Pre-procedural prognostic factors in acute decompensated aortic stenosis

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ABSTRACT

Background

Acute decompensated aortic stenosis (ADAS) is common and associated with poor outcomes. Myocardial remodelling and function, including a novel echo staging classification (0-4, representing increasing degrees of cardiac damage/dysfunction) impacts outcomes in stable aortic stenosis (AS). However, this has not been assessed among patients with ADAS. This study aims to evaluate the impact of the myocardium, echo staging classification and clinical parameters on mortality in ADAS.

Methods

ADAS was defined as an acute deterioration in symptoms (NYHA 4, CCS 3/4 or syncope) that warranted admission to hospital and urgent aortic valve replacement. Using a retrospective observational study design, 292 consecutive patients with ADAS undergoing transcatheter aortic valve implantation (TAVI) were identified and included in this study. Echocardiographic and clinical characteristics were evaluated using regression analysis. The outcome was all-cause mortality.

Results

At 1 year post-TAVI, advanced echo staging (>2) independantly predicted mortality (hazards ratio (HR): 1.85, 95% confidence interval (CI): 1.01-3.39; p=0.045). At a follow-up of 2.4 ± 1.4 years, myocardial, valvular and clinical parameters did not predict mortality, with the exception of frailty (HR: 2.31, 95% CI: 1.38-3.85; p=0.001).

Conclusion

Among ADAS patients, short-term mortality post-TAVI, is influenced by more advanced cardiac damage/dysfunction based on the echo staging classification, whilst mid-term mortality is driven by frailty rather than echo staging classification.

Abbreviations

ADAS- acute decompensated aortic stenosis

AS- aortic stenosis

CAD- coronary artery disease

CCS- Canadian Cardiovascular Society

CKD- chronic kidney disease

eGFR- estimated glomerular filtration rate

HR- hazards ratio

LA- left atrial

LV- left ventricular

NYHA- New York Heart Association

OR- odds ratio

TAPSE- tricuspid annular planar systolic excursion

TAVI- transcatheter aortic valve implantation

INTRODUCTION

Despite advances in our understanding of the natural history of aortic stenosis (AS), identification of novel prognostic markers [1] and development of risk stratification tools [2], many AS patients present with acute decompensation (ADAS)- characterised by severe symptoms warranting hospital admission and urgent aortic valve replacement. Our ability to predict ADAS is limited, which consequently accounts for 7-23% of all transcatheter aortic valve implantations (TAVI) [3–5]. Over the past decade, an increasing number of patients with ADAS are treated with TAVI [6]. Anecdottaly, the COVID-19 pandemic has resulted in delays for many patients awaiting elective aortic valve replacement and consequently patients are increasingly presenting with ADAS. Despite TAVI being safe and effective for these patients, mortality remains high; 5.3% at 30 days and 15.3% at 1 year post-TAVI [5]. Symptoms in AS are associated with changes in myocardial structure and function [7]. Additionally, greater degrees of myocardial and non-aortic valvular dysfunction are associated with worse outcomes according to a validated echocardiographic staging classification [2]. This suggests a key prognostic role played by the the degree of cardiac damage/dysfunction in patients with AS. However, ADAS patients represent a population close to 'end-stage' on the natural history spectrum of AS. Many patients develop acute kidney injury, haemodynamic instability, pulmonary oedema and cardiogenic shock. Although well studied in general AS populations, previous studies have not evaluated the prognostic impact of cardiac structure and function or frailty in ADAS [3,5,6]. The aim of this study was 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, and consequently might become useful in risk stratification alogorithms.

METHODS

This is a retrospective, observational study carried out at a single quarternary cardiac centre with a large TAVI service covering a population of six million. Myocardial and valvular structure and function were evaluated using pre-TAVI echocardiograms.

ADAS was defined as either dyspnoea at rest (NYHA 4), angina on minimal exertion or at rest (CCS 3/4) or syncope. Patients were included in this study if these symptoms were attributed to AS and developed within a week of admission to hospital. 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. Patients presenting with ADAS who received a TAVI between 2015 and 2019 were included in this study. Out of a cohort of 300 consecutive ADAS patients, 6 were excluded due to a lack of data. Frailty was defined as a Rockwood clinical frailty score >5 [8]. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60ml/min/1.73m^2. Multivessel CAD was defined as more than 1 epicardial coronary artery >50% stenosis or left main stem stenosis >50% stenosis.

All patients had a pre-TAVI echocardiography that was performed by British Society of Echocardiography accredited physiologists according to the British Echocardiographic Society guidelines [9]. 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 [2]. 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 [2]; 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 supplementary table 1. As the cohort populations were smaller than the original derivation and validation study, 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)/left ventricular (LV) systolic diameter in diastole. LV ejection fraction (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 [10].

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. Valve size and type was left to the discretion of the operator.

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 were evaluated using univariate Cox regression analysis. Variables that were significant were included into a multivariable Cox regression model which included known clinical prognostic factors. These clinical factors included in the multivariate model 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.

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. The study complied with the declaration of Helsinki.

RESULTS

292 ADAS patients were included in this study. Patients were followed up for an average of 2.4, SD 1.4 years.

Demographics and clinical comorbidities are shown in table 1. The median age of the study population was 84 (79- 88) years and 54.1% were male. The prevalence of echocardiographic stage >2 was 51.7%.

Univariate analysis was performed on echo parameters (LV structure, systolic/diastolic function, aortic valve severity and echo staging classification). 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) demonstrated an association with all-cause mortality (table 2).

There were 59 deaths at 1 year post-TAVI. Therefore 6 variables were included in the multivariate Cox regression models (table 3). 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).

A multivariate 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 4). 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 (HR 1.44, 95% CI: 0.93-2.23; p=0.098) and other clinical variables were not associated with mortality (table 3).

DISCUSSION

This study assessed myocardial and valvular 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 fraily, predicted mortality from TAVI in the mid-term. This has important clinical implications for the risk stratification of 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 [3,5,6]. 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. However, in the short term, the degree of myocardial and non-aortic valvular dysfunction as determined by an echo staging classification> 2 independantly predicted mortality. 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 [11,12] 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 [2,13], asymptomatic moderate to severe AS [14] and moderate AS [15].

The absence of a mid-term impact of echocardiographically characterised myocardial structure and function on mortality in ADAS is unexpected and important.

Echocardiographic findings, especially left ventricular ejection fraction, are often used as

part of the clinical decision making tree in the selection for TAVI; in our population such an approach would have been invalid and potentially led to the denial of treatment to patients who ultimately benifited. Several reasons may account for the failure of structural and functional echo assessment to predict mortality. Firstly, in this elderly, high-risk population, with multiple comorbidities, frailty (and possibly other comorbidities not studied) may have a greater impact than the myocardium, rendering it more important. Secondly, 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.

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 echocardiography data to accurately classify them into an echocardiographic stage.

CONCLUSIONS

Among ADAS patients, short-term mortality post-TAVI, is influenced by more advanced cardiac damage/dysfunction based on the echo staging classification, but with extended follow up, mortality is influenced by frailty and not by the echo staging classification. These parameters should be integrated into risk stratification and clinical decision making for

ADAS patients.

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