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High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis

Calvin W. L. Chin^{1,2*†}, Anoop S. V. Shah^{1†}, David A. McAllister³, S. Joanna Cowell¹, Shirjel Alam¹, Jeremy P. Langrish¹, Fiona E. Strachan¹, Amanda L. Hunter¹, Anna Maria Choy⁴, Chim C. Lang⁴, Simon Walker⁵, Nicholas A. Boon¹, David E. Newby¹, Nicholas L. Mills^{1‡}, and Marc R. Dweck^{1‡}

¹BHF/Centre for Cardiovascular Science, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, UK; ²National Heart Center Singapore, Singapore; ³Centre of Population Health Sciences, University of Edinburgh, UK; ⁴Division of Cardiovascular and Diabetes Medicine, Ninewells Hospital and Medical School, UK; and ⁵Department of Clinical Biochemistry, Royal Infirmary of Edinburgh, UK

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Aims

High-sensitivity cardiac troponin I (cTnI) assays hold promise in detecting the transition from hypertrophy to heart failure in aortic stenosis. We sought to investigate the mechanism for troponin release in patients with aortic stenosis and whether plasma cTnI concentrations are associated with long-term outcome.

Methods and results

Plasma cTnI concentrations were measured in two patient cohorts using a high-sensitivity assay. First, in the Mechanism Cohort, 122 patients with aortic stenosis (median age 71, 67% male, aortic valve area $1.0 \pm 0.4 \text{ cm}^2$) underwent cardiovascular magnetic resonance and echocardiography to assess left ventricular (LV) myocardial mass, function, and fibrosis. The indexed LV mass and measures of replacement fibrosis (late gadolinium enhancement) were associated with cTnI concentrations independent of age, sex, coronary artery disease, aortic stenosis severity, and diastolic function. In the separate Outcome Cohort, 131 patients originally recruited into the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact of REgression (SALTIRE) study, had long-term follow-up for the occurrence of aortic valve replacement (AVR) and cardiovascular deaths. Over a median follow-up of 10.6 years (1178 patient-years), 24 patients died from a cardiovascular cause and 60 patients had an AVR. Plasma cTnI concentrations were associated with AVR or cardiovascular death HR 1.77 (95% CI, 1.22 to 2.55) independent of age, sex, systolic ejection fraction, and aortic stenosis severity.

Conclusions

In patients with aortic stenosis, plasma cTnI concentration is associated with advanced hypertrophy and replacement myocardial fibrosis as well as AVR or cardiovascular death.

Keywords

Aortic stenosis • High-sensitivity troponin • Left ventricular hypertrophy • Myocardial fibrosis • Cardiac magnetic resonance

Introduction

Aortic stenosis is the commonest form of valvular heart disease in the western world, and its prevalence is expected to double in the next

two decades.¹ Current guidelines advocate aortic valve replacement (AVR) in patients with symptoms and severe valve narrowing.^{2,3} However, there is a poor correlation between the severity of stenosis and symptom onset making the management of asymptomatic

* Corresponding author: Tel: +44 131 242 6517, Fax: +44 131 242 6379, Email: cchin03m@gmail.com

† Equal contribution as first author.

‡ Equal contribution as senior author.

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patients controversial.² This apparent discrepancy might in part be explained by heterogeneity in the hypertrophic response to aortic stenosis, which itself is an independent marker of an adverse prognosis.^{4–6}

Hypertrophy occurs in response to the increased afterload imposed by aortic valve narrowing on the left ventricle. Initially this restores wall stress and maintains cardiac performance, but decompensation ultimately ensues and patients develop symptoms, adverse events, and the need for surgery. The transition from hypertrophy to heart failure is characterized by progressive cardiomyocyte death and replacement fibrosis.⁷ Myocardial fibrosis can be detected using two cardiovascular magnetic resonance (CMR) techniques: late gadolinium enhancement (replacement fibrosis) and T1 mapping (diffuse interstitial fibrosis) with data indicating that the former provides useful prognostic information.^{5,8} However, to date, a marker of myocyte cell death has been lacking.

Cardiac troponin is a structural protein present in cardiac muscle, with plasma troponin concentrations considered a highly specific marker for myocardial injury.⁹ Recent advances in assay technology have greatly improved sensitivity, now allowing quantification of troponin with a high degree of precision at extremely low plasma concentrations.¹⁰

In this study, we hypothesized that detection of myocardial injury by high-sensitivity troponin assays may provide an early indicator of left ventricular (LV) decompensation and be associated with future adverse events in patients with aortic stenosis.

Methods

Two cohorts of stable patients with aortic stenosis were recruited from cardiology outpatient clinics across three centres in Southeast Scotland. First, we determined the association between plasma cardiac troponin I (cTnI) concentrations and LV functional and structural abnormalities on cardiac magnetic resonance (Mechanism Cohort), and second, we examined the prognostic role of plasma cTnI concentrations in patients with aortic stenosis (Outcome Cohort). The study was conducted in accordance with the Declaration of Helsinki and approved by the local research ethics committee. Written informed consent was obtained from all participants.

Patient populations

Mechanism Cohort

Patients with mild to severe aortic stenosis were recruited prospectively. We excluded patients who had other significant (moderate or severe) valvular heart disease or cardiomyopathies (acquired or inherited). Presence of coronary artery disease was defined by previous infarction, clinical symptoms of angina (in those with mild or moderate aortic stenosis), evidence of myocardial ischaemia, or >50% luminal stenosis in a major epicardial vessel. In addition, thirteen age- and sex-matched healthy volunteers without clinically significant heart disease were recruited from the local community.

Outcome Cohort

The Outcome Cohort comprised patients recruited into the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact of REgression (SALTIRE) study. The study design and inclusion and exclusion criteria have been described previously.¹¹ In brief, from March 2001 to April 2002, 155 patients with asymptomatic moderate to severe aortic stenosis were randomly assigned to receive either atorvastatin 80 mg or placebo

once daily. Patients were excluded if they were already on a statin, if AVR was planned, or if they had moderate or severe LV systolic impairment. Only patients with plasma samples available for cTnI analysis were included in the present analysis.

Blood sampling and analysis

In the Mechanism Cohort, brain natriuretic peptide (BNP) concentration was analysed with the Triage BNP assay (Biosite, Inc., San Diego, CA, USA). The inter-assay coefficient of variation was 10% at 28.8 pg/mL, with a detection range of 5–1300 pg/mL.¹² In the Outcome Cohort, N-terminal proBNP (NT-proBNP) concentration was measured using the Elecsys 2010 analyzer (Roche Diagnostics Ltd, Lewes, UK). This assay has <0.001% cross-reactivity with bioactive BNP, and the inter-assay coefficients of variation range from 0.9 to 5.5%.¹³

Plasma cTnI concentrations were determined by the ARCHITECT STAT high-sensitivity cTnI assay (Abbott Laboratories, Abbott Park, IL, USA) in both cohorts. The lower limit of detection of this assay is 1.2 ng/L;¹⁰ the 99th percentile from a healthy reference population is 26 ng/L.¹⁴ Our inter-assay coefficient of variation is 10% at 6 ng/L (see Supplementary material online).

Echocardiography

All participants underwent a comprehensive echocardiographic assessment to determine the severity of aortic stenosis. Peak aortic jet velocity and mean pressure gradient were measured by velocity time integral spectral Doppler, and the aortic valve area derived using the continuity equation. The severity of aortic stenosis was assessed and classified according to the European Association of Echocardiography/American Society of Echocardiology guidelines.¹⁵ Trans-mitral early (E) and late diastolic velocities and deceleration time of early filling velocity were measured at the tips of the mitral valve leaflets using pulse-wave Doppler. Early (e') diastolic velocities of the medial and lateral mitral annulus were measured using pulse-wave tissue Doppler imaging. Diastolic function was determined using the E/e' ratio.

Cardiovascular magnetic resonance in the Mechanism Cohort

Cardiovascular magnetic resonance was performed using a 3T scanner (MAGNETOM Verio, Siemens AG, Healthcare Sector, Erlangen, Germany). Short-axis cine images were obtained using a balanced steady-state free precession sequence from the mitral valve annulus to the apex (8-mm parallel slices with 2 mm spacing) for the assessment of LV function and volumes. LV volumes, mass, and ejection fraction were assessed using dedicated software (Argus Ventricular Function, Siemens AG Healthcare Sector, Erlangen, Germany), and values were indexed to body surface area.

Focal myocardial fibrosis was assessed using the late gadolinium enhancement (LGE) technique, performed 10–15 min following 0.1 mmol/kg of gadobutrol (Gadovist, Bayer Pharma AG, Germany). Two approaches were used: an inversion-recovery fast gradient echo sequence and a phase-sensitive inversion-recovery sequence (performed in two phase-encoding directions for the exclusion of artefact). The inversion time was optimized to achieve satisfactory nulling of the myocardium. Assessment for the presence of mid-wall LGE was determined visually and independently by two experienced operators. The extent of mid-wall LGE was quantified with QMASS software (Medis Medical Imaging Systems, Leiden, the Netherlands) using a signal intensity threshold of >2 standard deviations above the mean value in an adjacent normal region of myocardium. Areas of inversion artefact, or contamination by blood pool or epicardial fat, were excluded.

Myocardial T1 mapping was performed to investigate diffuse myocardial fibrosis using the Modified Look-Locker Inversion-recovery sequence (flip angle 35°; minimum T1 100 ms; T1 increment of 80 ms; time delay of 150 ms with a heartbeat acquisition scheme of 3–3–5).¹⁶ We have previously described a standardized approach for the analysis of myocardial extracellular volume fraction (ECV) in patients with aortic stenosis, demonstrating that it offers improved reproducibility ($\pm 3\%$) and the ability to identify disease states compared with other T1 mapping techniques.¹⁷ In brief, regions of interest were drawn around the myocardium on short-axis pre-contrast motion-corrected myocardial T1 maps and then applied to corresponding 20-min post-contrast maps with minor adjustments made to avoid partial volume effects and artefact (OsiriX version 4.1.1, Geneva, Switzerland). Extracellular volume fraction values were calculated according to: $ECV = [\Delta R1_{\text{myocardium}} / \Delta R1_{\text{blood-pool}}] \times [1 - \text{haematocrit}]$, where $\Delta R1 = (1 / \text{post-contrast T1} - 1 / \text{pre-contrast T1})$. Haematocrit was determined at the time of CMR.

Computed tomography in the Outcome Cohort

Computed tomography calcium scoring of the coronary arteries and aortic valve was performed on ECG-gated non-contrast scans using a double helix scanner (Twin II Flash, Philips Medical Systems). All images were analysed by a single operator using the Picker Cardiac Scoring software as previously described.¹¹

Follow-up in the Outcome Cohort

Clinical outcomes were obtained and adjudicated by two independent investigators blinded to plasma cTnI and BNP concentrations. All in-hospital and community deaths were captured in a comprehensive national database: the General Register of Scotland. Cardiovascular death was based on the cause of death stated on the death certificate. We defined cardiovascular death as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, death due to cardiovascular procedures, and death due to other cardiovascular causes. Each death was classified as cardiac or non-cardiac by two independent investigators and any discrepancy resolved by consensus. All events were confirmed by independent review of each patient's electronic healthcare record where available. Surgical AVR (no patients underwent transcatheter aortic valve implantation in the follow-up period) was determined from individual patient medical records. All patients in the Outcome Cohort were managed in the tertiary cardiac centre, where patients are reviewed at a multi-disciplinary meeting prior to undergoing cardiac surgery. Only patients with established indications were referred for AVR according to the European Society of Cardiology recommendations.^{2,18}

Statistical analysis

Baseline characteristics are reported as percentages for categorical variables, mean \pm standard deviation or median [interquartile range], as appropriate. We used one-way analysis-of-variance to compare continuous parametric data and the Kruskal–Wallis test for non-parametric data. Chi-square tests were used for categorical baseline characteristics. Analyses were performed in R version 2.15.2 (Vienna, Austria) and SPSS Version 20.0.0 (Armonk, NY, USA: IBM Corp). Statistical significance was taken as a two-sided $P < 0.05$.

Mechanism Cohort

We assessed the association of plasma cTnI concentrations with measures of aortic stenosis and ventricular remodelling using univariate and

multivariable linear regression models. Plasma cTnI concentrations were log-transformed as this variable was highly skewed.

Outcome Cohort

Kaplan–Meier analysis was performed across tertiles of cTnI concentrations. To accommodate competing risks, the association between time to AVR or cardiovascular deaths and plasma cTnI concentrations (log-transformed [base 2]) was modelled as a composite endpoint in Cox proportional hazard models.

Furthermore, we examined whether relative change in cTnI concentrations at 1 year (cTnI at 1 year—baseline cTnI, both log-transformed) was associated with increased odds of an event at 3-year and 5-year follow-up independent of baseline cTnI concentrations (results in Supplementary material online).

Results

We recruited 122 patients into the Mechanism Cohort (71 [65–77] years, 67% males, aortic valve area $1.0 \pm 0.4 \text{ cm}^2$) and analysed 131 patients in the Outcome Cohort (69 [62–75] years, 70% males, aortic valve area $1.1 \pm 0.4 \text{ cm}^2$) (Tables 1 and 2). Thirteen healthy volunteers were recruited, who were well matched in terms of age (65 [57–75] years) and sex (62% male) compared with the other groups and did not have any history of diabetes mellitus, hypertension, or coronary artery disease.

Plasma cTnI concentrations above the lower limit of detection of 1.2 ng/L were present in 98% of our patients with aortic stenosis and increased in both cohorts compared with the healthy volunteers (Mechanism Cohort 6.6 [3.8–12.0] ng/L; Outcome Cohort 7.6 [5.7–13.2] ng/L; healthy volunteers 3.2 [1.3–11.0] ng/L). The distribution of plasma cardiac troponin I concentrations was skewed in a similar pattern across the two cohorts (see Supplementary material online). There were 10 patients (8.1%) in the Mechanism Cohort and 10 patients (7.6%) in the Outcome Cohort with plasma cTnI concentrations of $> 26 \text{ ng/L}$ (the 99th percentile derived from the healthy reference population). There was no difference in renal function across tertiles of cTnI in patients with aortic stenosis.

Mechanism for increased cardiac troponin I concentrations

In the Mechanism Cohort, patients with aortic stenosis had an increased LV mass index compared with healthy controls, although there was no difference in LV volumes or ejection fraction (Table 1). Furthermore, these patients had higher ECV values (27.7 ± 2.5 vs. $25.9 \pm 1.6\%$, $P = 0.01$), and 35 patients (28%) had a mid-wall pattern of LGE: an observation not seen among the healthy volunteers (Figure 1).

Plasma cTnI concentrations correlated with LV mass index, independent of coronary artery disease status ($r = 0.50$, $P < 0.001$; Figure 2). A weaker correlation was also observed between plasma cTnI concentrations and peak aortic jet velocity ($r = 0.32$, $P < 0.001$). Furthermore, patients with aortic stenosis and mid-wall LGE had a two-fold increase in plasma cTnI concentrations compared with those without (9.5 [5.7, 20.3] ng/L vs. 4.3 [3.3, 7.9] ng/L, $P = 0.02$; Figure 3).

With univariate analysis, age, mean pressure gradient, mean e' , the LV mass index, and measures of both diffuse and replacement fibrosis

Table 1 Baseline characteristics of patients with aortic stenosis in the Mechanism Cohort

	Healthy volunteers (n = 13)	Mechanism Cohort (n = 122)	P-value
Clinical characteristics			
Age, years	65 [57, 75]	71 [65, 77]	0.13
Male sex, n (%)	8 (62)	82 (67)	0.76
Diabetes mellitus, n (%)	0	14 (11)	–
Hypertension, n (%)	0	78 (63)	–
CAD, n (%)	0	41 (33)	–
SBP, mmHg	148 ± 12	149 ± 20	0.35
NYHA class, n (%)			
I	13 (100)	63 (52)	–
II	0	35 (28)	
III	0	24 (20)	
Creatinine, µmol/L	69 ± 8	78 ± 17	0.06
Cardiac troponin I concentration, ng/L	3.2 [1.3, 11.0]	6.6 [3.8, 12.0]	0.03
BNP, pg/mL	10.3 [5.6, 18.1]	26.4 [10.6, 53.9]	0.009
Echocardiography			
V _m , m/s	1.4 ± 0.2	3.7 ± 0.9	<0.001
MPG, mmHg	4 ± 1	32 ± 18	<0.001
AVA, cm ²	2.4 ± 0.7	1.0 ± 0.4	<0.001
Valvulo-arterial impedance, mmHg/mL/m ²	4.5 ± 1.1	4.5 ± 1.2	0.96
Mean e', cm/s	8.1 ± 2.7	6.2 ± 1.9	0.001
Mean E/e'	7.9 ± 2.2	14.8 ± 8.1	0.003
Cardiac MRI			
Indexed EDV, mL/m ²	73 ± 13	72 ± 14	0.71
Indexed ESV, mL/m ²	27 ± 7	24 ± 9	0.28
Indexed SV, mL/m ²	46 ± 7	48 ± 9	0.68
Ejection fraction, %	64 ± 3	67 ± 7	0.12
Indexed LVM, g/m ²	70 ± 14	89 ± 22	0.004
LVM/EDV, g/mL	0.96 ± 0.13	1.26 ± 0.28	<0.001
ECV, %	25.9 ± 1.6	27.7 ± 2.5	0.01

CAD, coronary artery disease; SBP, systolic blood pressure; BNP, brain natriuretic peptide; V_m, peak aortic jet velocity; MPG, mean pressure gradient; AVA, aortic valve area; EDV, end diastolic volume; ESV, end systolic volume; LVM, left ventricular mass; ECV, extracellular volume fraction; %LGE, amount of late gadolinium enhancement.

were all associated with plasma cTnI concentrations (Table 3; all $P < 0.05$). However, only age, LV mass index, and %LGE were independently associated with plasma cTnI concentrations (Model 1; Table 3).

Interestingly, there was no difference in plasma cTnI concentrations between patients with and without coronary artery disease (6.9 [4.0, 13.5] ng/L vs. 6.2 [3.5, 10.0] ng/L, $P = 0.28$). This was supported by data from the Outcome Cohort where no correlation was observed between the coronary calcium scores and plasma cTnI concentrations ($r = -0.03$, $P = 0.71$).

Prognostic value of cardiac troponin I concentrations

Patients in the Outcome Cohort were stratified by tertiles of plasma cTnI concentration (Table 2). In comparison with the lowest tertile, patients in the highest tertile were older (70 ± 9 vs. 64 ± 12 years, $P = 0.03$) and had an increased ventricular mass (393 ± 100 vs.

327 ± 111 g, $P = 0.02$). However, there were no differences in comorbidity, severity of aortic stenosis, or coronary calcium scores across the tertiles ($P > 0.1$ for all; Table 2).

Over a median of 10.6 years of follow-up (1178 patient-years), 60 patients had an AVR, 24 died from a cardiovascular cause, and 47 died from non-cardiovascular causes. Ten-year event-free survival rate for AVR or cardiovascular deaths differed across the tertiles of cTnI concentrations (log rank test for trend, $P = 0.016$, Figure 4). Plasma cTnI concentration was associated with an increased risk of AVR or cardiovascular deaths in unadjusted analysis (HR 1.65 per two-fold increment in cTnI concentration; 95% CI, 1.15–2.38, $P = 0.007$) with minimal attenuation in the effect estimate after adjusting for age, sex, and ejection fraction (Table 4). Moreover, this association persisted after further adjustment for severity of aortic stenosis (HR 1.77; 95% CI, 1.22–2.35, $P = 0.002$) as well as the coronary artery and aortic valve calcium scores (HR 2.10; 95% CI, 1.22–3.61, $P = 0.007$).

Table 2 Characteristics of patients in the Outcome Cohort by tertiles of troponin I concentrations

	All patients (n = 131)	Tertile 1 (≤6.3 ng/L) (n = 42)	Tertile 2 (6.4–10.6 ng/L) (n = 45)	Tertile 3 (≥10.7 ng/L) (n = 44)	P-value
Clinical characteristics					
Age, years	67 ± 10	64 ± 12	69 ± 10	70 ± 9	0.03
Male sex, n (%)	91 (70)	24 (57)	32 (71)	35 (79)	0.08
Diabetes Mellitus, n (%)	4 (3)	1 (2)	1 (2)	2 (5)	–
Hypertension, n (%)	66 (50)	18 (43)	22 (49)	26 (59)	0.31
CAD, n (%)	22 (16)	6 (14)	7 (16)	9 (21)	0.72
SBP, mmHg	145 ± 20	139 ± 17	148 ± 21	146 ± 19	0.07
NYHA class, n (%)					
I	117 (89)	38 (90)	41 (91)	38 (86)	0.53
II	14 (11)	4 (10)	4 (9)	6 (14)	
Creatinine, μmol/L	91 ± 21	86 ± 17	92 ± 20	95 ± 25	0.12
NT-pro-BNP, pg/mL	198.0 [113.5, 530.5]	129.5 [76.3, 228.0]	180.0 [89.0, 416.0]	507.0 [181.5, 1103.0]	0.008
Echocardiography					
V _m , m/s	3.4 ± 0.7	3.4 ± 0.6	3.4 ± 0.6	3.5 ± 0.7	0.45
MPG, mmHg	26 ± 11	25 ± 10	25 ± 10	28 ± 13	0.35
AVA, cm ²	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	0.72
Indexed AVA, cm ² /m ²	0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.66
LVM, g	357 ± 107	327 ± 111	350 ± 102	393 ± 100	0.02
Indexed LVM, g/m ²	180 ± 50	165 ± 54	172 ± 49	196 ± 49	0.06
Fractional shortening, %	40 ± 8	42 ± 9	42 ± 8	37 ± 6	0.004
Ejection fraction, %	70 ± 10	72 ± 11	72 ± 9	66 ± 8	0.007
LVH, n (%)	109 (95)	34 (81)	36 (80)	39 (89)	0.49
Impaired LVEF <50%, n (%)	4 (3)	1 (2)	2 (4)	2 (5)	0.84
Computed tomography					
Coronary calcium score, log AU	1.6 ± 1.3	1.5 ± 1.3	1.5 ± 1.3	1.8 ± 1.1	0.53
Aortic valve calcium score, log AU	3.6 ± 0.6	3.6 ± 0.5	3.6 ± 0.5	3.7 ± 0.8	0.61

CAD, coronary artery disease; SBP, systolic blood pressure; BNP, brain natriuretic peptide; V_m, peak aortic jet velocity; MPG, mean pressure gradient; AVA, aortic valve area; EDV, end diastolic volume; ESV, end systolic volume; LVM, left ventricular mass; LVH, left ventricular hypertrophy, based on ASE/EAE sex-specific criteria; LVEF, left ventricular ejection fraction.

Mechanism and prognosis associated with BNP concentrations

Serum BNP concentrations were higher in patients with aortic stenosis compared with healthy volunteers (26.4 [10.6,53.9] vs. 10.3 [5.6,18.1] ng/mL, $P = 0.009$; Table 1). In patients with aortic stenosis, BNP concentrations increased with age, disease severity, diastolic dysfunction, LV mass index myocardial fibrosis, the presence of coronary artery disease, and symptoms (all $P < 0.05$; see Supplementary material online). However, on multivariable analysis, only age was significantly associated with BNP concentrations ($P < 0.001$; see Supplementary material online).

In the Outcome Cohort, NT-proBNP was not associated with AVR or cardiovascular deaths in both unadjusted (HR 1.15 per two-fold increment in NT-proBNP concentration; 95% CI, 0.86–1.53, $P = 0.34$) and adjusted analyses (see Supplementary material online). Importantly, NT-proBNP concentration did not modify the association between troponin and time to AVR or cardiovascular deaths (HR 1.60; 95% CI 1.10–2.34, $P = 0.01$).

Discussion

This is the first dataset to explore mechanisms and outcomes associated with cTnI concentrations using a high-sensitivity assay in patients with aortic stenosis. In more than 250 patients with aortic stenosis, we have demonstrated that levels are detectable in 98% of subjects and increased compared with age- and sex-matched healthy volunteers. Plasma cTnI concentrations were not associated with the presence of co-existent coronary artery disease or the severity of valve narrowing on multivariable analysis. Instead, plasma cTnI concentrations demonstrated a close association with the magnitude of LV hypertrophy and the presence of mid-wall myocardial fibrosis. Moreover, high-sensitivity plasma cTnI concentration showed an independent association with long-term risk of AVR or cardiovascular deaths. We therefore believe that high-sensitivity plasma cTnI concentrations hold potential as an objective marker of LV decompensation in patients with aortic stenosis and as a potential early trigger to AVR.

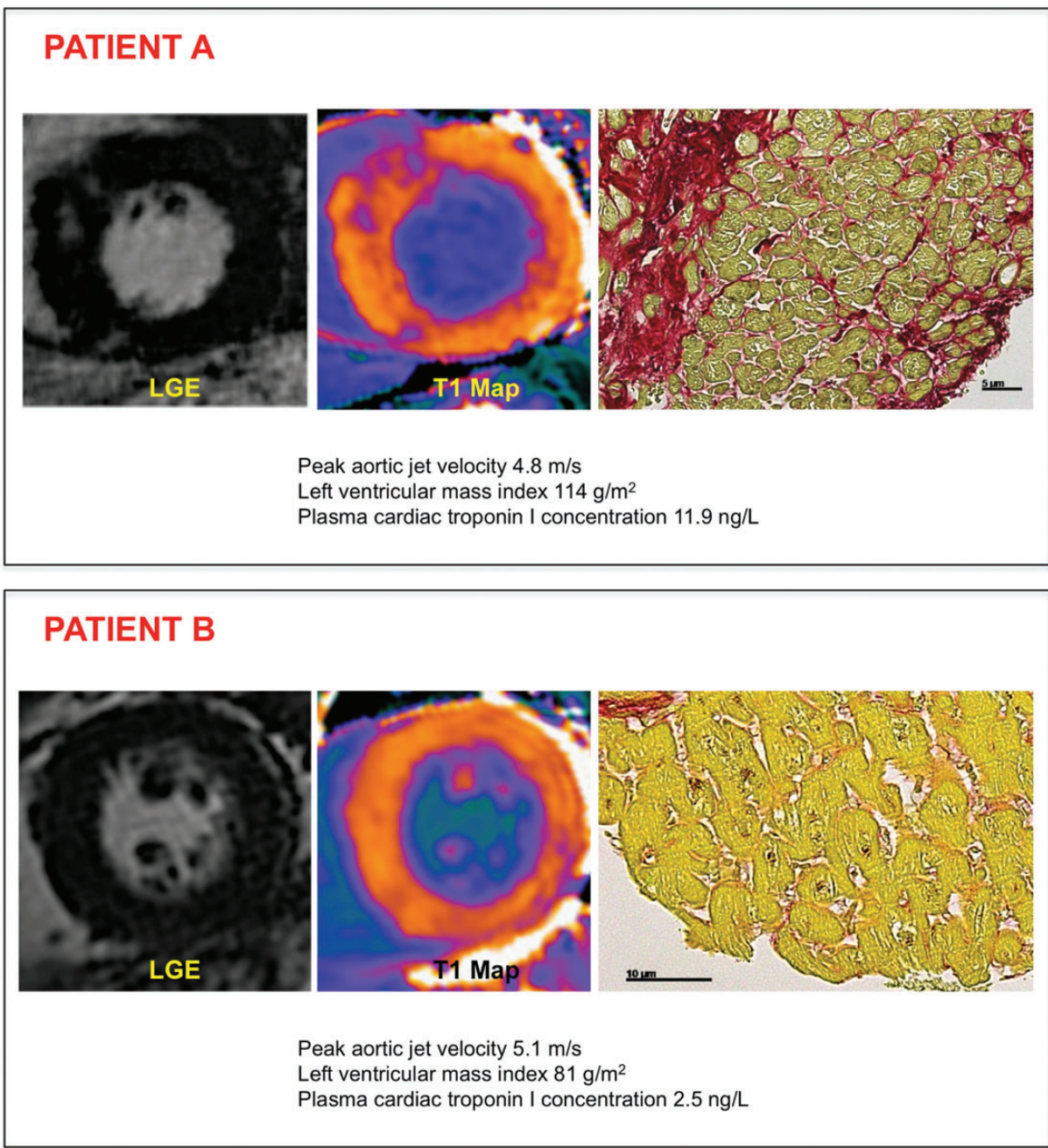


Figure 1 Comparison of two patients with severe aortic stenosis. Both had similar severity of aortic valve narrowing (peak aortic jet velocity in Patient A was 4.8 m/s and Patient B 5.1 m/s) and neither had significant coronary artery disease. However, the high-sensitivity troponin I concentration was more than four-fold higher in Patient A (11.9 ng/L) compared with Patient B (2.5 ng/L), consistent with the more advanced hypertrophic response observed in this patient (left ventricular mass index in Patient A was 114 g/m² and Patient B was 81 g/m²). Furthermore, Patient A had evidence of focal mid-wall fibrosis on late gadolinium imaging (LGE) and myocardial T1 mapping (Patient B did not) and more extensive collagen staining with picosirius red staining on myocardial biopsy.

Aortic stenosis is defined not only by the development of progressive valve narrowing but also by the LV hypertrophic response that ensues. Whilst this initially restores wall stress, decompensation due to progressive cell death and fibrosis ultimately occurs and patients transition from hypertrophy to heart failure.⁴ Because of

the associated adverse prognosis, current guidelines recommend surgery in patients with severe stenosis and evidence of such decompensation, detected either on the basis of symptom development or an ejection fraction of <50%. Unfortunately, symptoms are often frequently difficult to assess whereas an ejection fraction of <50%

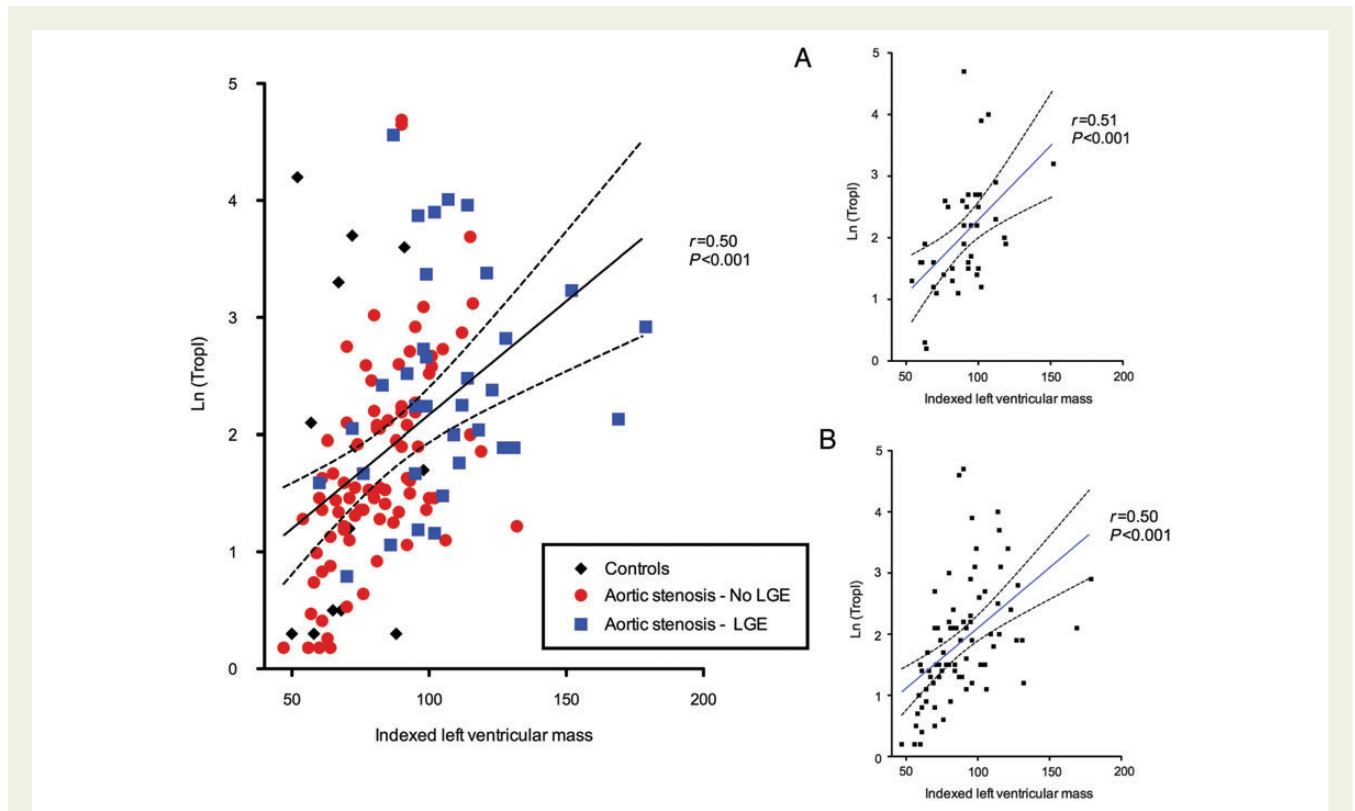


Figure 2 Correlation between indexed left ventricular mass and plasma cardiac troponin I concentrations (log-transformed). Similar correlation was seen in patients with (A) and without (B) coronary artery disease.

occurs late in the disease process and is often irreversible. There is therefore emerging interest in developing novel, objective biomarkers of decompensation for patients with aortic stenosis. Data from our study suggests that troponin has the potential to be such a marker.

To date elevated cardiac troponin has been considered the *sine qua non* for the diagnosis of myocardial infarction.¹⁹ However, marked improvements in assay sensitivity now allow quantification of plasma cTnI concentrations in the majority of the healthy population.¹⁰ In our study, cTnI was detectable in 98% of patients with aortic stenosis and exceeded the recommended diagnostic threshold for myocardial infarction in 7.9%. Patients with stable coronary disease have been reported to have higher plasma troponin concentrations, with elevated levels being associated with long-term cardiovascular risk.²⁰ However in our cohort of patients with aortic stenosis, there were no differences in plasma troponin concentrations between those with and without coronary artery disease. Instead plasma troponin concentrations were independently associated with an advanced hypertrophic response and replacement myocardial fibrosis. Indeed, the latter occurred over and above the effects of LV mass, supporting our hypothesis that cTnI release relates to the myocardial injury that accompanies ventricular decompensation and myocardial fibrosis.

The poor prognosis associated with increased troponin concentrations offers further support for this model. At 10 years, more than a half of patients in the highest tertile of plasma cTnI had undergone an AVR or died from cardiovascular disease. Moreover, plasma

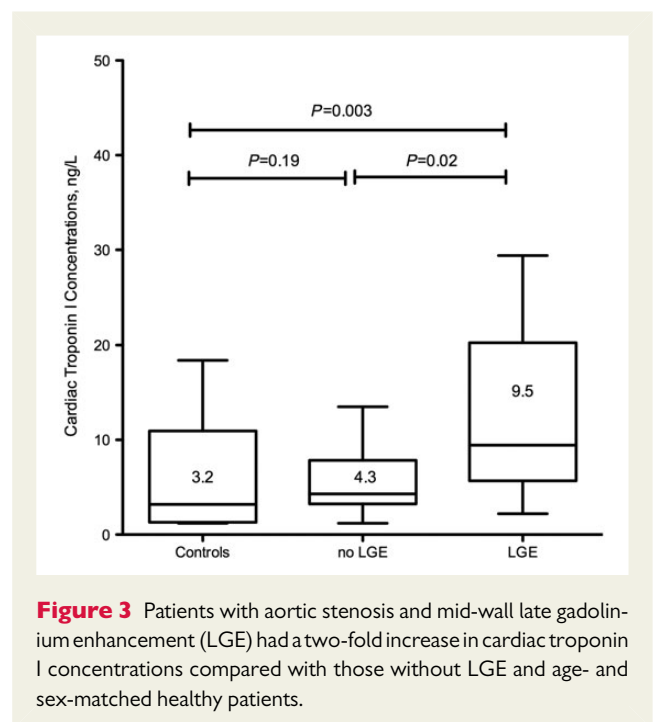


Figure 3 Patients with aortic stenosis and mid-wall late gadolinium enhancement (LGE) had a two-fold increase in cardiac troponin I concentrations compared with those without LGE and age- and sex-matched healthy patients.

cTnI concentrations were associated with AVR or cardiovascular deaths, independent of the burden of coronary atherosclerosis (as assessed using coronary calcium scoring) as well as age, sex,

Table 3 Univariate and multivariable linear regression analysis to examine association of variables with plasma cardiac troponin I concentrations

Variables	Univariate		Multivariable—Model 1 (included %LGE)		Multivariable—Model 2 (included ECV)	
	Relative change in troponin I concentration (95% CI)	P-value	Relative change in troponin I concentration (95% CI)	P-value	Relative change in troponin I concentration (95% CI)	P-value
Age, per 10 years	1.32 (1.07–1.44)	0.004	1.49 (1.14–1.80)	0.002	1.36 (1.09–1.72)	0.006
Male sex	1.31 (0.90–1.92)	0.16	0.79 (0.44–1.42)	0.44	0.80 (0.46–1.39)	0.42
Diabetes mellitus	0.92 (0.52–1.61)	0.76				
Hypertension	1.21 (0.83–1.74)	0.33				
CAD	1.20 (0.82–1.75)	0.35	1.01 (0.58–1.73)	0.96	1.17 (0.72–1.91)	0.53
MPG, per 10 mmHg	1.17 (1.02–1.35)	0.02	0.92 (0.79–1.06)	0.27	0.93 (0.73–1.06)	0.28
Mean e', cm/s	0.86 (0.78–0.95)	0.002	1.08 (0.93–1.27)	0.30	1.02 (0.88–1.19)	0.78
Indexed LVM, per 10 g/m ²	1.23 (1.15–1.32)	<0.001	1.34 (1.15–1.55)	<0.001	1.41 (1.23–1.62)	<0.001
%LGE, %	1.13 (1.08–1.17)	<0.001	1.11 (1.03–1.19)	0.006		
ECV, %	1.15 (1.07–1.23)	<0.001			1.11 (1.00–1.21)	0.05

See Table 1 for abbreviations.

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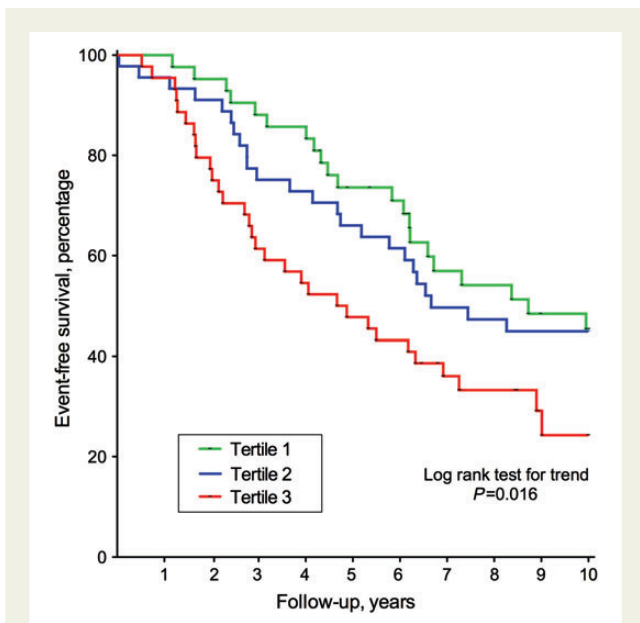


Figure 4 Ten-year event-free survival for composite endpoint of aortic valve replacement or cardiovascular death by tertiles of cardiac troponin I concentrations. Patients in the highest tertile were associated with lower survival rates compared with patients in the other tertiles (log rank test for trend, $P = 0.016$).

Table 4 Hazard ratios predicting time to valve replacement or cardiovascular death for troponin I concentrations in adjusted and unadjusted analyses

Model	Hazard ratio (95% CI)	P-value
Model 1	1.65 (1.15–2.38)	0.007
Model 2	1.61 (1.11–2.35)	0.01
Model 3	1.63 (1.11–2.38)	0.01
Model 4	1.77 (1.22–2.55)	0.002
Model 5	2.10 (1.22–3.61)	0.007

Model 1—unadjusted; Model 2—adjusting for age and sex; Model 3—as model 2 additionally adjusting for systolic ejection fraction; Model 4—as model 2 additionally adjusting for mean pressure gradient; Model 5—as model 2 additionally adjusting for coronary and aortic valve calcium score.

systolic ejection fraction, echocardiographic measures of aortic stenosis severity, and the aortic valve calcium score.

A recent study demonstrated an association between high-sensitivity cardiac troponin T concentrations and echocardiographic measures of LV modelling in aortic stenosis.²¹ Our data confirm and

extend these findings using CMR, which has allowed us to investigate the remodelling response in greater detail and crucially assess the relationship with myocardial fibrosis, thereby providing additional mechanistic data. We therefore believe that the plasma cTnI concentration measured by a high-sensitivity assay has considerable potential as an early biomarker of LV decompensation and as a powerful prognostic tool in patients with aortic stenosis. Moreover, this test is inexpensive and easy to perform making any future transition into routine clinical practice readily achievable. However, considerable overlap was observed between patients with aortic stenosis and our control cohort. This is perhaps unsurprising, given cTnI is released as a consequence of a wide range of myocardial insults. A future strategy where asymptomatic aortic stenosis patients with elevated or increasing plasma troponin concentrations subsequently proceed to CMR for confirmation of myocardial fibrosis and LV

decompensation is therefore attractive. Large-scale prospective studies are now required to investigate the use of these two biomarkers in the management and risk stratification of patients with aortic stenosis and whether the above approach might identify asymptomatic patients who would benefit from early surgery.

In contrast to troponin, BNP did not have prognostic value in our study. BNP is an endogenous cardiac hormone released in response to increasing LV wall stress and most commonly used in the assessment of patients with heart failure. It is therefore only likely to be released late in the transition from hypertrophy to heart failure, making it of limited value in detecting signs of early decompensation in asymptomatic patients. Given that this is the group in whom novel biomarkers of LV decompensation are most likely to be useful, we believe that troponin holds greater clinical promise than BNP.

Limitations

CMR was not available at the inception of the SALTIRE study. Therefore, we needed to recruit another patient population to investigate the mechanism for troponin release in aortic stenosis. However, plasma cTnI concentrations in the Outcome Cohort also displayed a close association with LV mass determined by echocardiography and were unrelated to the burden of coronary atherosclerosis or the severity of valvular stenosis. Similar mechanisms would therefore seem to govern cTnI release across both groups. Another limitation is the lack of more sensitive markers of LV systolic dysfunction in the Mechanism Cohort, for example CMR tagging techniques. However, we elected not to perform these due to concerns about lengthening the scanning protocol in this elderly cohort of patients and compromising the detection of myocardial fibrosis. Finally, data on short-term biological variability (the change in concentration from one occasion to another) are very limited in disease states. However, we do not anticipate significant short-term variability in chronic conditions such as aortic stenosis, although this will require further validation.

Conclusions

In patients with aortic stenosis, plasma cTnI concentrations are a marker of LV decompensation and myocardial fibrosis that are associated with cardiovascular deaths and AVR. High-sensitivity troponin assays hold major promise as a future clinical tool for patients with this condition.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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