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Screening for cardiac amyloidosis in aortic stenosis

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Introduction

In this editorial, I review the most recent in a series of papers documenting the prevalence of the dual pathology of cardiac amyloidosis with significant aortic stenosis (AS). Are we at a point where screening for dual pathology is worth doing, and if so, with which modalities?

Aortic stenosis is the most commonly intervened upon valvular heart disease. Intervention, whether that be surgical or transcatheter aortic valve replacement (SAVR or TAVR, respectively), improves the natural history of pressure overload and reduces symptoms and mortality. The prevalence of at-least moderate AS at ages ≥65 was 4.1% in population-based sampling and 6.0% in the Olmsted County community study.[1] In a UK community population aged >18 and referred for echo for suspected heart failure, the prevalence of at least moderate AS was 3.2%.[2] The values differ because participants were randomly selected from the population for prospectively mandated echocardiography in the former case, while the community study sample was that population who had a medical contact and then an echo requested on clinical grounds.

Take Home Messages

- Between 5-15% of patients with severe aortic stenosis have concomitant cardiac amyloidosis. Dual pathology may have implications for the natural history (e.g. worsening heart failure) and management of severe aortic stenosis (severe cardiac amyloidosis may limit the number of quality life years gained after aortic valve replacement). Dual pathology also presents an opportunity for screening for cardiac amyloidosis.
- Non-invasive screening for cardiac amyloidosis involves electrocardiography, echocardiography, bone scintigraphy and cardiac magnetic resonance imaging. The relative strengths of these techniques have not previously been compared in a single patient sample; the reviewed paper is the first to attempt this.
- The argument that performing a subset of non-invasive tests might be as good as performing all of them, although supported by the presently reviewed paper, is not supported by previous studies.
- The true population prevalence of cardiac amyloidosis remains unknown, as population studies of bone scintigraphy combined with echocardiography do not exist. The prevalence of cardiac amyloidosis in moderate or severe AS also remains unknown, since all (but one) screening studies to date have only enrolled patients put forward for AVR.

Cardiac amyloidosis is a condition characterised by excess deposition of extracellular amyloid fibrils in the myocardium. Most common is systemic transthyretin (TTR) cardiac amyloidosis, which may be senile (wild-type) or hereditary (mutant, autosomal dominant). These subtypes refer to the deposition of genetically wild-type or mutant TTR

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Dr Mark Peterzan is an ST6 trainee based in South London. He completed a DPhil investigating creatine kinase kinetics in the hearts of patients with severe valvular heart disease and in athletic remodelling at the Oxford Centre for Clinical Magnetic Resonance Research (John Radcliffe Hospital, Oxford), and plans to train in imaging and heart failure.

fibrils respectively. Much less common is light-chain (AL) cardiac amyloidosis, where the amyloidogenic protein is a light-chain variant produced by a plasma cell dyscrasia. Diagnostic options for cardiac amyloidosis include histology on biopsy samples (the gold standard); ^{99m}Tc-labelled 3,3-diphosphono-1,2-propanodicarboxylic-acid (DPD) bone scintigraphy, and cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE). Significant cardiac amyloidosis increases the risks of heart failure, premature mortality, and futility of treatment with AVR; both TTR and AL cardiac amyloidosis are treatable. The prevalence of cardiac amyloidosis in several series of patients with AS referred for aortic valve replacement (AVR) or cardiac magnetic resonance (CMR) is estimated at up to 15%,[3] although there has been variation in the selection of previously studied cohorts and the methods used to look for cardiac amyloidosis (see **Table 1**).

Given the above, one might expect an imaging enthusiast to make arguments for the routine screening for cardiac amyloidosis in all patients with at-least-moderate AS. However, this is not currently routine clinical practice. Although dual pathology is not uncommon in severe AS (i.e. with a prevalence of at least 5%, see **Table 1**), it has only been recognised in the last five years, probably because the techniques required for non-invasive characterisation of cardiac amyloidosis are relatively modern, and none in isolation has perfect accuracy for both TTR and AL cardiac amyloidosis. Whether, and how frequently, concomitant cardiac amyloidosis meaningfully impacts disease progression in severe AS is unknown, and how co-existing cardiac amyloidosis should inform the management of AS and vice-versa, is still largely a matter of expert consensus. Up until the most recent paper, none of the cohorts of dual pathology hearts had used all of echocardiography, bone scintigraphy and CMR to screen for coexistent cardiac amyloidosis and AS. The relative strengths of diagnostic modalities has therefore not been compared in a single patient sample. The paper reviewed here, however, has recently attempted to do just this, and also raises the question whether screening for cardiac amyloidosis solely using echocardiography and electrocardiography (ECG) may be helpful.[4]

Cardiac amyloidosis – suspicion and confirmation criteria

The typically reported cardiac phenotype in cardiac amyloidosis is biventricular hypertrophy and stiffening with restrictive physiology: heart failure with preserved ejection fraction. There is also a high prevalence of atrial arrhythmia, atrioventricular dissociation, intracardiac thrombus, and pericardial effusion. Current diagnosis depends on the identification of suspicion criteria or 'red flags' that prompt further testing.[3]

Clinical suspicion criteria include age ≥65, heart failure with preserved ejection fraction, disproportionate heart failure symptoms, predominant right-sided heart failure, premature severe conduction disease, carpal tunnel syndrome, lumbar spinal stenosis and deafness. **ECG suspicion criteria** include discordant low voltage relative to left ventricular (LV) wall thickness and pseudo-infarction pattern (Q-waves) in the absence of prior myocardial infarction. **Echocardiographic suspicion criteria** include: severe concentricity (LV relative wall thickness (RWT) >0.5, where RWT = 2 × posterior wall thickness / LV internal diameter, and normal RWT <0.42), disproportionate hypertrophy (LV wall thickness ≥15 mm), disproportionate diastolic dysfunction (grade ≥2, E/e' >16), severe LV longitudinal systolic dysfunction with apical sparing (mitral S' ≤6 cm/s, LV global longitudinal strain ≥-12%, apex/base longitudinal strain ratio >2), right ventricular (RV) wall thickening (≥5 mm), moderate-severe pulmonary hypertension, myocardial granular sparkling, atrial septal thickening and bi-atrial dilation, and atrioventricular valve thickening. **Biomarker suspicion criteria** include chronic troponin elevation in the absence of significant coronary artery disease or renal dysfunction, and disproportionate N-terminal-pro-Brain Natriuretic Peptide (NT-proBNP) elevation.

On CMR, circumferential and extensive LGE starting at the subendocardium and basal segments,[5] abnormal gadolinium kinetics with difficulty nulling myocardium, reverse order appearance of T1 inversion scout images, and severely elevated native T1 and extracellular volume fraction (ECV) are red flags for cardiac amyloidosis.

Confirmation criteria for cardiac amyloidosis include: Perugini grade 2 or 3[6] cardiac uptake on bone scintigraphy in the absence of monoclonal

protein in serum or urine (TTR cardiac amyloidosis),[7] monoclonal free light chain in serum and/or urine and abnormal CMR or bone scintigraphy (AL cardiac amyloidosis), and on histology of endomyocardial or extracardiac biopsy, positive Congo red staining and apple-green birefringence on polarizing microscopy.

Cardiac amyloidosis – treatment options

General principles of management have been reviewed elsewhere,[3,8,9] and include avoidance of beta-blockers and calcium channel antagonists – as the heart with restrictive physiology depends on increasing heart rate rather than preload to modulate its output; cautious use of angiotensin converting enzyme-inhibitors in hypertension and caution regarding exaggerated hypotension; cautious diuresis to decongest and optimise filling pressures; avoidance of digoxin; low threshold for anticoagulation in supraventricular arrhythmias or intracardiac thrombus; and low threshold for permanent pacing in syncope with bifascicular block. Targeted therapy in AL cardiac amyloidosis requires chemotherapy +/- heart transplantation. Targeted therapy in TTR cardiac amyloidosis was previously limited to heart and liver transplantation in hereditary TTR with no specific treatment for wild-type TTR cardiac amyloidosis. Recently, however, the Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT)[10] and APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin-Mediated Polyneuropathy[11] randomized controlled trials demonstrated the efficacy of tafamidis and patisiran respectively in TTR cardiac amyloidosis.

Study - Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome

Study design

This study screened 238 consecutive patients with severe degenerative AS scheduled for TAVR at the Vienna General Hospital, Austria.[12] 191 were eligible for the final analysis, i.e. completed clinical and biomarker (NT-proBNP) assessment, ECG, echocardiography, and bone scintigraphy; of these, 156/191 (82%) also completed CMR (LGE, T1 mapping, and ECV mapping). Primary and secondary endpoints were all-cause death and cardiovascular hospitalization.

Study definitions

TTR cardiac amyloidosis was defined as Perugini grade ≥2 cardiac uptake on bone scintigraphy in the absence of serum and urine free light chains. AL cardiac amyloidosis was defined as positive endomyocardial or extracardiac biopsy and immunohistochemistry, plus elevated levels of the corresponding monoclonal free light chain in serum or urine. ECG voltage/mass ratio was defined as the Sokolow-Lyon index (S-wave in lead V1 plus R-wave in V5 or V6) divided by the LV mass index determined on M-mode echocardiography. Myocardial contraction fraction was defined as stroke volume / myocardial volume, with stroke volume derived from left ventricular outflow tract (LVOT) pulsed-wave Doppler and myocardial volume calculated from linear dimensions in the parasternal long-axis view.

Results

16/191 (8.4%) cases of cardiac amyloidosis were observed: 15 TTR and one AL. One TTR cardiac amyloidosis patient had grade one uptake on bone scintigraphy but positive cardiac biopsy; the remaining TTR patients had grade 2 or 3 uptake. A further five patients with grade one uptake declined cardiac biopsy so cardiac amyloidosis could not be confirmed. Compared with those without cardiac amyloidosis, cardiac amyloidosis patients were older (median age 84 vs 82, $p = 0.024$), had lower systolic blood pressure (median 119 vs 132 mmHg, $p = 0.01$), and had a higher prevalence of pacemakers (31 vs 12%, $p = 0.04$). On ECG, cardiac amyloidosis patients had reduced Sokolow-Lyon index (1.7 vs 2.2 mV, $p = 0.03$) and voltage-mass ratio ($p = 0.001$).

On echocardiography, cardiac amyloidosis patients had lower aortic valve peak and mean gradients (median 60 vs 77 and 35 vs 47.5 mmHg, $p = 0.001$ and 0.004 respectively), increased LV mass index (by 18%, $p = 0.016$), reduced stroke volume index (by 41%, $p < 0.001$), decreased myocardial contraction fraction (by 31%, $p = 0.001$), and worse longitudinal strain at basal and midventricular levels

(both p = 0.04). LV ejection fraction and end-diastolic volumes were not different. On CMR, LV volumes, ejection fraction and mass were not significantly different (LV mass index increased by 18%, p = 0.16); however, median ECV fraction was increased (by 13%, p = 0.003). Of the 11 cardiac amyloidosis patients who underwent CMR, typical LGE pattern was present in only 4 cases (all TTR); the remaining 7 had unremarkable ECV values and LGE patterns.

Over a median follow-up of 15.3 months, the presence of cardiac amyloidosis was not associated with poorer outcome following TAVR.

In the summary, the best discriminators for the presence of cardiac amyloidosis in AS were stroke volume index by echocardiography (AUC 0.773), voltage mass ratio (AUC 0.770), ECV by CMR (AUC 0.756) and myocardial contraction fraction (AUC 0.754). Multivariate logistic regression controlling for age, myocardial contraction fraction and Sokolow-Lyon index found that voltage-mass ratio (p = 0.016) and stroke volume index by echocardiography (p = 0.027) remained associated with the presence of cardiac amyloidosis.

Discussion

The key point about this study is its design: multi-modality screening in a severe AS population – prior studies have not required bone scintigraphy and CMR in all screened patients. The authors observed a lower than expected pick-up rate for cardiac amyloidosis with CMR, a better than expected pick-up rate with combined echocardiography and ECG, and a neutral effect of cardiac amyloidosis on prognosis after TAVR.

The authors suggest that screening solely with variables based on echocardiography and ECG may be worthwhile. If shown to be true, this would be an important claim. The recent development of targeted therapies for TTR cardiac amyloidosis and its distinct prognosis from other cardiomyopathies presents an opportunity for screening. However, I would suggest we are not there just yet. A fundamental test for any screening argument is whether the proposed screening test sets in train a set of investigations and treatments that on average reduce all-cause mortality, not solely disease-related mortality. The recent NELSON trial of volume CT screening to reduce lung cancer mortality showed reduced lung cancer mortality but no difference in all-cause mortality.[13] There are several other hurdles for an argument regarding screening for cardiac amyloidosis in AS to pass: first, dual pathology is uncommon, so screening may not be cost-effective; second, the population is elderly, so treatments for cardiac amyloidosis must have major effects on the natural history of cardiac amyloidosis to improve life expectancy; third, the concomitant condition (AS) may be more advanced or more serious than the cardiac amyloidosis, so treatments for cardiac amyloidosis may be futile without treatments for AS; fourth, there may be an interaction between cardiac amyloidosis and AS (particularly increased heart failure) such that AVR is less effective at improving life expectancy in dual pathology. It is the question of prevalence of dual pathology which has been the focus here.

These findings should be set in context of previous and ongoing studies screening for cardiac amyloidosis (see **Tables 1 and 2** respectively).

What remains unknown?

We already knew that there are echocardiographic and CMR suspicion criteria that may help select patients to refer for bone scintigraphic scanning before AVR. The most recent study replicates several previously described echocardiographic, ECG and CMR criteria that are discriminatory for cardiac amyloidosis in the presence of AS, and builds on previous studies by requiring all of echo, ECG, CMR and bone scintigraphy (as do the ongoing studies mentioned). It is now established that bone scintigraphy is the most sensitive technique to screen for TTR cardiac amyloidosis, which is the most common form of cardiac amyloidosis, but is insensitive for AL cardiac amyloidosis. A screening study should ideally use both echo and CMR to detect AL cases and to phenotype cardiac mass, volumes, and flow (i.e. to stage the AS, see below).

However, the true population prevalence of cardiac amyloidosis remains unknown, as population studies of bone scintigraphy combined with echocardiography do not exist. Even if such a study was performed, it is unknown how many patients with early (subclinical, endomyocardial biopsy positive, non-invasive testing negative) stage cardiac amyloidosis are missed when using the threshold of grade 2 or 3 cardiac uptake. Furthermore, none of the studies documenting cardiac amyloidosis prevalence mentioned here can

Table 1. Previous studies screening for cardiac amyloidosis

Screening strategy and population	Study description
Autopsy	The prevalence of wtTTR amyloid deposits in the LV on autopsy studies is 11-29% depending on the patient sample, ages included, and amyloid detection technique.[15–18] In a Japanese study of 181 hearts aged ≥40 from consecutive autopsies, 11.5% of those aged ≥80 had ventricular wtTTR. Atrial amyloid started to be observed in hearts aged ≥50, and wtTTR was only observed in hearts aged ≥70.[15] In a study from Olmsted County, Minnesota, moderate or severe interstitial wtTTR deposition consistent with TTR cardiac amyloidosis as the primary cause of HF-pEF was found in 5% of HF-pEF patients at autopsy,[17] and the age- and sex-adjusted prevalence of wtTTR was commoner in HF-pEF patients than in controls (odds ratio 3.8, 95% CI 1.5-11.3, p = 0.03). In 17 autopsied patients who died post TAVR, 5 (29%) had previously unrecognised myocardial amyloidosis.[14]
Bone scintigraphy in HF-pEF	In a prospective study screening 120 consecutive patients aged ≥60 and admitted to a Madrid tertiary hospital due to HF-pEF with LV hypertrophy (≥12 mm), systematic bone scintigraphy found cardiac amyloidosis in 16/120 (13%).[19] All had wild-type TTR cardiac amyloidosis. Exclusion criteria were at-least moderate valve disease, significant coronary artery disease, and prior myocardial infarction. Compared with non-cardiac amyloidosis patients, cardiac amyloidosis patients had higher median NT-proBNP values (p = 0.019), higher median troponin I values (p < 0.001), lower voltage mass ratios (p = 0.005), and (on echo) reduced myocardial contraction fraction (p = 0.003) and increased LV mass index (p < 0.001).
Bone scintigraphy for oncologic or rheumatological indications	A retrospective study of 12,521 patients undergoing bone scintigraphy with oncologic (95%) or rheumatologic (5%) indications (mean age 74, range 65-82) and excluding patients with suspected cardiac amyloidosis (n = 121) found unexpected moderate or strong myocardial tracer uptake in 45/12,400 cases (0.36%, median age 81, range 77-84).[20] The prevalence at age ≥80 was 1.4%.[21] All cases subsequently undergoing echocardiography had increased LV wall thickness, i.e. were highly likely to have TTR cardiac amyloidosis.
Bone scintigraphy in severe AS with or without echocardiography as gate-keeper	A single-centre study (Bologna, Italy) prospectively screened patients with AS referred for AVR who had echocardiographic 'red flags' with bone scintigraphy.[21] 5/43 (12%) were referred for bone scintigraphy, and all had strong myocardial uptake confirmed to be wild-type TTR cardiac amyloidosis on endomyocardial biopsy. The Columbia University group prospectively screened 151 patients aged ≥65 with severe symptomatic calcific AS undergoing TAVR with bone scintigraphy: 24/151 (16%) screened positive for TTR cardiac amyloidosis.[22] Compared with non-cardiac amyloidosis AS patients, cardiac amyloidosis AS patients were older (mean age 86 vs 83, p = 0.038), more commonly had a stage D2 AS phenotype (29 vs 11%, p = 0.045), had lower systolic blood pressure (mean 125 vs 144 mmHg, p = 0.009), lower voltage mass ratio (1.0 vs 1.4, p = 0.028), and on echocardiography had raised LV mass index (by 33%, p = 0.002), lower stroke volume index (by 16%, p = 0.009), increased E/A ratio, reduced myocardial contraction fraction (by 36%, p < 0.001), and worse mitral S' (39% lower, p < 0.001) and global longitudinal strain. The best predictor of positive cardiac uptake on bone scintigraphy on multivariable logistic regression was mean mitral S' ≤6 cm/s.
CMR and intraoperative biopsy in severe AS patients undergoing SAVR	The Barts Heart Centre group prospectively screened 146 patients with severe AS undergoing SAVR with CMR and intraoperative biopsy. Cardiac amyloidosis was identified in 6/146 patients, all with calcific AS and age >65 (prevalence 6/112 = 5.6% in calcific AS and age >65). All cases were wild-type TTR. CMR findings were of definite cardiac amyloidosis in 2/6 but could be explained solely by AS in 4/6. Clinical echocardiography did not find red flags or raise suspicion of cardiac amyloidosis in any of the 6 cases. Bone scintigraphy was performed only in those with cardiac amyloidosis confirmed on biopsy and was positive in all cases tested. At a median 2.3 year follow-up, TTR cardiac amyloidosis was independently associated with death (hazard ratio 9.5, 95% CI 2.5-35.8).
Moderate or severe AS and referred for CMR	The University of Pittsburgh group retrospectively assessed 113 patients with moderate or severe AS referred for CMR for clinical indications (bicuspid aortic valve, LV dysfunction, echocardiographic suspicion of cardiac amyloidosis, AS severity, myocardial ischaemia).[23] Cardiac amyloidosis, defined as strongly suggestive of cardiac amyloidosis on CMR grounds only, was present in 9/113 (8%, mean age 88) and in 9/57 (16%) of those > age 74 years. Patients with dual pathology had increased 1-year all-cause mortality. A weakness of the study is that the prevalence may have been underestimated as biopsy and bone scintigraphy were not employed; the strengths would be that cases of AL cardiac amyloidosis (not detectable on bone scintigraphy) could have been detected, and a broader pool of patients than that selected for AVR was assessed.

AS aortic stenosis, AL light chain, AVR aortic valve replacement, CI confidence interval, CMR cardiac magnetic resonance imaging, HF-pEF heart failure with preserved ejection fraction, LV left ventricular, NT-proBNP N terminal-pro brain natriuretic peptide, SAVR surgical aortic valve replacement, TAVR transcutaneous aortic valve replacement, TTR transthyretin, wt wild type.

Table 2. Ongoing studies screening for cardiac amyloidosis in AS

Screening strategy and population	Study description
Aged ≥75, severe AS considered for SAVR, TAVR or medical therapy	The ATTRact-AS study (NCT03029026) is screening 250 patients using echocardiography and bone scintigraphy in all and intraoperative biopsy and CMR in the SAVR cohort. A pre-specified interim analysis of 101 patients found TTR cardiac amyloidosis in 14/101 (14%, mean age 88).[24]
AS and indication for SAVR	Amylo-CARTESIAN (NCT02260466) is screening 180 patients with echocardiography, bone scintigraphy, CMR and intraoperative biopsy. Completion date is set as 31.03.2021.

AS aortic stenosis, ATTRact-AS The Role of Occult Cardiac Amyloid in the Elderly With Aortic Stenosis, CMR cardiac magnetic resonance imaging, SAVR surgical aortic valve replacement, TAVR transcutaneous aortic valve replacement, TTR transthyretin.

exclude referral and survival bias. The studies using CMR would also have excluded patients with pacemakers.

The prevalence of cardiac amyloidosis in moderate or severe AS also remains unknown, since screening studies to date (except one, which did not use bone scintigraphy[23] have enrolled patients put forward for AVR. It would be interesting to screen patients before this selection step with all modalities. Another point of interest would be to categorise the prevalence of cardiac amyloidosis for different severe AS phenotypes. Stage D2 AS, classical low-flow low-gradient severe AS with reduced left ventricular ejection fraction (LVEF), and stage D3 AS, low-flow low-gradient AS with paradoxically normal LVEF, are phenotypically more similar to cardiac amyloidosis than to stage D1 AS (symptomatic severe high-gradient AS),[25] and also carry a worse prognosis. The impact of concomitant cardiac amyloidosis in low-flow AS is unknown.

Besides the question of prevalence, it remains unknown whether treatment for cardiac amyloidosis improve all-cause mortality in the context of AS, whether AVR improves all-cause mortality in the context of cardiac amyloidosis, and whether screening is cost-effective. Ongoing screening studies are addressing the outcome of patients with AS with or without cardiac amyloidosis in larger prospective follow-up studies. Future studies will need to estimate the effect of any screening strategy on this, and how to define imaging, ECG or blood biomarkers of disease stage for each of cardiac amyloidosis and AS in the presence of dual pathology.

Disclosures

None.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368(9540):1005-1011. doi:http://dx.doi.org/10.1016/S0140-6736(06)69208-8

2. Marciniak A, Glover K, Sharma R. Cohort profile: prevalence of valvular heart disease in community patients with suspected heart failure in UK. BMJ Open 2017;7(1):e012240. doi:10.1136/bmjopen-2016-012240

3. Ternacle J, Krapf L, Mothy D, et al. Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol 2019;74(21):2638-2651. doi:10.1016/j.jacc.2019.09.056

4. Nitsche C, Kammerlander AA, Knechtelsdorfer K, et al. Determinants of Bioprosthetic Aortic Valve Degeneration. JACC Cardiovasc Imaging 2020;13(2):345-353. doi:10.1016/j.jcmg.2019.01.027

5. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular Magnetic Resonance in Clinically Suspected Cardiac Amyloidosis: Noninvasive Imaging Compared to Endomyocardial Biopsy. J Am Coll Cardiol. 2008;51(10):1022-1030. doi:10.1016/J.JACC.2007.10.049

6. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using 99mTc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy. J Am Coll Cardiol 2005;46(6):1076-1084. doi:10.1016/J.JACC.2005.05.073

7. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016;133(24):2404-2412. doi:10.1161/CIRCULATIONAHA.116.021612

8. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation 2005;112(13):2047-2060. doi:10.1161/CIRCULATIONAHA.104.489187

9. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation 2012;126(10):1286-1300. doi:10.1161/CIRCULATIONAHA.111.078915

10. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689

11. Solomon SD, Adams D, Kristen A, et al. Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis. Circulation 2019;139(4):431-443. doi:10.1161/CIRCULATIONAHA.118.035831

12. Nitsche C, Aschauer S, Kammerlander AA, et al. Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. Eur J Heart Fail February 2020:1-11. doi:10.1002/ejhf.1756

13. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020;382(6):503-513. doi:10.1056/NEJMoa1911793

14. Nietlispach F, Webb JG, Ye J, et al. Pathology of Transcatheter Valve Therapy. JACC Cardiovasc Interv 2012;5(5):582-590. doi:10.1016/J.JCIN.2012.03.012

15. Ueda M, Horibata Y, Shono M, et al. Clinicopathological features of senile systemic amyloidosis: an ante- and post-mortem study. Mod Pathol 2011;24(12):1533-1544. doi:10.1038/modpathol.2011.117

16. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: A population-based autopsy study. Ann Med 2008;40(3):232-239. doi:10.1080/07853890701842988

17. Mohammed SF, Mirzoyev SA, Edwards WD, et al. Left Ventricular Amyloid Deposition in Patients With Heart Failure and Preserved Ejection Fraction. JACC Hear Fail 2014;2(2):113-122. doi:10.1016/j.jchf.2013.11.004

18. Cornwell GG, Murdoch WL, Kyle RA, Westermark P, Pitkänen P. Frequency and distribution of senile cardiovascular amyloid: A clinicopathologic correlation. Am J Med 1983;75(4):618-623. doi:10.1016/0002-9343(83)90443-6

19. González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36(38):2585-2594. doi:10.1093/eurheartj/ehv338

20. Longhi S, Guidalotti PL, Quarta CC, et al. Identification of TTR-Related Subclinical Amyloidosis With 99mTc-DPD Scintigraphy. JACC Cardiovasc Imaging 2014;7(5):531-532. doi:10.1016/j.jcmg.2014.03.004

21. Longhi S, Lorenzini M, Gagliardi C, et al. Coexistence of Degenerative Aortic Stenosis and Wild-Type Transthyretin-Related Cardiac Amyloidosis. JACC Cardiovasc Imaging 2016;9(3):325-327. doi:10.1016/J.JCMG.2015.04.012

22. Castaño A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J. 2017;38(38):2879-2887. doi:10.1093/eurheartj/ehx350

23. Cavalcante JL, Rijal S, Abdelkarim I, et al. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson. 2017;19(1):98. doi:10.1186/s12968-017-0415-x

24. Scully PR, Treibel TA, Fontana M, et al. Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2018;71(4):463-464. doi:10.1016/j.jacc.2017.11.037

25. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):2438-2488. doi:http://dx.doi.org/10.1016/j.jacc.2014.02.537