



Cardiac Amyloidosis Screening in Aortic Stenosis: Prevalence, Imaging Strategy and Its Effect on Valve Decisions

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Introduction

Severe aortic stenosis (AS) and transthyretin cardiac amyloidosis (ATTR-CA) share a patient: elderly, often frail, and increasingly referred for transcatheter aortic valve replacement (TAVR). For years the two conditions were considered separately, with amyloidosis treated as a rare confounder to be excluded rather than a common fellow traveller to be actively sought. Bone-avid scintigraphy tracers -- 99mTc-pyrophosphate (PYP) in North America, 99mTc-DPD in Europe -- changed that picture by making non-invasive diagnosis of ATTR-CA practical at scale, and a series of screening studies in AS and TAVR cohorts has since converged on a consistent, uncomfortable finding: concomitant ATTR-CA is common, not rare, once a valve team actually looks for it.

This review sets out what systematic screening in AS and TAVR populations has actually found, how the imaging strategy for confirming ATTR-CA is structured, and what dual pathology means for the decision between TAVR, surgical AVR (SAVR), and medical management -- while being explicit about where the evidence is still thin.

The clinical stakes are real. AS and ATTR-CA produce overlapping phenotypes -- concentric hypertrophy, reduced longitudinal strain, low-flow physiology -- so amyloidosis can masquerade as simply advanced AS-related remodelling unless specifically screened for. Missing it means a patient with the wrong prognostic label and no access to amyloid-specific

disease-modifying therapy; but screening everyone with severe AS is also not free, in scan time, incidental findings, or cost, which is itself an active subject of modelling rather than settled practice.

Material and Methods

This is a narrative review drawing on prospective screening cohorts (Castano et al., Nitsche/Scully et al., Cavalcante et al.), two independent systematic reviews and meta-analyses (Arshad et al., Myasoedova et al.), a state-of-the-art imaging review (Jaiswal et al.), an echocardiographic strain sub-study (the AMYTAVI study), and a formal cost-effectiveness model of ATTR-CA diagnostic strategies (Ge et al.), identified through targeted literature search and citation tracking between them, without a pre-registered protocol or systematic search string. All prevalence figures, hazard ratios, odds ratios, and cost estimates reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated beyond what the source itself reports.

Results

Prevalence: consistently double-digit once systematically sought

Castano et al. screened 151 elderly patients (mean age 84 years) undergoing TAVR with 99mTc-PYP scintigraphy within 30 days of the procedure and found 16% (24/151) screened positive for ATTR-CA, with reduced mitral annular tissue-Doppler s' velocity (≤ 6 cm/s) the strongest single predictor and a strong male predominance (91.7% of positive patients) [1]. In a larger, 407-patient multicentre cohort using 99mTc-DPD scintigraphy, Nitsche, Scully, and colleagues found DPD-positive uptake (Perugini grade 1-3) in 11.8% (48/407), of whom 7.9% (32/407) showed grade 2/3 uptake diagnostic of ATTR-CA and 3.9% (16/407) showed equivocal grade-1 uptake, one of which proved to be light-chain (AL) rather than transthyretin amyloidosis on further work-up [2]. Cavalcante et al. screened 113 consecutive AS patients by cardiac MRI and found CA in 8% overall (9/113), rising to 16% (9/57) among patients above the cohort's median age of 74 years, and to 32% (8/25) when restricted to men in that older half [3]. Figure 1 sets these headline figures out side by side, alongside the two pooled estimates below.

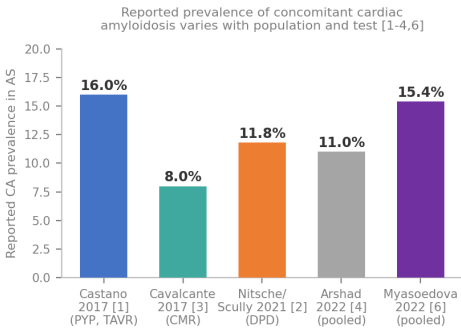


Figure 1: Reported prevalence of concomitant cardiac amyloidosis across five key studies in aortic stenosis, by screening method [1-4,6].

Two independent meta-analyses converge on a similar order of magnitude despite covering different but overlapping study sets: Arshad et al. pooled 9 studies totalling 1,321 AS patients, of whom 131 had concomitant CA, for a pooled prevalence of 11% [4]; Myasoedova et al. pooled 17 studies totalling 1,988 subjects (1,658 AS alone, 330 AS+CA) for a mean prevalence of 15.4%, stratified as 7.1% under 80 years and 18.2% at or beyond 80 years [6]. Figure 2 sets this age gradient out directly, together with Cavalcante's own age- and sex-stratified findings, and Table 1 summarises the five studies' design and headline numbers together.

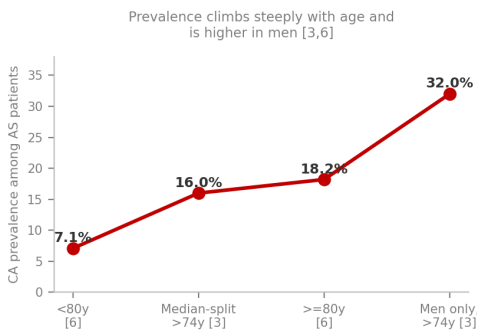


Figure 2: Prevalence of concomitant cardiac amyloidosis in aortic stenosis rises with age and is higher in men [3,6].

Study	N	Method	Prevalence	Notes
Castano 2017 [1]	151	99mTc-PYP	16% (24/151)	TAVR cohort; low mitral s' predictive
Cavalcante 2017 [3]	113	CMR	8% overall; 16% if >74y	78% low-flow/low-gradient in CA
Nitsche/Scully 2021 [2]	407	99mTc-DPD	11.8% (48/407)	7.9% grade 2/3; 1 AL case found
Arshad 2022 [4]	1,321 (9 studies)	Pooled	11%	Meta-analysis
Myasoedova 2022 [6]	1,988 (17 studies)	Pooled	15.4%	7.1% <80y vs 18.2% >=80y

Table 1: Design, screening method, and headline prevalence of concomitant cardiac amyloidosis across the five key studies reviewed here [1-4,6].

A recurring theme across these cohorts is that low-flow, low-gradient physiology is disproportionately represented among patients with confirmed amyloidosis: Cavalcante et al. reported it in 78% (7/9) of CA-positive patients versus 45% of isolated AS [3], a pattern also flagged as a screening "red flag" in Jaiswal et al.'s review [7]. This matters practically, because low-flow, low-gradient AS is exactly the subgroup in which the severity of the valve lesion itself is hardest to adjudicate, so amyloid infiltration and true-severe AS can both be in play in the same discordant Doppler picture.

Imaging strategy: scintigraphy anchors diagnosis, other modalities support it

Bone-avid scintigraphy is the backbone of non-invasive ATTR-CA diagnosis, graded by the Perugini scale from 0 (negative) to 3 (strongly positive, myocardial uptake exceeding bone). Grade 2/3 uptake, once light-chain amyloidosis has been excluded by serum and urine free light chains and immunofixation, is considered diagnostic of ATTR-CA without requiring endomyocardial biopsy; grade-1 uptake is equivocal and, as Nitsche and Scully's cohort illustrates, can still conceal AL amyloidosis, so it warrants further work-up rather than a default ATTR label [2,7]. Figure 3 sets this screening pathway out as a flow diagram.

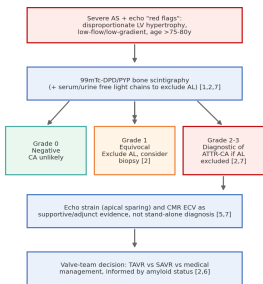


Figure 3: Suggested imaging pathway from echocardiographic suspicion to a confirmed amyloid diagnosis, informing the valve-team decision [1,2,7].

Perugini grade	Myocardial tracer uptake	Interpretation
0	None	ATTR-CA unlikely
1	Mild, less than adjacent rib/bone	Equivocal; exclude AL, consider biopsy [2]
2	Moderate, equal to bone	Diagnostic of ATTR-CA if AL excluded [2,7]
3	Strong, exceeds bone uptake	Diagnostic of ATTR-CA if AL excluded [2,7]

Table 2: The Perugini visual grading scale applied to 99mTc-DPD/PYP scintigraphy, and its clinical interpretation in a patient with severe aortic stenosis [2,7].

This grading scale is the practical hinge of the whole pathway: grade 0 all but excludes ATTR-CA, grades 2 and 3 are accepted as diagnostic once a paraprotein work-up has excluded AL amyloidosis, and grade 1 is the genuinely awkward category, common enough that Nitsche and Scully's own cohort produced a grade-1 patient who in fact had AL disease rather than ATTR -- a reminder that a bone scan alone, without the accompanying light-chain assays, is not a complete diagnostic strategy regardless of how confidently a single grade is reported [2].

Echocardiographic strain imaging contributes a complementary, non-scintigraphic signal: relative apical sparing of longitudinal strain -- preserved strain at the apex with reduced strain at the base -- has reported sensitivity of

93% and specificity of 82% for cardiac amyloidosis in Jaiswal et al.'s summary of the strain literature [7]. In the AMYTAVI study of 324 TAVI patients (strain analysable in 243), a relative apical sparing pattern (RELAPS>1) was present in 46% (111/243) of the cohort, and DPD grade 2/3 CA was more frequent among RELAPS>1 patients than RELAPS<1 patients (15% vs 4.5%, p=0.006) -- but the pattern itself carried no 1-year mortality difference (6.4% vs 6.3%, p=1), underlining that apical sparing is a diagnostic clue, not a prognostic marker in its own right [5]. Figure 4 illustrates the pattern schematically. Cardiac MRI extracellular volume (ECV) offers a third, quantitative axis: Jaiswal et al. cite an area-under-curve of 0.756 for ECV discriminating AS-CA from AS alone, useful as supportive evidence but well short of a stand-alone diagnostic test [7].

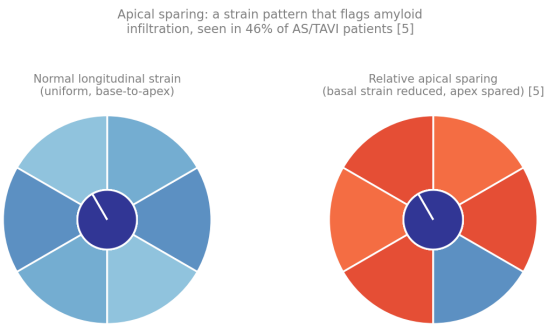


Figure 4: Schematic bullseye strain maps: normal base-to-apex longitudinal strain (left) versus the relative apical sparing pattern associated with amyloid infiltration (right), seen in 46% of the AMYTAVI cohort [5].

Prognosis and the TAVR-versus-SAVR question

Concomitant amyloidosis is consistently associated with worse survival than AS alone. Cavalcante et al. reported 1-year mortality of 56% versus 20% (log-rank p<0.0001), with CA remaining independently associated with mortality after adjustment for AVR, STS-predicted risk, and ejection fraction (adjusted HR 2.92, 95% CI 1.09-7.86, p=0.03) [3]. Myasoedova et al.'s pooled analysis of 178 AS+CA versus 1,220 AS-alone patients found a mortality odds ratio of 2.25 (95% CI 1.23-3.94, p=0.004) [6]. Figure 5 sets both risk estimates out as a forest plot.

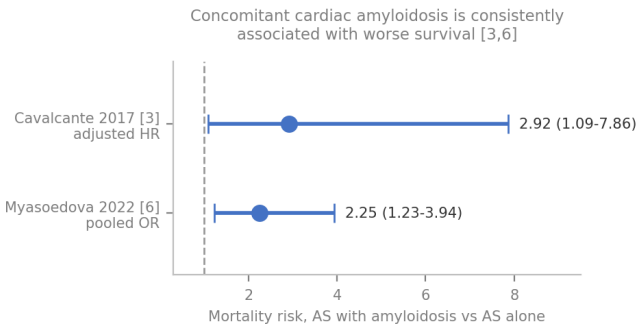


Figure 5: Mortality risk of concomitant cardiac amyloidosis versus lone aortic stenosis, as reported by two independent cohorts [3,6].

What complicates a simple "amyloidosis means worse outcome, full stop" reading is what happens once these patients are actually treated. In Nitsche and Scully's cohort, overall 1-year mortality was higher in AS-CA than lone AS (24.5% vs 13.9%), yet among patients who underwent TAVR specifically, post-procedural survival was statistically comparable between the two groups ($p=0.36$) -- the authors explicitly concluded that TAVR should not be withheld on the basis of a positive amyloid screen [2]. Myasoedova et al.'s meta-analysis reaches a compatible conclusion from the surgical side: SAVR and TAVI produced similar mortality benefit relative to medical management alone in AS+CA patients, with no significant difference between the two valve strategies ($p=0.217$) [6]. Table 3 sets these two management-relevant findings out together.

Study	Comparison	Result
Nitsche/Scully 2021 [2]	AS-CA vs lone AS, post-TAVR survival	Comparable ($p=0.36$)
Myasoedova 2022 [6]	SAVR vs TAVI in AS+CA, mortality benefit	No difference ($p=0.217$)
Myasoedova 2022 [6]	SAVR/TAVI vs medical management, AS+CA	Both superior to medical management

Table 3: Valve-treatment-relevant findings in patients with concomitant aortic stenosis and cardiac amyloidosis [2,6].

Taken together, the honest reading is that amyloidosis worsens the natural history of AS overall, but does not appear, on the evidence assembled here, to be a reason to deny valve replacement -- TAVR or SAVR -- to an otherwise eligible patient. What neither study can settle is whether earlier detection followed by concurrent amyloid-specific disease-modifying therapy changes that trajectory further; both are describing outcomes after valve intervention alone.

This distinction also matters for timing. Symptomatic severe AS itself carries a substantial mortality risk the longer valve replacement is delayed, so an amyloid work-up that holds up an otherwise indicated TAVR or SAVR risks trading one hazard for another. In practice, the cohorts reviewed here screened for ATTR-CA around the time of the TAVR work-up rather than as a precondition for it -- Castano et al.'s scintigraphy was performed within 30 days after the procedure, not before it [1] -- which is consistent with amyloid status being used to inform prognosis and follow-up rather than to gate access to the valve procedure itself.

Cost-effectiveness: a real but unresolved constraint on universal screening

Whether every severe-AS patient should be screened is not only a sensitivity-and-specificity question but a cost-effectiveness one. Ge et al. modelled seven diagnostic strategies for suspected ATTR cardiomyopathy and found that a PYP-scintigraphy-only strategy carried the lowest base-case lifetime cost per person (\$209,415), with CMR-then-PYP-if-positive (\$212,985, ICER \$120,000/QALY), PYP-then-CMR-if-negative (\$215,126, ICER \$130,000/QALY), and endomyocardial biopsy alone (\$215,881, ICER \$200,000/QALY) all costing more per quality-adjusted life-year gained [8]. Figure 6 sets these four strategies' modelled costs out directly. Critically, this analysis assumed a lower tafamidis price than its current US list price of roughly \$225,000 per year; at that current pricing, the authors reported that no diagnostic strategy met a \$100,000/QALY willingness-to-pay threshold, with the PYP-only ICER rising to roughly \$1,200,000/QALY [8]. This is not an AS-specific analysis -- it models suspected ATTR cardiomyopathy generally -- but it applies directly to any AS-population screening programme that would lead, on a positive result, to tafamidis being considered.

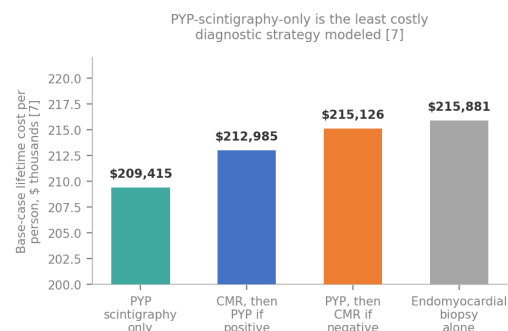


Figure 6: Modelled base-case lifetime cost per person of four diagnostic strategies for suspected transthyretin cardiac amyloidosis [8].

Discussion

The evidence assembled here supports three conclusions with reasonable confidence. First, concomitant ATTR-CA in severe AS is common enough -- roughly one in nine to one in six patients depending on population and test, rising further with age and in low-flow, low-gradient disease -- that it cannot be treated as a curiosity. Second, imaging diagnosis is a structured pathway, not a single test: scintigraphy anchors the diagnosis but requires exclusion of AL amyloidosis, while strain and CMR-ECV contribute supportive rather than definitive evidence. Third, and most clinically consequential, a positive amyloid screen in a patient who is otherwise a reasonable TAVR or SAVR candidate does not appear to be a reason to withhold valve intervention: post-procedural survival differences between amyloid-positive and amyloid-negative patients were not statistically significant in the two studies that looked directly at treated cohorts [2,6].

What remains genuinely unresolved is where the screening threshold should sit. No trial has compared universal AS screening against a targeted, red-flag-triggered strategy (age, low-flow physiology, disproportionate hypertrophy) head-to-head for downstream outcomes, and the cost-effectiveness modelling available is not AS-specific and is highly sensitive to a treatment drug price that is itself unsettled. A valve team's practical answer today is therefore closer to targeted screening of older, red-flag-positive patients than to scanning every severe-AS referral, but this is a pragmatic compromise rather than an evidence-based threshold.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and the prevalence figures it cites come from cohorts that differ in age, referral pattern (surgical vs transcatheter candidates), and screening test, so they should be read as a consistent range rather than a single true prevalence. The two meta-analyses (Arshad et al., Myasoedova et al.) draw on overlapping primary studies, so their pooled estimates are not fully independent confirmations of one another. The AMYTAVI findings on apical sparing come from a conference abstract rather than a full peer-reviewed manuscript, and its 1-year follow-up is short relative to amyloidosis's typically slower natural history. The cost-effectiveness analysis cited models suspected ATTR cardiomyopathy broadly, not an AS-screening-specific pathway, and its conclusions are sensitive to a disease-modifying drug price that changes over time and by country. Finally, none of the mortality comparisons summarised here come from a randomised comparison of amyloid-directed treatment strategies in AS patients specifically, so this review can describe association and observed post-procedural outcomes, but not establish that any particular screening or treatment strategy causally changes survival.

Conclusion

Concomitant transthyretin cardiac amyloidosis is a common, not a rare, finding in patients referred for severe aortic stenosis, particularly older TAVR candidates and those with low-flow, low-gradient physiology, and it is associated with meaningfully worse unadjusted survival. The available evidence does not, however, support withholding TAVR or SAVR from an otherwise eligible patient on the basis of a positive amyloid screen: post-procedural outcomes in the studies reviewed here were statistically comparable between amyloid-positive and amyloid-negative patients. Imaging diagnosis is achievable non-invasively through bone-avid scintigraphy with light-chain exclusion, supported by echocardiographic strain and CMR-ECV, but the optimal threshold for whom to screen, and how that screening decision should weigh against its cost, remain open questions this literature has not yet settled.

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