European Heart Journal Supplements (2021) **23** (Supplement E), E128–E132
The Heart of the Matter
doi:10.1093/eurheartj/suab107

ESC European Society of Cardiology

Transthyretin amyloidosis in aortic stenosis: clinical and therapeutic implications

Gioele Fabbri[1], Matteo Serenelli[1], Anna Cantone[1], Federico Sanguettoli[1], and Claudio Rapezzi[1,2]*

[1]*Centro Cardiologico, Università di Ferrara, via Aldo Moro 8, Cona, 44124 Ferrara, Italy; and*
[2]*Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy*

KEYWORDS
Amyloidosis;
Aortic stenosis;
Transthyretin;
TAVI

About one in seven elderly patients with severe calcific aortic stenosis (AS) also have ATTR amyloid cardiomyopathy (AC-TTR). The reasons for this close association are not fully known, but the two entities are not only related by common epidemiology. For example, it is possible to hypothesize that an amyloidotic infiltration of the aortic valve, even partial, can act as a trigger for the development of endothelial damage and subsequent calcification. Another hypothesis is the increased myocardial strain induced by AS may locally favour the process of amyloidogenesis and tissue infiltration. In a patient with AS, the coexistence of AC-TTR can be suspected by careful analysis of the echocardiogram and the ECG, especially if a clinical history of carpal tunnel syndrome coexists. Bone tracer scintigraphy allows a diagnosis of certainty. Recently, several studies have evaluated the prognostic implications of the coexistence of the two entities in candidates for percutaneous aortic valve replacement, showing how amyloidosis would not significantly impact the results of the procedure, but would only be associated with a greater risk of distant heart failure. In patients with AS associated with AC-TTR, valve replacement should not be ruled out in the presence of the usual clinical-haemodynamic indications.

The relationship between transthyretin cardiac amyloidosis (AC-TTR) and aortic stenosis (AS) is acquiring progressive interest in contemporary cardiology in light of the increase in the diagnosis of AC-TTR linked to the use of bone tracer scintigraphy, and, on the other hand, the diffusion of the percutaneous treatment of severe AS: the transcatheter aortic valve replacement (TAVR).

Recently, several studies have evaluated the prognostic implications of the coexistence of AC-TTR and severe AS in TAVR candidates, showing how amyloidosis would not significantly impact the survival of patients with severe AS, and especially how TAVR intervention would improve outcome in patients in which the two pathologies coexist.[1,2]

Although the literature helps us to clarify some aspects of the topic, it necessarily leaves a number of questions open.

How frequently do as and AC-ATTR coexist?

In the first studies aimed at investigating this combination, the co-presence of AS and AC-TTR was not systematically sought, but (by bone scan) only in patients with clinical and echocardiographic red flags suggesting AC-TTR. This led to an initial overestimation of the prevalence. Considering only the prospective studies that carried out a systematic search for AC-TTR and AS, the prevalence of amyloid cardiomyopathy (AC) varies between 4% and 16% (*Table 1*).[1,3-7]

In general, the prevalence of AC-TTR among patients with AS is mainly influenced by the age of the patients, by the criteria with which the diagnostic process for the search for AC-TTR was initiated, and by the way in which the diagnosis was made. For example, cardiac magnetic resonance imaging (CMR) has a lower sensitivity than scintigraphy in detecting AC-TTR. The lowest prevalence (~4%) was found in cardiac surgery patients undergoing aortic valve replacement (AVR), in whom the diagnosis was

*Corresponding author. Email: claudio.rapezzi@unife.it

Table 1 Main series of severe aortic stenosis treated with TAVR or surgical valve replacement comparing patients with or without associated cardiac amyloidosis

Author Journal, year	Rosenblum H Eur J Heart Fail 2020		Scully PR *Eur Heart J* 2020		Nitsche C Eur J Heart Fail 2020		Castaño A *Eur Heart J* 2017		Treibel TA Circ Cardiovasc Imaging 2016		Nitsche C[a] J Am Coll Cardiol 2021	
Diagnosis	Scintiscan		Scintiscan		Non-invasive test		Scintiscan		Biopsy		Scintiscan	
Type of study	Prospective, screening per TAVR		Prospective, screening per TAVR		Prospective, screening per TAVR		Prospective, screening per TAVR		Prospective, indication, and AVR		Prospective, screening per TAVR	
	AS + CA	AS	AS + CA	AS	AS + CA	AS	AS + CA	AS	AS + CA	AS	AS + CA	AS
STS Score	7.0 ± 4.6	6.5 ± 3.5	NA	NA	4.7 (3.5-5.7)	3.5 (2.5-5.1)	NA	NA	NA	1.9 ± 1.4	NA	NA
N° di pz	27 (13%)	177 (87%)	26 (13%)	174 (87%)	16 (8.4%)	175 (91.6%)	24 (16%)	127 (84%)	6 (4%)	112 (96%)	32 (8%)	359 (92%)
Age (years)	86 ± 5	82 ± 10	88 ± 5	88 ± 5	84.0 (81.0-89.0)	82.0 (77.0-85.2)	86.3 ± 5.7	83.3 ± 6.3	75 (69-85)	75 ± 6	86.6 (84.1-91.8)	83.6 (72.3-87.6)
Male (%)	90	63	62	48	62.5	48.3	91.7	63	66	58	65.6	48.2
AVA (cm^2)	0.80 ± 0.15	0.76 ± 0.23	0.74 ± 0.23	0.73 ± 0.22	NA	NA	0.80 ± 0.16	0.77 ± 0.19	0.41 ± 0.17	0.41 ± 0.17	0.7 (0.5-0.9)	0.7 (0.6-0.8)
LF-LG (% pz)	7	14	12	9	12.5	9.2	28.2	10.6	NA	NA	28.1	16.4
LF-LG Paradoxical (% pts)	30	12	19	15	43.8	15.5	8.3	7.3	NA	NA	28.1	16.4
IVS (cm)	1.4 ± 04	1.2 ± 0.3	1.4 ± 0.3	1.3 ± 1.1	1.5 (1.3-2)	1.5 (1.4-1.7)	1.3 ± 0.3	1.1 ± 0.2	17.6 ± 2.3	NA	16.0 (14.0-19.0)	14.0 (12.0-16.0)
PW (cm)	1.1 + 0.4	1.0 ± 0.3	1.3 ± 0.4	1.2 ± 0.2	NA	NA	1.1 ± 0.4	0.9 ± 0.2	NA	NA	NA	NA
LV mass (g/m^2)	136 ± 47	106 ± 31	136 ± 36	118 ± 38	159.0 (132.0-185.5)	135.0 (111.8-162.3)	129.8 ± 43.6	97.9 ± 25.4	121 ± 20	85 ± 24	150 (119-177)	127 (101-151)
LVEF (%)	48 ± 17	55 + 15	54 ± 14	54 ± 11	62.0 (44.0-70.0)	62.0 (54.0-70.0)	47.6 ± 17.6	56.1 ± 14.1	67 ± 5	69 ± 15	51.0 (42.0-64.0)	58.0 (44.0-64.0)
SV (mL/m^2)	31 ± 11	35 + 10	34 ± 10	38 ± 11	27.4 (22.3-33.7)	46.6 (29.0-63.7)	29.9 ± 10.5	35.7 ± 9.6	NA	NA	35.8 (27.4-44.0)	40.1 (31.4-48.0)
MCF (%)	25 ± 11	37 + 15	20.3 ± 8.8	23.8 ± 8.8	15.1 (9.75-19.1)	21.9 (17.1-27.2)	26.4 ± 10.1	41.0 ± 15.5	43 ± 12	53 ± 16	24.5 (20.6-29.3)	33.6 (25.4-45.1)
S' (cm/s)	4.5 ± 1.4	6.3 + 1.6	0.05 ± 0.01	0.06 ± 0.02	NA	NA	4.0 ± 1.1	6.6 ± 1.5	NA	NA	NA	NA
MV dec time (ms)	196 ± 73	247 + 83	241 ± 88	237 ± 86	NA	NA	176 (144-198)	257 (209-313)	NA	240 ± 79	196 (158-246)	217 (166-281)
RBBB (% pz)	39	17	26	13	18.8	11.3	37.5	15.8	NA	NA	18.8	8.7
hsTnT (ng/L)	0.12 (TnI) (0.08-0.35)	0.02 (TnI) (0.01-0.10)	41 (25-84)	21 (14-34)	47 (24-72)	28 (20-49)	0.18 (0.06-0.33)	0.06 (0.05-0.08)	NA	NA	49 (33-87)	24 (15-39)
NT-proBNP (ng/L)	NA	NA	3702 (1286-5626)	1254 (598-2769)	3634 (1241-6323)	1839 (727-5664)	522 (302-1023)	275 (124-722)	306 (51-510)	186 (5-1307)	4855 (1412-7494)	1606 (640-3843)
N° pz treated	27	177	16	133	15	170	0	0	6	112	72.7%	85.0%
Median length of follow-up (months)	25 (14-37)		19 (10-27)		Media 15.3 ± 7.9		NA	NA	24.3 (0.5-56)		23.3 ± 9.7	
Total mortality (%)	34	31	23	21	19	17	NA	NA	50	7.5	19.6	13.7
Hospitalization for HF	0.372 (N/individual year)	0.114 (N/individual year)	NA	NA	12.5%	11.4%	NA	NA	NA	NA	NA	NA

AS, aortic stenosis; AV, aortic valve; AVR, aortic valve replacement; AC, amyloidotic cardiomyopathy; HF, heart failure; hsTnT, high sensitivity troponin T; IVS, interventricular septum; LF, low flow; LG, low gradient; LV, left ventricle; LVEF, left ventricular ejection fraction; MCF, myocardial contraction fraction; MV, mitral valve; NT-proBNP, N-terminal precursor of the atrial natriuretic; NA, not available; PW, posterior wall; STS, society of thoracic surgeons; SV, stroke volume; TAVR, transcatheter aortic valve replacement.

[a]The population of this study is partially composed of patients from other studies shown in this table.

systematically made by biopsy at the time of surgery.[7] In the vast majority of reported cases, the aetiology of AC was ATTR wild-type (AC-ATTRwt), with a minimal epidemiological contribution (<5%) from the AL form.

It is interesting to observe the association of AC and AS also from the 'point of view' of amyloidosis (and not of aortic stenosis). In a cohort of 1240 consecutive patients with AC-TTR followed at the National Amyloidosis Center (NAC) in London (the largest series on this topic), only 1.8% of patients had severe AS on echocardiography.[8] In a smaller cohort of 171 patients with AC, Sperry *et al.*[9] describe a higher prevalence (15.7%). Patients in whom the two pathologies were associated were more often elderly, anaemic and with a higher left ventricular end-diastolic diameter. In this analysis, mortality was the same regardless of treatment for severe AS, suggesting that AC-TTR-CA has a greater impact on medium-term mortality than the haemodynamic effects of AS.

What is the mechanism behind the association between the two diseases?

The question of whether AC is the cause or consequence of AS, or whether they are simply two entities 'epidemiologically related' has not yet been answered. The hypotheses are broadly three:

(1) the association could be attributable to the fact that the prevalence of both diseases increases with age, thus ending up 'invading' the same epidemiological substrate of the population;
(2) amyloidosis could be the common cause of both cardiomyopathy and AS; and
(3) cardiomyopathy could be the consequence of AS.

The first hypothesis is reasonable and is partly supported by epidemiological data that show a progressive increase in the prevalence of both AS and AC-TTR with advancing age, with a peak after 75–80 years. In fact, severe AS affects more than 3% of the population over 75 years of age, with ultrasound characteristics similar to those of AC-TTR.[10]

Data on the prevalence of AC-TTR in the general population are less certain: ~25% of people over 85 have amyloid TTR within their heart, as has been shown by some autopsy studies, but not necessarily these deposits constitute a real cardiomyopathy.[11] Some studies have estimated the presence of myocardial uptake on bone tracer scintigraphy (performed for non-cardiac reasons), reporting values ranging between 2% and 14% in males over 85 years[11,12]; the estimated prevalence for the standard European population over 75 years of age is 4.15% in males and 1.03% in females.[13] These prevalence values are lower than 8–16% reported in the previously commented cases. In particular, a recent international multicenter registry of 408 patients with AS all studied with bone tracer scintigraphy reports an overall prevalence of AC of 11.8%, with about one-third of patients classified as Perugini score 1 and the remaining two-thirds as Perugini score 2 or 3.[2] Therefore, a purely 'epidemiological' explanation is not fully convincing.

The hypothesis that systemic amyloidosis has a pathogenetic role in AS remains possible but still speculative. Since in cases of overt amyloidotic cardiomyopathy also the heart valves, in particular', the mitral valve, often appear 'infiltrated' on the echocardiogram, it is possible to hypothesize that aortic valve involvement, even partial, can act as a trigger for the development of endothelial damage and subsequent calcification. Kristen *et al.*[14] analysed 100 samples from surgically removed stenotic aortic valves, finding amyloid deposits in 74 cases. In any case, on immuno-histochemical examination, none of the most common proteins that usually form amyloid deposits were identified and the deposition of amyloid seemed to be secondary to a condition of athero-inflammation and high haemodynamic shear-stress.

On the other hand, as a third hypothesis, degenerative AS may be able to both aggravate and accelerate the progression of amyloid heart disease. The increased tangential wall stress and greater myocardial strain, typical characteristics of AS, could act as a mechanical contributing cause, locally favouring the process of amyloidogenesis, and tissue infiltration (mechanical-enzymatic hypothesis).[2,15,16]

Who are the patients with the highest probability of dual pathology, and how to identify them?

AS and AC-TTR have similar echocardiographic characteristics, paradoxically, making it more complex to identify patients affected by both pathologies. Considering the published studies as a whole (*Table 1*), a common echocardiographic profile is in fact outlined. This 'phenotype' includes a low-flow low-gradient AS pattern, a reduced ejection fraction (EF) and myocardial fractional contraction (CFM) of the left ventricle, a reduced longitudinal systolic function (reduced S'), a pattern of restrictive trans-mitral flow, lower stroke volume (SV), and worse left ventricular diastolic function. In addition, other non-echocardiographic features help identify the above profile, such as a low ratio of QRS ECG voltages to left ventricular mass, older age, history of bilateral carpal tunnel syndrome, a higher level of biomarkers (NT-proBNP and high-sensitivity troponin I/T).

In search of a non-invasive diagnosis, or in any case of a high degree of diagnostic suspicion useful to guide subsequent examinations, Nietsche *et al.* proposed a score (RAISE score) that could help the clinician in identifying the subjects affected by both diseases. This score takes into account five main elements giving a different weight to each of them: (i) carpal tunnel syndrome (3 points), (ii) intra-ventricular electrical conduction disturbances (2 points for right bundle branch block, 1 point for low peripheral voltages, or a Sokolow–Lyon index <1.9 mV), (iii) restrictive myocardial remodelling (1 point for septal hypertrophy >18 mm, 1 point for altered *E*/*A* ratio), (iv) substrate of chronic myocardial damage (1 point for TnT HS >20 ng/L), (v) 1 point for age >85 years.[2]

In this multicentre and international study conducted on subjects included in a TAVR path, this score was first defined in the Austrian cohort, and then validated in the London cohort. Scores ≥2 and ≥3 demonstrated a good

ability to identify subjects with AC-TTR and AS, respectively with a sensitivity between 93.6% and 72.3% and a specificity between 52.1% and 83.6%.

More recently, Pibarot *et al.*, pointed out that this RAISE score could probably be further improved by adding or replacing some elements, such as biventricular hypertrophy, a tricuspid annular plane excursion (TAPSE) <1.4 cm and an S' of the tricuspid annulus <6 cm/s; the latter element, in fact, was found to be the most accurate predictor of AC-TTR with a sensitivity of 100% in a previous study.[4,15]

It should be positively noted that the proposed scores were not delineated using sophisticated or invasive methods, but using tests that fall within the standard clinical routine, interpreted with a 'clinical eye' trained in the search for amyloidosis. A correct evaluation of these phenotypic characteristics can guide the clinician towards the request for a bone scan and in the search for monoclonal proteins with the aim of defining the diagnosis of AC.

It has recently been reported that computed tomography (CT) with contrast medium is able to provide a quantitative estimate of myocardial extracellular volume.[17] Since CT is an integral part of the preoperative process before performing the TAVR, this examination can provide an interesting 'red flag' and could therefore be performed routinely, but using CT with contrast medium.

It is interesting to note that two findings considered frequent and specific to AC are much less frequent and lose specificity when AS coexists: the high prevalence of the male gender and the 'apical sparing' in the alteration of the longitudinal strain of the left ventricle. There is still no explanation as to why patients with dual pathology have a higher prevalence of female sex than isolated AC-TTR; on the other hand, this epidemiological distribution has also been described for those patients with heart failure with preserved EF (HFpEF) and AC. As for the lack of 'apical sparing', probably the increased parietal stress and the greater after-load induced by AS cause the apex to be less protected by the deposition of amyloid substance or to be in any case more mechanically stressed.

Does the coexistence of ac have consequences on the results of aortic valve replacement?

The doubt that the coexistence of AS and amyloidotic cardiomyopathy could negatively influence the results of TAVR or aortic valve replacement surgery arises from anecdotal reports and small descriptive studies that cannot represent 'evidence'. A prospective study would theoretically be required to randomize patients with AC-TTR and AS to TAVR vs. optimized medical therapy, possibly stratifying patients by severity of cardiomyopathy. A trial designed in this way, however, is neither available nor in progress at the moment, and is also difficult to implement.

A lower, but still reasonable, level of evidence can be provided by prospective non-randomized studies comparing the results of TAVR interventions in patients with AS with or without AC within the same centre (*Table 1*). AC-ATTR does not appear to affect mortality in any of the prospective studies with follow-up data, although patients' age is frequently higher, left ventricular systolic and diastolic function more impaired, hypertrophy more severe, and the form low-flow low-gradient appears to be the most represented.

In all these studies, the confidence interval of the hazard ratio for all-cause mortality is wide, suggesting the possibility of an under-dimensioning of the sample size and therefore of insufficient study power. Recently, Nitsche *et al.* published a multicenter study of 408 patients (which also includes patients from previous studies). This study analyses the outcome of patients undergoing TAVR with and without AC-TTR, with greater statistical power.[2] The overall analysis tends to support the hypothesis of the absence of significant differences in the post-TAVR outcome.

In support of this hypothesis, there is also the comparison between the mortality calculated in these studies and that reported in the Placement of Aortic Transcatheter Valve (PARTNER) trials.[18-20] The PARTNER 1A study reports 1-, 2-, and 5-year mortality rates of 24%, 34%, and 68%, respectively, while the PARTNER 2A study reports a 1- and 2-year global mortality rate of 12% and 16%, respectively. The overall survival rates in the studies reported in *Table 1* are positioned exactly between these values.

These studies also confirm the data from PARTNER studies that patients with severe AS managed with optimal medical therapy alone, with or without amyloid cardiomyopathy, have poor survival.[2]

Regardless of mortality, from the analysis of published studies, two other observations appear clinically relevant: a higher incidence of heart failure during medium-term follow-up, and a higher rate of peri-procedural atrioventricular block with the need for pacemaker implantation.[1,21]

Unlike TAVR, patients with AC-TTR and concomitant severe AS undergoing aortic valve replacement surgery show higher mortality (*Table 1*), probably related to simultaneous cardiopulmonary bypass and the risks of open-heart surgery.

In conclusion, what are the clinical implications of the coexistence of cardiac amyloidosis and aortic stenosis?

Correct recognition of the association has relevant clinical consequences. The score proposed by Nitsche *et al.*[2] allows patients with AC to be recognized with good sensitivity among those undergoing screening for aortic valve replacement, without overloading the resources of the centres and can therefore be proposed as a reasonable starting point. Regarding the decision to proceed with valve replacement or not, although the evidence is relatively limited (no more than 100 patients studied in prospective non-randomized studies), all the above considerations make it reasonable to state that in patients with severe AS and associated AC-TTR, valve replacement should not be excluded when clinically indicated, nor delayed by an invasive diagnostic work-up (biopsy) for the recognition of AC-TTR.[2]

In fact, other things being equal, the coexistence of AC can guide the choice between the aortic valve replacement

methods towards the TAVR procedure, also considering the fact that often the patients are more fragile overall.[15]

Patients with associated AC should be monitored with particular care after the procedure, given the increased likelihood of developing heart failure related to amyloidosis.

Once TAVR is performed, these patients could likely benefit from disease-modifying therapy for amyloid cardiomyopathy. Since these patients generally have advanced forms of AC and have not yet been included in any of the phase 3 trials,[22] a dedicated randomized trial is highly desirable.

Conflict of interest: none declared.

References

1. Rosenblum H, Masri A, Narotsky DL, Goldsmith J, Hamid N, Hahn RT, Kodali S, Vahl T, Nazif T, Khalique OK, Bokhari S, Soman P, Cavalcante JL, Maurer MS, Castaño A. Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. *Eur J Heart Fail* 2021;**23**:250–258.
2. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, Wollenweber T, Ahmed N, Thornton GD, Kelion AD, Sabharwal N, Newton JD, Ozkor M, Kennon S, Mullen M, Lloyd G, Fontana M, Hawkins PN, Pugliese F, Menezes LJ, Moon JC, Mascherbauer J, Treibel TA. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol* 2021;**77**:128–139.
3. Longhi S, Lorenzini M, Gagliardi C, Milandri A, Marzocchi A, Marrozzini C, Saia F, Ortolani P, Biagini E, Guidalotti PL, Leone O, Rapezzi C. Coexistence of degenerative aortic stenosis and wild-type transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imaging* 2016;**9**:325–327.
4. Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, Hartman N, Hawkins PN, Menezes LJ, Moon JC. Prevalence of cardiac amyloidosis in patients referred for transcatheter aortic valve replacement. *J Am Coll Cardiol* 2018;**71**:463–464.
5. Nitsche C, Aschauer S, Kammerlander AA, Schneider M, Poschner T, Duca F, Binder C, Koschutnik M, Stiftinger J, Goliasch G, Siller-Matula J, Winter M-P, Anvari-Pirsch A, Andreas M, Geppert A, Beitzke D, Loewe C, Hacker M, Agis H, Kain R, Lang I, Bonderman D, Hengstenberg C, Mascherbauer J. Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. *Eur J Heart Fail* 2020;**22**:1852–1862.
6. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:2879–2887.
7. Treibel TA, Fontana M, Gilbertson JA, et al. Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. *Circ Cardiovasc Imaging* 2016;**9**:e005066 https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.116.005066 (16 June 2021).
8. Chacko L, Martone R, Bandera F, Lane T, Martinez-Naharro A, Boldrini M, Rezk T, Whelan C, Quarta C, Rowczenio D, Gilbertson JA, Wongwarawipat T, Lachmann H, Wechalekar A, Sachchithanantham S, Mahmood S, Marcucci R, Knight D, Hutt D, Moon J, Petrie A, Cappelli F, Guazzi M, Hawkins PN, Gillmore JD, Fontana M. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. *Eur Heart J* 2020;**41**:1439–1447.
9. Sperry BW, Jones BM, Vranian MN, Hanna M, Jaber WA. Recognizing transthyretin cardiac amyloidosis in patients with aortic stenosis: impact on prognosis. *JACC Cardiovasc Imaging* 2016;**9**:904–906.
10. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJJC, Piazza N, Kappetein AP. Aortic stenosis in the elderly. *J Am Coll Cardiol* 2013;**62**:1002–1012.
11. Tanskanen M, Peuralinna T, Polvikoski T, Notkola I-L, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. 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**:232–239.
12. Longhi S, Guidalotti PL, Quarta CC, Gagliardi C, Milandri A, Lorenzini M, Potena L, Leone O, Bartolomei I, Pastorelli F, Salvi F, Rapezzi C. Identification of TTR-related subclinical amyloidosis with 99mTc-DPD scintigraphy. *JACC Cardiovasc Imaging* 2014;**7**:531–532.
13. Mohamed-Salem L, Santos-Mateo JJ, Sanchez-Serna J, Hernández-Vicente Á, Reyes-Marle R, Castellón Sánchez MI, Claver-Valderas MA, Gonzalez-Vioque E, Haro-del Moral FJ, García-Pavía P, Pascual-Figal DA. Prevalence of wild type ATTR assessed as myocardial uptake in bone scan in the elderly population. *Int J Cardiol* 2018;**270**:192–196.
14. Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, Koch A, Sack F-U, Katus HA, Linke RP, Dengler TJ. High prevalence of amyloid in 150 surgically removed heart valves—a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions. *Cardiovasc Pathol* 2010;**19**:228–235.
15. Pibarot P, Lancellotti P, Narula J. Concomitant cardiac amyloidosis in severe aortic stenosis. *J Am Coll Cardiol* 2021;**77**:140–143.
16. Mangione PP, Verona G, Corazza A, Marcoux J, Canetti D, Giorgetti S, Raimondi S, Stoppini M, Esposito M, Relini A, Canale C, Valli M, Marchese L, Faravelli G, Obici L, Hawkins PN, Taylor GW, Gillmore JD, Pepys MB, Bellotti V. Plasminogen activation triggers transthyretin amyloidogenesis in vitro. *J Biol Chem* 2018;**293**:14192–14199.
17. Oda S, Takashio S, Nagamatsu S, Yamashita T, Uchimura R, Kidoh M, Utsunomiya D, Nakaura T, Tsujita K, Yamashita Y. Myocardial extracellular volume quantification using CT for the identification of occult cardiac amyloidosis in patients with severe aortic stenosis referred for transcatheter aortic valve replacement. *Amyloid* 2019;**26**:97–98.
18. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;**374**:1609–1620.
19. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;**366**:1696–1704.
20. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
21. Castaño A, Bokhari S, Maurer MS. Could late enhancement and need for permanent pacemaker implantation in patients undergoing TAVR be explained by undiagnosed transthyretin cardiac amyloidosis? *J Am Coll Cardiol* 2015;**65**:311–312.
22. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.