

TABLE 3 – Univariable Predictors of Outcome.

At median follow-up of 2.3 years (0.02-4.7 years), 11 calcific aortic stenosis (cAS) patients had died whereas all of the bicuspid aortic stenosis (bAS) patients were alive. On multivariate analysis, the presence of ATTR amyloid had the highest hazard ratio for death (HR [95% CI], $p=0.001$, univariable Cox regression analysis).

	cAS and bAS (n=146) HR (95%CI)	<i>p-value</i>	cAS (n=11) HR (95%CI)
ATTR amyloid deposits	9.5 (2.5-35.8)	0.001	6.5 (1.7-24.5)
Age (years)	1.1 (1.02-1.23)	0.02	1.1 (1.02-1.23)
Gender	1.8 (0.5-6.9)	0.37	1.9 (0.5-6.9)
Aortic Valve			
Peak Velocity (m/sec)	0.5 (0.2-1.1)	0.09	0.5 (0.2-1.1)
Mean Gradient (mmHg)	0.96 (0.92-1.00)	0.06	0.96 (0.92-1.00)
Area, indexed (cm/m²)	0.42 (0.01-23.2)	0.7	0.6 (0.01-23.2)
CMR parameters			
LVEF (%)	0.97 (0.94-1.00)	0.07	0.97 (0.94-1.00)
LV mass, indexed (g/m²)	1.03 (1.00-1.52)	0.05	1.03 (1.00-1.52)
Myocardial Contraction Fraction (%)	0.04 (0.001-1.74)	0.10	0.07 (0.001-1.74)
Blood parameters			
NT-proBNP, pmol/L	2.1 (1.3-3.6)	0.004	2.2 (1.3-3.6)
eGFR, ml/min/1.73 m²	0.99 (0.97-1.03)	0.8	1.0 (0.97-1.03)

FIGURES

Figure 1: Myocardial biopsy of patient with severe aortic stenosis and widespread overt myocardial ATTR amyloid deposits. Histological slides stained with Congo red under brightfield light (Congo Red), under cross polars with typical apple green birefringence (AGB) and under fluorescent (FL) microscopy. Separate slide prepared by transthyretin-specific immunohistochemistry (TTR) showing widespread ATTR amyloid staining (brown).

Figure 2: Myocardial biopsy of patient with severe aortic stenosis without clinical evidence of cardiac amyloid. Histological slides stained with Congo red under brightfield light (Congo Red), under cross polars with typical apple green birefringence (AGB) and under fluorescent (FL) microscopy. Separate slide prepared by transthyretin-specific immunohistochemistry (TTR). All showing patchy ATTR amyloid deposits.

Figure 3: Multi-modality imaging of patient with clinical features of cardiac amyloidosis. Although the echocardiogram showed left ventricular hypertrophy (B), this was attributed to the myocardial response to severe aortic stenosis. DPD scintigraphy showed Perugini Grade 2 cardiac uptake on bone scan (C) and SPECT (B). Cardiac magnetic resonance showed overt left ventricular hypertrophy and impaired systolic function on cine imaging (D), and transmural late gadolinium enhancement with higher signal from the myocardium than the blood pool (E).

Figure 4: Multi-modality imaging of patient with amyloid deposits on biopsy but no clinical features of amyloidosis. Neither pre-operative echocardiogram nor CMR highlighted any features consistent with cardiac amyloidosis. DPD scintigraphy showed Perugini Grade 1 cardiac uptake on bone scan (C – there is subtle uptake in the basal third of the left ventricle [see arrows]), which is more obvious on SPECT (B). There was no left

ventricular (LV) hypertrophy and good LV systolic function on CMR cine imaging (D), and only subtle patchy, non-ischemic late gadolinium enhancement in the basal lateral wall (E).

Figure 5: Kaplan-Meier plot of cumulative survival comparing aortic stenosis patients (n=146) with ATTR amyloid on myocardial biopsy and those without. At median follow-up of 2.3 years (0.02-4.7 years), 11 patients with calcific aortic stenosis (AS) had died whereas all patients with bicuspid AS were alive. Three out of six cAS with wild-type ATTR amyloid (50%) died compared to 8 out of 106 (7.5%) in the remaining calcific AS cohort.