology Society Winter meeting (poster presentation)*

2010 **Patel K**, Noronha S, Sheppard M. Variation in both histological features of arrhythmogenic right ventricular cardiomyopathy (ARVC), *International Pathology conference (poster presentation)*

10.6. Supervision

I have had the opportunity to supervise junior doctors and medical students throughout my PhD on various projects.

- Dr Nikoo Aziminia- CMR strain in patients undergoing SAVR
- Dr Nida Ahmed- Outcomes with medical management of AS
- Dr Asha Pavithran- Outcomes in patients with AS-CAD & safety and efficacy of early pacing in TAVI patients
- Dr Rangeena Assadi- Outcomes in patients with AS-CAD & safety and efficacy of early pacing in TAVI patients

- Dr Michael McKenna- AR registry and mixed aortic valve disease risk stratification
- Giulia Esposito- Predictors of conduction abnormalities in bicuspid aortic stenosis
- Niraj Kumar- Predictors of conduction abnormalities in bicuspid aortic stenosis
- Mohit Vijayakumar- The myocardium in ADAS: an echo evaluation
- Ajithish Ganeshalingham- The myocardium in ADAS: an echo evaluation
- Joshua Sapir- Outcomes with Mitraclip: a retrospective simulation study