Prognostic Significance of Cardiac Amyloidosis in Patients with Aortic Stenosis: a Systematic Review and Meta-Analysis.

Running title: Prognosis of dual aortic stenosis and amyloid pathology.

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Aortic stenosis (AS) and transthyretin cardiac amyloidosis (CA) are common conditions affecting the elderly and both carry high morbidity and mortality, particularly if left untreated. Dual AS-CA pathology is getting increasingly recognized, but with uncertain prognostic significance[1, 2].

We performed a systematic review and meta-analysis to clarify whether concurrent transthyretin CA portends excess mortality in patients with AS and to explore potential factors explaining outcome variability reported in the literature.

Our systematic review sought observational studies published through April 2020 reporting summary-level outcome data of all-cause mortality in AS patients with or without concurrent CA. Pooled estimate of Mantel-Haenszel odds ratio (ORs) and 95% confidence interval (CI) for all-cause death was assessed under random- and fixed-effect models. Heterogeneity of the effect across studies was evaluated using Cochran's Q and I^2 statistics. To address the source of the between-study heterogeneity and to explore the effect of clinically-relevant baseline covariates on the association between dual AS-CA pathology and all-cause death, we performed a study-level random-effect model meta-regression analysis and a subgroup analysis stratified by maximum left ventricular wall thickness (LVWT).

We identified 4 studies[2-5] including 609 AS patients (9% AS-CA; 69% men; age, 80±5 years). Of these, 55 (9%) had dual AS-CA pathology (100% transthyretin CA) and 554 (91%) had lone AS. Mean follow-up duration was 20±5 months. Overall, 17 (30%) and 108 (19%) patients died in the AS-CA and lone AS pooled study groups, respectively. The four included studies were accepted by the appropriate Institutional Review Board at main study site. Compared with lone AS, AS-CA was associated with a two-fold increase in all-cause mortality (random-effect model pooled OR: 2.30; 95%CI:1.02-5.18; I^2=62%; P=0.04; fixed-effect model pooled OR: 2.03; 95%CI:1.25-3.30; I^2=62%; P=0.004) (Figure 1A). Meta-regression analysis identified maximum LVWT as the sole significant effect modifier of the

association between dual pathology and mortality (P=0.009), showing stronger relationship proportional to the degree of LVWT (Figure 1B), particularly regardless of age, left ventricular ejection fraction (LVEF) and aortic valve replacement (AVR). In subgroup analysis, pooled ORs (95% CI) for all-cause mortality were 1.29 (0.65-2.22) for maximum LVWT <16 mm and 4.81 (2.19-10.56) for maximum LVWT ≥16 mm (test for subgroup interaction P =0.006; I^2=86.5%) (Figure 1A).

Overall, our study-level meta-analysis provides evidence of a significant association between CA and risk of all-cause death in the context of AS, demonstrating a two-fold excess mortality in patients with dual pathology compared with lone AS. Notably, greater LVWT, as a reflection of disease severity, was significantly related with adverse outcome and explained much of the observed between-study variance. In patients with dual pathology, there have been uncertainties as to which disease process was the primary driver of poor outcome. Chacko et al. demonstrated the independent prognostic role of severe AS in the setting of transthyretin CA reporting a two-fold excess mortality[1]. However, the combination of evidence by which dual pathology yields higher mortality compared with both lone AS[2-5] and lone transthyretin CA[1], would rather favour the hypothesis of an interaction between the two diseases inducing or worsening adverse cardiac remodeling and synergistically affecting mortality.

In conclusion, transthyretin CA heralds significantly higher risk of all-cause death in elderly patients with AS and the degree of maximum LVWT appears to be a major prognostic determinant in patients with dual pathology, regardless of age, LVEF and AVR. Pending further evidence from randomized controlled trials on the efficacy of both amyloid- and valve-directed therapies across different disease severity phenotypes, therapeutic decisions in patients with dual pathology should be evaluated by local heart team and the benefit-risk ratio discussed with each patient individually.

References

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Figure Legend

Figure 1. All-cause mortality. (A) Outcome comparison in patients with aortic stenosis and cardiac amyloidosis versus lone aortic stenosis. (B) Study-level meta-regression analysis describing the effect of maximum LV wall thickness on all-cause mortality.