Review Article

The Role of Cardiac Magnetic Resonance in patients with Amyloidosis and Aortic Stenosis

O Papel da Ressonância Magnética Cardíaca em Pacientes com Amiloidose e Estenose Aórtica

Pedro Macedo Esmeraldo Barbosa[1]; *Tiago Augusto Magalhães*[1]
[1]*Hospital do Coração, São Paulo, SP, Brazil.*

Abstract

Cardiac magnetic resonance imaging (CMR) plays an important role in the diagnosis and prognosis of various heart diseases. The incidence of cardiac amyloidosis and aortic stenosis has been increasing in recent years, especially with the aging population, and their possible coexistence has created frequent diagnostic challenges in clinical practice. CMR assumes an important value in this context due to its unique capacity for multiparametric assessment evaluations that include anatomical, functional, and histopathological aspects. The present review aimed to increase our knowledge of the diagnosis and prognosis of amyloidosis in the presence of aortic stenosis and highlighted the importance of CMR in this scenario.

Introduction

The coexistence of cardiac amyloidosis (CA) and aortic stenosis (AS) has increasing relevance in clinical practice due to its high prevalence, diagnostic difficulty, and therapeutic management challenges. Primary CA forms feature amyloid light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) as the main presentations affecting up to 25% of octogenarians,[1] especially the latter. On the other hand, AS has a prevalence of up to 4% among individuals over 70 years,[2] with calcific degeneration as its main etiological landmark. CA[3] affects an estimated 5–16% of patients with major AS, reaching 30% in cases of low-flow low-gradient AS.[2]

The correlation between the two diseases can be explained by several factors, with the common prevalent age group being the most important. The second factor is related to the histological analysis of valves removed in valve replacement surgeries, demonstrating amyloid deposits in 74% of stenotic aortic valves, inferring the possibility of AS and CA having a similar pathophysiological pathway.[4] Another possible factor is mediated by increased AS afterload, which would potentially trigger amyloid protein accumulation in the ventricular myocardium.[4]

Keywords

Magnetic resonance imaging; Heart; Amyloidosis; Aortic valve stenosis.

Mailing Address: Tiago Augusto Magalhães •
Rua Desembargador Eliseu Guilherme, 147, Paraíso. CEP: 04004-030
São Paulo, SP, Brazil.
E-mail: tiaugusto@gmail.com
Manuscript received 6/24/2022; revised 7/11/2022; accepted 8/9/2022

Editor responsible for the review: Tiago Senra Garcia dos Santos

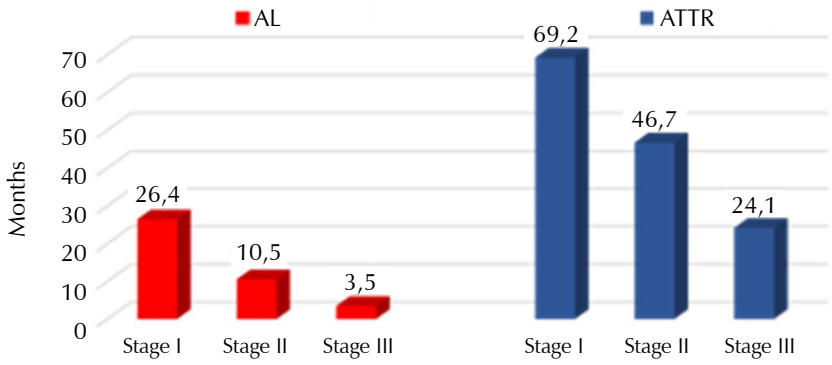
DOI: 10.47593/2675-312X/20223503eabc320i

The prognosis of patients with CA and AS tends to be worse than that of patients with isolated AS, which directly interferes with its therapeutic management. CA alone has a variable prognosis. The reported median survival of patients with ATTR is 24.1–69.2 months, while that of patients with AL is 3.5–26.4 months[5] (Figure 1). In a retrospective study, patients with ATTR + major AS had significantly better 1-year overall mortality than those with major AS alone (56% vs. 20%, $p < 0.0001$).[6] A study of patients with ATTR + AS versus AS alone showed that the former had an overall mortality that was almost twice as high (mean follow-up, 1.7 years) regardless of transcatheter aortic valve replacement (TAVR) or exclusive clinical maintenance (24.5% vs. 13.9%; $p < 0.05$). There is also evidence of no difference in 2-year mortality rates between patients with isolated ATTR and those with major ATTR + AS (33% vs. 37%, respectively; hazard ratio, 1.22; 95% confidence interval, 0.62–2.42; $p = 0.566$), even among the latter undergoing valve replacement, which suggests that ATTR would have a greater impact on mortality.[6] On the other hand, there is evidence of improved prognosis among patients with ATTR + AS undergoing valve replacement versus those remaining on clinical treatment,[3,7] while small studies reported the superiority of TAVR to surgical aortic valve replacement (SAVR) in patients with ATTR + AS.[2] Due to the higher prevalence of ATTR versus AL, it is important to emphasize that most patients with CA + AS included in the studies have the ATTR form.

Due to the high prevalence and impact of the association between CA and AS, it is essential to investigate CA in patients with AS who are eligible for valve replacement. Diagnostic flow involves three main steps: 1) identifying suspected signs; 2) performing scintigraphy/monoclonal protein peak surveys; and 3) defining the diagnosis (with vs. without biopsy or genotyping). Cardiac magnetic resonance imaging (CMRI) is a fundamental diagnostic method for CA in the presence of AS (Figure 2) due to its ability to detect relevant morphological functional changes. CMRI can also individualize the prognosis of CA and AS by aiding the identification of patients who will benefit most from valve replacement.

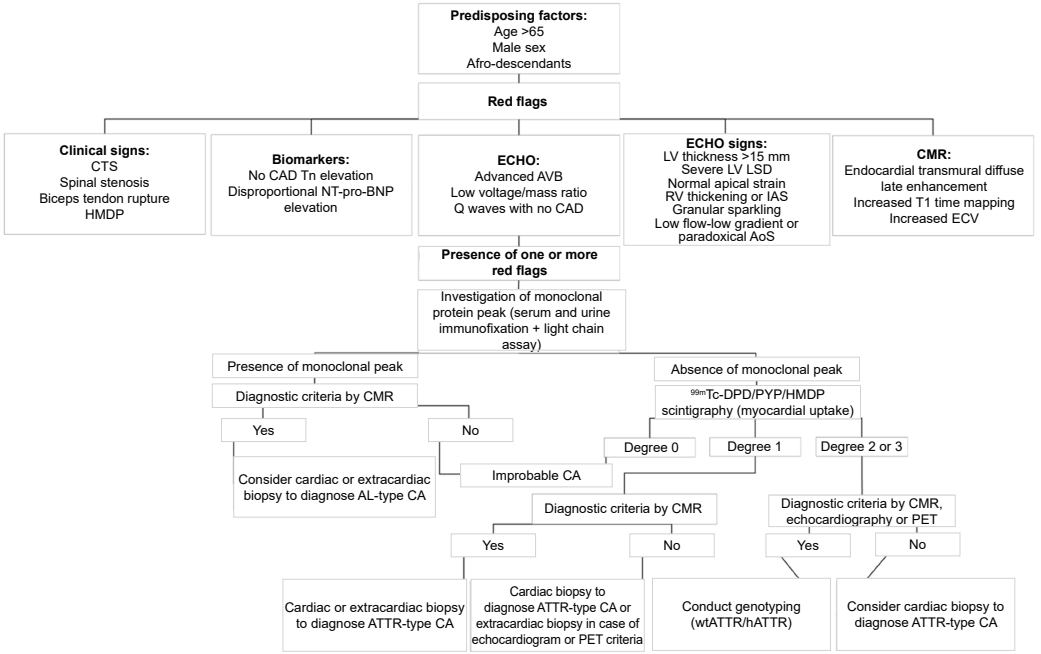
CMRI diagnosis

Cardiac adaptations to increased afterload by AS are similar to those that occur in CA (e.g., concentric left ventricle remodeling). In addition, the presence of other diseases, such as coronary insufficiency and systemic arterial hypertension, interferes with the accuracy of several methods in the diagnosis of AS-associated CA. In this context, CMRI performs well (sensitivity, 85%; specificity, 92%) for diagnosing CA.[8] Due to its multiparameter analysis, it is also fundamental in the diagnosis of AS-associated CA (Figure 2) or AS alone.



Source: adaptado de Cappelli et al.[5] AL amyloidosis staging: I: cTnI < 0.1 µg/L and NT-proBNP < 332 ng/L; II: cTnI ≥ 0.1 µg/L or NT-proBNP ≥ 332 ng/L; III: cTnI ≥ 0.1 µg/L and NT-proBNP ≥ 332 ng/L. ATTR amyloidosis staging: I: eGFR ≥ 45 mL/min/1.73 m2 Pand NT-proBNP ≤ 3000 ng/L; II: eGFR < 45 mL/min/1.73 m2 or NT-proBNP > 3,000 ng/L; III: eGFR < 45 mL/min/1.73 m2 and NT-proBNP > 3,000 ng/L eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; TnI, cardiac troponin I; TnT, cardiac troponin T .

Figure 1 – *Median survival of patients with AL vs. ATTR amyloidosis.*



AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; AVB, atrioventricular block; CA, cardiac amyloidosis; CTS, carpal tunnel syndrome; Tc-99m-DPD, technetium-99m with 3,3-diphosphono-1,2-propanedicarboxylic acid; ECV, extracellular volume; hATTR, hereditary transthyretin amyloidosis; HMDP, hydroxymethylenediphosphonate; LSD, longitudinal systolic dysfunction; PPM, permanent pacemaker; PYP, pyrophosphate; Tn, troponin; wATTR, wild (senile) transthyretin amyloidosis. Cardiac magnetic resonance imaging diagnostic criteria: myocardial thickening, ECV ≥ 40%, diffuse late myocardial enhancement, or myocardial inversion time < blood inversion time. Echocardiographic diagnostic criteria: myocardial thickening > 12 mm, apical longitudinal/mid-basal longitudinal strain > 1, or diastolic dysfunction grade ≥ 2.

Figura 2 – *Proposed diagnostic algorithm for CA in the presence of AS. Positron emission tomography diagnostic criteria: target–to–blood pool ratio > 1.5 or retention index > 0.030 min-1.*

Anatomical functional parameters

Left ventricular (LV) myocardial mass thickening and increases, atrial dilatation, and LV diastolic and systolic dysfunction are common in ATTR and AS but more severe when coexistent.

Patients with ATTR + AS versus AS alone have a higher LV mass index (105 ± 21 vs. 73 ± 21 g/m^2) as well as a lower LV ejection fraction and stroke volume (43 ± 17 vs. 52 ± 18% and 33 ± 10 vs. 44 ± 13 mL/m^2, respectively).[1] Myocardial thickening tends to be septally asymmetrical in the presence of ATTR, with a prevalence of 79%, versus concentrically thickened in AL.

Characteristics that are common in CA but uncommon in

AS are pericardial effusion, interatrial septal thickening, biatrial dilatation (Figure 3), atrioventricular valve thickening, and RV thickening (with or without isolated systolic RV dysfunction). Atrial wall thickening occurs in up to 70% of patients with ATTR + AS.[6]

Histological parameters

Noninvasive myocardial histological analysis by CMRI is based on the proton relaxation properties of each tissue used to identify the presence of localized or diffuse fibrosis. Different techniques (late enhancement, native myocardial T1 mapping, myocardial extracellular space volume calculations, myocardial-blood inversion time rate analysis, and myocardial edema investigation) can be used for cardiac tissue characterizations with quantitative measurements that assess the extent of damaged induced by amyloid substance deposits.

Native myocardial T1 mapping

Native myocardial T1 mapping, which analyzes the magnetic characteristic of tissue proton relaxation, is performed without a gadolinium injection. Its primary advantage involves the early identification of myocardial fibrosis, especially that with diffuse distribution, which may not be identified by late enhancement, making the diagnostic evaluation more sensitive. Normal myocardial T1 values may vary according to the machine used and are usually between 950 and 1,050 ms. Patients with isolated CA, CA + AS, or isolated AS may present with a prolonged T1, being significantly higher in patients with CA. Patients with ATTR + AS have higher native T1 values than those with isolated AS (native T1: 1,125 ± 49 vs. 1,035 ± 60 ms; $p = 0.002$).[6]

Myocardial edema research

Myocardial edema may be present in CA but is uncommon in isolated AS. It is diagnosed through T2 time mapping or specific T2-weighted sequences without the need for a gadolinium injection. The presence of myocardial edema with AS should prompt the investigation of other concomitant heart diseases.

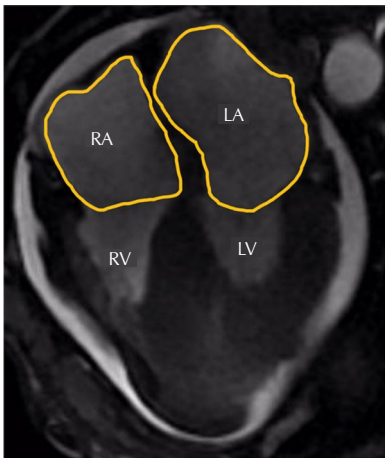
Late myocardial enhancement

Late enhancement, which is based on preferential gadolinium uptake in tissues rich in extracellular matrix, aids in the contrast of healthy and pathological myocardium minutes after its administration. The enhancement pattern changes according to etiology. In ATTR, there a basal-apical enhancement distribution occurs that can spare the apical segments (Figure 4). AL has its own characteristics with circumferential subendocardial involvement. The presence of late enhancement in the atrial myocardium (Figure 5) or the RV is frequent in CA, with a prevalence of atrial enhancement of up to 90% and of RV enhancement of 37–97% of ATTR + AS cases.[6] Late enhancement occurs in up to 40% of isolated AS cases, being mainly present in the LV with a focal mesocardial pattern.

Extracellular volume (ECV) analysis is estimated based on native myocardial T1 time, post-contrast T1 time, and patient hematocrit at the time of the examination (normal ECV values are <25 to 27%).[9] Both CA and AS can increase myocardial ECV, but greater increases are seen in the presence of CA, particularly the ATTR type. Patients with ATTR + AS have higher ECV values than those with isolated AS (41.2 ± 16.7 vs. 27.9 ± 4.1%; $p < 0.001$).[6] ECV values > 40% are rare in diseases other than CA. In advanced CA stages, ECV can be more important for the diagnosis than T1 mapping.

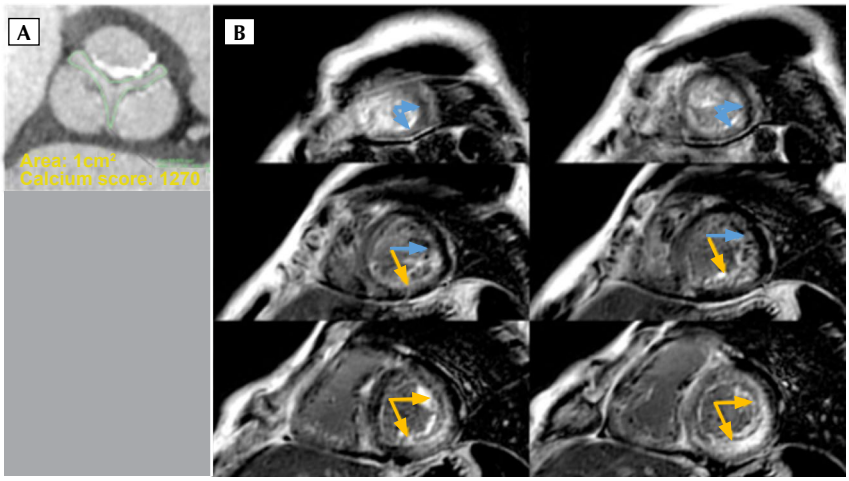
Prognosis by CMRI

Patients with CA + AS lack formal therapeutic recommendations regarding the approach to AS, which makes its treatment challenging. A prognostic evaluation before valve replacement is essential, and CMRI can aid the decision, especially through late enhancement analysis and



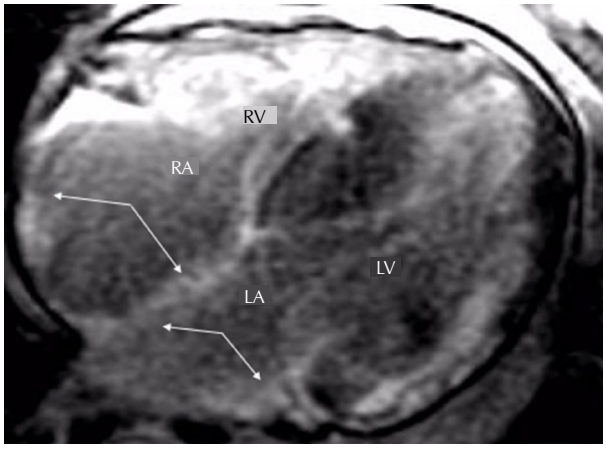
Source: collection Dr. Pedro Macedo. ATTR, transthyretin amyloidosis; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. .

Figure 3 – *Cine-resonance image taken of a patient with ATTR amyloidosis showing biatrial dilatation, increased myocardial thickness, and a mild pericardial effusion.*



Source: collection Dr. Tiago Serna.

Figura 4 – *Images taken of a patient with AS and ATTR amyloidosis. (A) Computed tomography image demonstrating calcific AS (valve area, 1 cm2; valvular calcium score, 1,270). (B) Cardiac magnetic resonance images showing diffuse late myocardial enhancement more evident in the mid-basal segments compatible with the diagnosis of ATTR CA (orange arrow: late enhancement present; blue arrow: late enhancement absent).*



Source: collection Dr. Pedro Macedo. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Figure 5 – *Images of atrial fibrosis (white arrows) in a patient with ATTR amyloidosis.*

ECV. Late enhancement is a poor independent prognostic factor for all heart diseases. Moderate to severe AS carries an eight-fold increased risk of mortality regardless of stenosis severity. An increased relative risk of major cardiovascular events after aortic valve replacement in the presence of late enhancement has also been documented, as has the possibility of left ventricular dysfunction maintenance post-aortic valve replacement in the presence of late enhancement.[10]

ECV has excellent prognostic value in patients with ATTR + AS since it is correlated with mortality (Figure 6). An ECV < 25% is protective regardless of exclusive clinical treatment or valve replacement, with no reports of cardiovascular death within 1 year.[1]

Increased native myocardial T1 mapping interpreted in isolation showed only a tendency to be correlated with prognosis in patients with ATTR + AS, but the difference was not statistically significant (Figure 6).[1] Further studies with a greater number of patients may provide additional information about the use of native myocardial T1 mapping in the prognostic definition of this patient group.

Conclusion

CA and AS are increasingly encountered in clinical practice, mainly due to an increased number of diagnoses and continued population aging. The diagnosis of CA

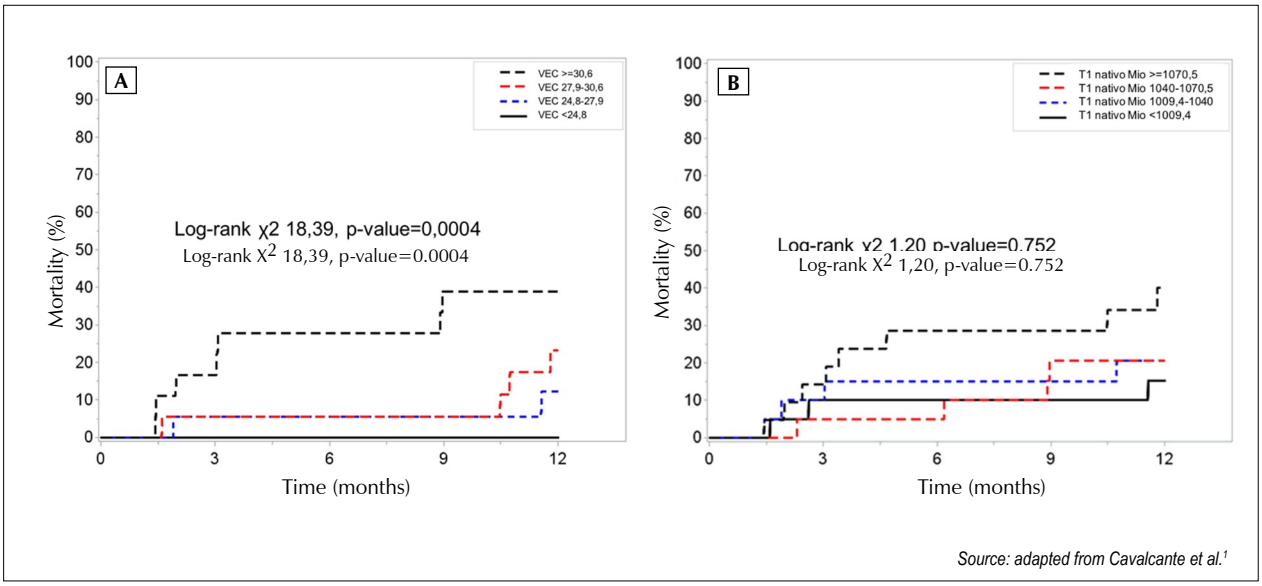


Figure 6 – *Mean survival of patients with CA + AS by ECV (A) or T1 time (B).*

should be considered in cases of suspicious signs or when phenotypic cardiac changes are noted beyond those expected according to AS severity. CMRI, which plays an important role in the diagnosis and prognosis of patients with CA + AS, is a fundamental test that enables more assertive therapeutic decisions.

Authors' contributions

Research conception and design: Barbosa PME, Magalhães TA; data collection: Barbosa PME, Magalhães TA; data analysis and interpretation: Barbosa PME, Magalhães TA; statistical analysis: Barbosa PME, Magalhães TA; funding: Barbosa PME, Magalhães TA; manuscript writing: Barbosa PME, Magalhães TA; critical review of the manuscript for important intellectual content: Barbosa PME, Magalhães TA.

Conflict of interest

The author declares that he has no conflict of interest

References

1. Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, 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: https://doi.org/10.1186/s12968-017-0415-x
2. Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, Gallet R, et al. Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;74(21):2638-51. doi: https://doi.org/10.1016/j.jacc.2019.09.056
3. Nitsche C, Aschauer S, Kammerlander AA, Schneider M, Poschner T, Duca F, et al. Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. Eur J Heart Fail. 2020;22(10):1852-62. doi: https://doi.org/10.1002/ejhf.1756
4. Galat A, Guellich A, Bodez D, Slama M, Dijos M, Zeitoun DM, et al. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? Eur Heart J. 2016;37(47):3525-31. doi: https://doi.org/10.1093/eurheartj/ehw033
5. Cappelli F, Perfetto F, Martone R, Di Mario C. Cardiac Amyloidosis in Patients Undergoing TAVR: Why We Need to Think About It. Cardiovasc Revasc Med. 2021;22:109-14. doi: https://doi.org/10.1016/j.carrev.2020.06.005
6. Balciunaite G, Rimkus A, Zurauskas E, Zaremba T, Palionis D, Valeviciene N, Aidietis A, et al. Transthyretin cardiac amyloidosis in aortic stenosis: Prevalence, diagnostic challenges, and clinical implications. Hellenic J Cardiol. 2020;61(2):92-8. doi: https://doi.org/10.1016/j.hjc.2019.10.004
7. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR Amyloidosis: Current and Emerging Management Strategies: *JACC: CardioOncology* State-of-the-Art Review. JACC CardioOncol. 2021;3(4):488-505. doi: https://doi.org/10.1016/j.jaccao.2021.06.006
8. Yilmaz A. The "Native T1 Versus Extracellular Volume Fraction Paradox" in Cardiac Amyloidosis: Answer to the Million-Dollar Question? JACC Cardiovasc Imaging. 2019;12(5):820-2. doi: https://doi.org/10.1016/j.jcmg.2018.03.029
9. Sado DM, Flett AS, Banypersad SM, White SK, Maestrini V, Quarta G, Lachmann RH, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart. 2012;98(19):1436-41. doi: https://doi.org/10.1136/heartjnl-2012-302346
10. Bohbot Y, Renard C, Manrique A, Levy F, Maréchaux S, Gerber BL, Tribouilloy C. Usefulness of Cardiac Magnetic Resonance Imaging in Aortic Stenosis. Circ Cardiovasc Imaging. 2020;13(5):e010356. doi: https://doi.org/10.1161/CIRCIMAGING.119.010356

11. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 2 of 2-Diagnostic criteria and appropriate utilization. J Nucl Cardiol. 2020;27(2):659-73. doi: https://doi.org/10.1007/s12350-019-01761-5. Erratum in: J Nucl Cardiol. 2021;28(4):1763-7.

12. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, et al. Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. J Am Coll Cardiol. 2021;77(2):128-39. doi: https://doi.org/10.1016/j.jacc.2020.11.006

13. Kristen AV, Schnabel PA, Winter B, Helmke BM, Longerich T, Hardt S, et al. 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(4):228-35. doi: https://doi.org/10.1016/j.carpath.2009.04.005

14. Longhi S, Lorenzini M, Gagliardi C, Milandri A, Marzocchi A, Marrozzini C, et al. Coexistence of Degenerative Aortic Stenosis and Wild-Type Transthyretin-Related Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2016;9(3):325-7. doi: https://doi.org/10.1016/j.jcmg.2015.04.012

15. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, 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):2879-87. doi: https://doi.org/10.1093/eurheartj/ehx350

16. Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. Eur Heart J. 2020;41(29):2759-67. doi: https://doi.org/10.1093/eurheartj/ehaa170

17. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, 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(8):e005066. doi: https://doi.org/10.1161/CIRCIMAGING.116.005066

18. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, 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(8):e005066. doi: https://doi.org/10.1161/CIRCIMAGING.116.005066