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UNIVERSITY OF MEDICINE AND PHARMACY
„CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
DOMAIN: MEDICINE

CARDIAC AMYLOIDOSIS – FROM RECOGNITION AND PHENOTYPING TO RISK STRATTIFICATION FOR ARRHYTHMIAS

DOCTORAL THESIS SUMMARY

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List of published papers

1. First author

1.1. Articles published in extenso:

1.1.1. Neculae G*, **Adam R***, Jercan A, Bădeliță S, Tjahjadi C, Draghici M, Stan C, Bax JJ, Popescu BA, Marsan NA, Coriu D, Jurcuț R. Cardiac amyloidosis is not a single disease: a multiparametric comparison between the light chain and transthyretin forms. ESC Heart Fail. 2024 May 16. doi: 10.1002/ehf2.14852. Epub ahead of print. PMID: 38757395.

Impact Factor 3.2 – Personal cotributions, Chapter 5;

*Authors with equal contribution as first author

1.1.2. **Adam RD**, Coriu D, Jercan A, Bădeliță S, Popescu BA, Damy T, Jurcuț R. Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. ESC Heart Fail. 2021 Aug;8(4):2380-2396. doi: 10.1002/ehf2.13443. Epub 2021 Jun 5. PMID: 34089308; PMCID: PMC8318516

Impact factor 3.2 – Literature Review, Chapter 3;

1.1.3. **Adam R**, Neculae G, Stan C, Jurcut R. Current Challenges of Cardiac Amyloidosis Awareness among Romanian Cardiologists. Diagnostics (Basel). 2021 May 6;11(5):834. doi: 10.3390/diagnostics11050834. PMID: 34066384; PMCID: PMC8148147

Impact factor 3.992 – Personal Contributions – Chapter 4;

1.1.4. **Adam R**, Munteanu A, Mititelu R, Onciul S, Deleanu D, Iliescu VA, Popescu BA, Jurcut R. Severe Aortic Stenosis and ATTRwt Amyloidosis - Beware in the Aging: A Case Report and Review of the Literature. Clin Interv Aging. 2020 Oct 2;15:1863-1872. doi: 10.2147/CIA.S265103. PMID: 33061335; PMCID: PMC7537991.

Factor de impact 4.458 – Literature review, Chapter 2.

1.2. Oral presentations:

1.2.1. **Robert Adam**, Gabriela Neculae, Sorina Bădeliță, Jan Stassen, Andreea Jercan, Monica Roșca, Andreea Călin, Carmen Beladan, Roxana Enache, Marinela Serban, Daniel Coriu, Jeroen Bax, Cristian Băicuş, Nina Ajmone Marsan, Bogdan A. Popescu, Ruxandra Jurcuț, Left atrial function and the risk of new onset atrial fibrillation in cardiac amyloidosis. 2nd prize in the Young Invastigator Award session, National Congress of Cardiology, Sinaia 2023;

1.2.2. **R Adam**, G Neculae, S Badelita, et al. Left atrial function and the risk of new-onset atrial fibrillation in cardiac amyloidosis, Oral presentation at the ESC Congress 2023;

1.2.3. **R Adam**, A Jercan, S Badelita, D Coriu, C Stan, M Rosca, AM Balahura, BA Popescu, R Jurcut. Cardiac amyloidosis is not a single disease. Echocardiographic Study of light chain and transthyretin types. 3rd prize in the Young Invastigator Award session, National Congress of Cardiology, Sinaia 2019;

1.3. Abstracts presented in international congresses published in ISI Journals:

1.3.1. **Robert Adam**, Gabriela Neculae, Sorina Nicoleta Badelita, Catherina Tjahjadi, Andreea Jercan, Catalina Sabina Cremeneanu, Monica Roșca, Andreea Călin, Carmen Beladan, Marinela Șerban, Daniel Coriu, Jeroen Bax, Cristian Băicuș, Bogdan A. Popescu, Nina Ajmone Marsan, Ruxandra Jurcut, Left atrial mechanical dispersion as a novel predictor biomarker of new-onset atrial arrhythmias in cardiac amyloidosis. International Symposium on Amyloidosis 2024;

1.3.2. **R Adam**, A Jercan, S Badelita, D Coriu, C Stan, M Serban, C Beladan, M Rosca, AM Balahura, C Ginghina, BA Popescu, R Jurcut. Cardiac amyloidosis is not a single disease. An echocardiographic study of light chain vs. transthyretin forms. Euroecho 2019;

1.3.3. **R Adam**, A Jercan, S Badelita, A Fruntelata, R Ciudin, BA Popescu, C Ginghina, M Draghici, C Stan, D Coriu, R Jurcut. Heart failure aggravated

by beta blockers. Could this suggest the etiology? Heart Failure Congress 2019.

2. Co-author:

2.1. Articles published in extenso:

2.1.1. Jan Stassen, Catherina Tjahjadi, **Robert Adam** et al. Left Ventricular Myocardial Work to Differentiate Cardiac Amyloidosis From Hypertrophic Cardiomyopathy. J Am Soc Echocardiogr. 2023 Feb;36(2):252-254. doi: 10.1016/j.echo.2022.08.015. Epub 2022 Sep 13

Impact Factor 5.4;

2.1.2. Claudiu Stan, Raluca Mititelu, **Robert Adam** et al. Awareness of Nuclear Medicine Physicians in Romania Regarding the Diagnostic of Cardiac Amyloidosis—A Survey-Based Study. Diagnostics (Basel). 2022 Feb 21;12(2):556. doi: 10.3390/diagnostics12020556

Imapct Factor 3.6;

2.1.3. Ruxandra Jurcuț, Sebastian Onciul, **Robert Adam** et al. Multimodality imaging in cardiac amyloidosis: a primer for cardiologists. Eur Heart J Cardiovasc Imaging. 2020 Aug 1;21(8):833-844. doi: 10.1093/ehjci/jeaa063

Impact Factor 6.875.

2.2. Abstracts presented in international congresses published in ISI Journals:

2.2.1. Sorina Nicoleta Badelita, Andreea Jercan, Larisa Emilia Zidaru, Ruxandra Jurcut, **Robert Adam**, Mirela Ramona Draghici, Popescu Monica, Daniel Coriu, DRD vs D-VCD in patients with newly diagnosed AL amyloidosis. International Symposium on Amyloidosis 2024;

2.2.2. Sorina Nicoleta Badelita, Andreea Jercan, Larisa Emilia Zidaru, Mirela Ramona Draghici, Daniela Neagu, Ruxandra Jurcut, **Robert Adam**, Claudiu-Adrian Stan, Daniel Coriu, Clinical phenotype of Romanian patients with transthyretin-type hereditary amyloidosis due to Val 107

mutation. International Symposium on Amyloidosis 2024;

2.2.3. G. Neculae, **R. Adam**, R. Beyer, C. Berbescu, S. Onciul, S. Bădeliță, C. Stan, M. Drăghici, A. Jercan, D. Coriu, R. Jurcuț, Novel transthyretin variant linked to cardiac amyloidosis in the Romanian population. JESFC 2024;

2.2.4. G Neculae, **R Adam**, S Badelita, S Onciul, A Jercan, D Neagu, M Draghici, D Coriu, B A Popescu, R Jurcut, Cardiac MRI as a possible alternative to echocardiography for therapeutic response monitoring in ATTR cardiomyopathy: a multiparametric evaluation in patisiran treated patients, EACVI Congress 2023;

2.2.5. G. Neculae, **R. Adam**, A. Jercan, S. Badelita, M. Draghici, C. Stan, M. Rosca, C. Beladan, D. Coriu, B.A. Popescu, R. Jurcut. Cardiac amyloidosis is not a single disease: a multiparametric comparison between the light chain and transthyretin forms. ESC Congress 2022;

2.2.6. Catherina Tjahjadi, **Robert Adam**, Philippe Debonnaire, Mathias Claeys, Maarten Desmet, Kensuke Hirasawa, Bogdan Alexandru Popescu, Ruxandra Jurcut, Victoria Delgado, Jeroen Bax, Nina Marsan. Constructive work and longitudinal strain-derived apical sparing pattern differentiate cardiac amyloidosis from hypertrophic cardiomyopathy. The American College of Cardiology's (ACC) 70th Annual Scientific Session&Expo, 2021;

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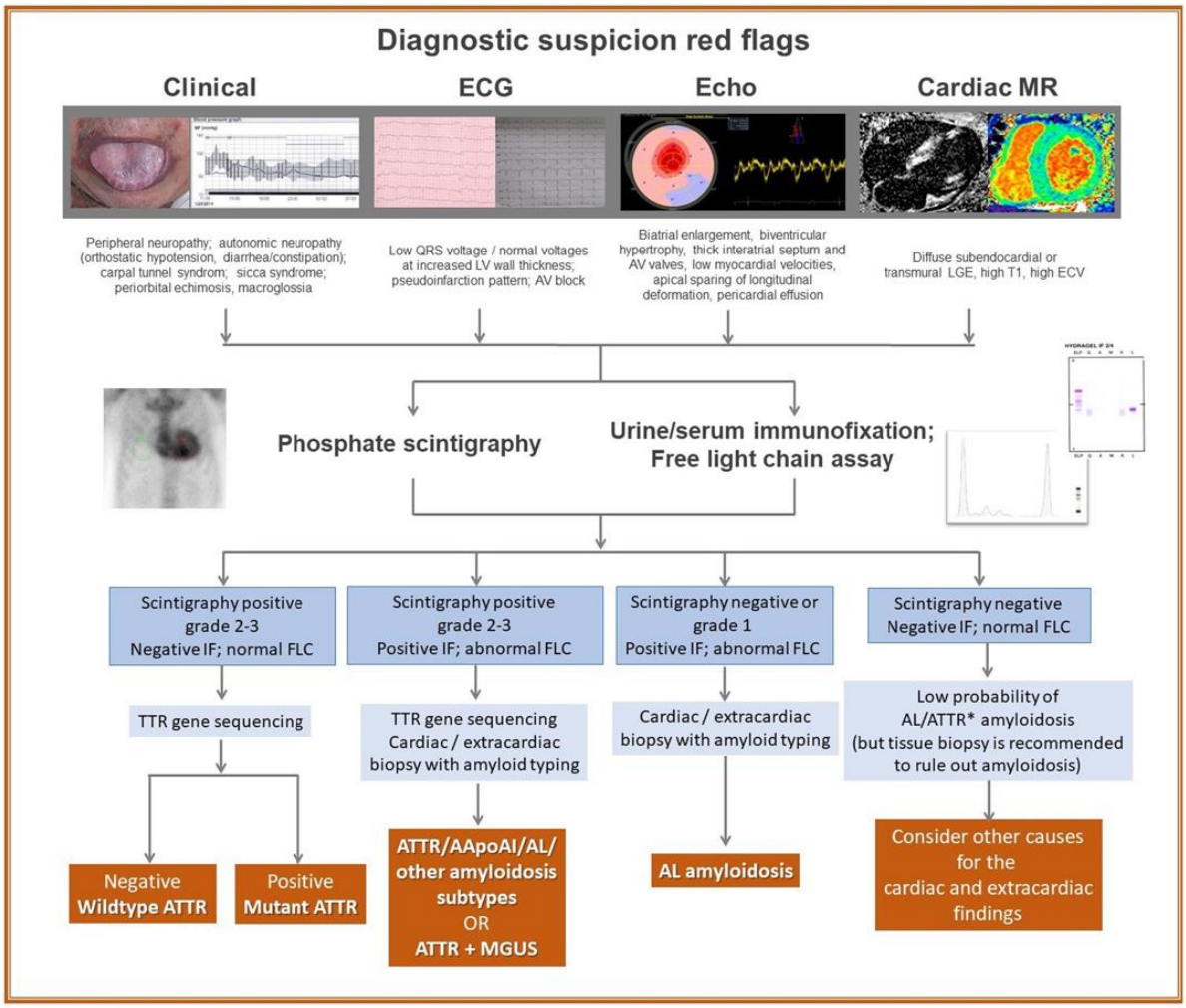
Literature review

Cardiac amyloidosis (CA) is described as a rare but severe condition, presenting as a major challenge in cardiology (1). The choice of this research topic was driven by the urgent need to improve the early recognition and treatment of this disease, which significantly affects the quality of life and prognosis of patients. Although cardiac amyloidosis has been the subject of intense research globally, in Romania, the awareness and diagnosis of this disease remain insufficient.

Considered until recent years a rare disease (2), CA, both the light chain type (AL) and the transthyretin type (ATTR), usually manifests as restrictive cardiomyopathy associated with a wide range of systemic manifestations, from polyneuropathy to renal failure and hematological disease (3–5). This constellation of symptoms represents the base of clinical suspicion as the first part of the diagnostic algorithm (6–8). Constructed on the elements of multimodality imaging, from echocardiography to cardiac magnetic resonance and bone scintigraphy, the diagnosis of cardiac amyloidosis needs to establish the exact type of amyloid precursor in order to guide specific treatment (Figure 1) (9). Given the current advances in specific treatment in ATTR and AL with the emergence of gene silencers and immunotherapy respectively, the prognosis for these patients has been continuously improving in the past years (10). Even so early recognition of disease remains a must as the delay in diagnosis may lead to unfavorable evolution (11).

For now, patients with cardiac amyloidosis do not benefit from heart failure dedicated guideline-directed medical therapy even in the presence of reduced ejection fraction, with diuretics remaining the first line of therapy for symptom management and decongestion (6–8). Moreover, as disease progression is associated with important atrial dysfunction the evolution of these patients may be aggravated by thromboembolic complications (12–16). The need for anticoagulation remains a highly debated topic in patients with sinus rhythm but the emerging of new parameters predicting atrial fibrillation may provide more clarity on the matters (17–20).

As clinical studies continue, and the field of precision medicine evolves through gene therapies, we expect new developments in terms of both specific treatment and heart failure management in cardiac amyloidosis.



* Except in genotype positive / phenotype negative mutant ATTR relatives or specific mutations with known low myocardial uptake like TTR Phe64Leu.
Legend: FLC, free light chains; MGUS, monoclonal gammapathy of unknown significance
For all other abbreviations see text.

Figure 1. Noninvasive diagnostic algorithm for Cardiac amyloidosis

Personal Contributions

Current challenges of Cardiac Amyloidosis Awareness among Romanian Cardiologists

Introduction: Cardiac amyloidosis is often underdiagnosed in Romania due to a lack of awareness and education among cardiologists. This section of the study explores the level of awareness and knowledge of Romanian cardiologists about this disease through a detailed survey.

Materials and Methods: The study included a survey addressed to cardiologists in Romania, which assessed their experience with patients with cardiac amyloidosis, the diagnostic methods used, and their knowledge of available treatments (21).

Results

Study participants: The majority of participants were cardiologists with varying levels of professional experience, ranging from young specialists to physicians with many years of practice. A total of 195 cardiologists responded, evenly distributed across Romania and from all stages of training – residents (33%), specialists (31%), and senior consultants (36%).

Experience with Cardiac Amyloidosis Patients: The majority of cardiologists reported having encountered very few patients with this condition, indicating a possible underdiagnosis.

Diagnostic developement: Only a small percentage of participants reported using advanced diagnostic methods, such as cardiac magnetic resonance imaging or bisphosphonate scintigraphy.

Knowledge of tratment options: Many cardiologists were not familiar with the modern treatments available for cardiac amyloidosis, highlighting an urgent need for ongoing medical education in this field.

Discussion:

Prevalence and treatmnet of ATTRwt: The study revealed that ATTRwt is often underdiagnosed and inadequately treated.

Prevalence of ATTRv in Romania: Awareness of hereditary types of amyloidosis is low, and delayed diagnosis is common (22).

The Diagnosis of Cardiac Amyloidosis: Delayed diagnosis is a major issue, caused by a lack of awareness and the insufficient use of modern diagnostic tools.

Treatment options: Therapeutic options are limited by insufficient knowledge and reduced access to modern therapies.

Study limitations: The small number of participants and potential reporting errors are acknowledged as limitations.

Conclusions: The study highlights the urgent need to increase awareness and education among Romanian cardiologists about cardiac amyloidosis, in order to improve the diagnosis and treatment of this disease.

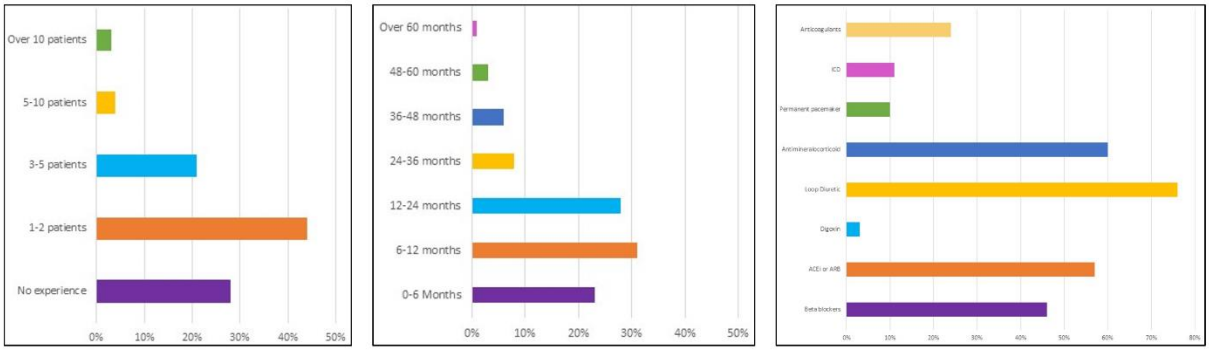


Figure 2. Representative responses to the questionnaire regarding the respondents' experience with amyloidosis patients (A), diagnostic delay (B), and therapeutic options (C).

Cardiac amyloidosis is not a single disease: a multiparametric comparison between the light chain and transthyretin forms

Introduction: Systemic amyloidosis represents a heterogeneous group of diseases resulting from amyloid fibre deposition. The purpose of this study is to establish a differential diagnosis algorithm targeted towards the two most frequent subtypes of CA.

Materials and Methods: We prospectively included all consecutive patients with ATTR and AL evaluated between 2018 and 2022 in two centres in a score derivation cohort and a different validation sample. All patients had a complete clinical, biomarker, electrocardiographic, and imaging evaluation. Confirmation of the final diagnosis with amyloid typing was performed according to the current international recommendations (23).

Rezultate: The study population included 81 patients divided into two groups: ATTR (group 1, *n* = 32: 28 variant and 4 wild type) and AL (group 2, *n* = 49). ATTR patients were younger (50.7 ± 13.9 vs. 60.2 ± 7.3 years, *P* = 0.0001), and significantly different in terms of NT-proBNP [ATTR: 1472.5 ng/L (97–4218.5) vs. AL 8024 ng/L (3058–14 069) *P* = 0.001], hs-cTn I [ATTR: 10 ng/L (4–20) vs. AL 78 ng/L (32–240), *P* = 0.0002], GFR [ATTR 95.4 mL/min (73.8–105.3) vs. AL: 68.4 mL/min (47.8–87.4) *P* = 0.003]. At similar left ventricular (LV) wall thickness and ejection fraction, the ATTR group had less frequently pericardial effusion (ATTR: 15% vs. AL: 33% *P* = 0.0027), better LV global longitudinal strain (ATTR: _13.1% ± 3.5 vs. AL: _9.1% ± 4.3 *P* = 0.04), RV strain (ATTR: _21.9% ± 6.2 vs. AL: _16.8% ± 6 *P* = 0.03) and better reservoir function of the LA strain (ATTR: 22% ± 12 vs. AL: 13.6% ± 7.8 *P* = 0.02). Cut-off points were calculated based on the Youden method. We attributed to 2 points for parameters having an AUC > 0.75 (NT-proBNP AUC 0.799; hs-cTnI AUC 0.87) and 1 point for GFR (AUC 0.749) and TTE parameters (GLS AUC 0.666; RV FWS AUC 0.649, LASr AUC 0.643). A score of equal or more than 4 points has been able to differentiate between AL and ATTR (sensitivity 80%, specificity 62%, AUC = 0.798). The differential diagnosis score system was applied to the validation cohort of 52 CA patients showing a sensitivity of 81% with specificity of 77%.

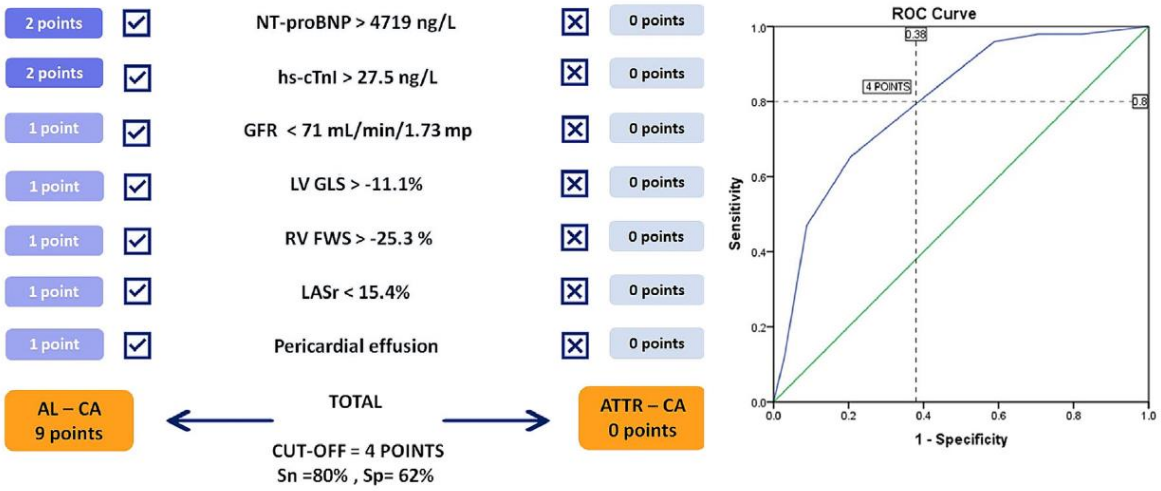


Figura 3: A. The multiparametric scoring system based on optimal threshold values as calculated through the Youden method; **B.** ROC curve of the final score (AUC= 0.798)

Discussion:

Clinical and Imaging Characteristics: The study demonstrated significant differences between AL and ATTR, highlighting the importance of differential diagnosis.

Disease Management: Therapeutic approaches need to be specifically adapted for each form of amyloidosis, considering the pathogenic substrate, clinical characteristics, and serum biomarkers.

Study limitations: The small number of patients and the difficulties in obtaining complete data are acknowledged.

Conclusions: CA is a complex entity and requires extensive testing for a positive diagnosis. This study highlights a series of non-invasive checkpoints, which can be useful in guiding the decision-making process towards a more accurate and rapid differential diagnosis.

Left atrial mechanical dispersion as a novel predictor biomarker of new-onset atrial arrhythmias in cardiac amyloidosis

Introduction: Cardiac amyloidosis (CA) is an infiltrative disease characterized by the accumulation of misfolded proteins into the extracellular matrix of the myocardium. Ventricular but also atrial myopathy are described in CA, with higher risk of atrial arrhythmias (AA) and cardioembolic events even during sinus rhythm. We aimed to investigate which parameters of left atrial (LA) structure and function could predict new-onset AA (NOAA) in patients with CA, aiding in improved follow-up.

Materials and Methods: We prospectively included patients diagnosed with CA, both light chain (AL) and variant transthyretin (ATTRv) with no history of AA, from 2 tertiary European centers. Cardiac involvement was assessed according to current European recommendations. Comprehensive echocardiographic studies were performed at baseline with measurement of both classical structure and function parameters and the new parameters derived from speckle tracking echocardiography. LA strain was measured in the four- and two- chamber views and LA mechanical dispersion was defined as the standard deviation of time-to-peak positive strain and reported as percentage from the R-R interval. The primary outcome was NOAA.

Results: Of the 179 patients diagnosed with CA, 86 were excluded due to history of AF, unacceptable image quality and non-AL or non-ATTR diagnosis. Finally, 93 patients with CA were included (mean age 54.3±9.8, 58% males), and 44 patients (47%) developed NOAA during a median follow up of 11 (3.5-36.0) months.

Patients with NOAA had heavier hearts (LVMi 155.5±39.6 vs. 136.6±44.3 g/m2, p= 0.034), worse global LV function (LVEF 46.7±10.9 vs. 53.8±11.2 %, p= 0.003), more LV longitudinal impairment (GLS -10.0±4.7 vs. -13.4±3.7 %, p< 0.001), larger atria (LAVi 44.6±14.3 vs. 35.4±13.6 mL/m2, p= 0.002) and worse LA function (LAEF 28.5±15.5 vs. 44.9±14.6 %, p< 0.001). The LA reservoir strain (LASr) was significantly lower (13.6±11.3 vs. 20.5±10.4 %, p= 0.003) and the LAMD significantly higher (9.2±3.9 vs. 5.9±3.5) in

patients who developed NOAA.

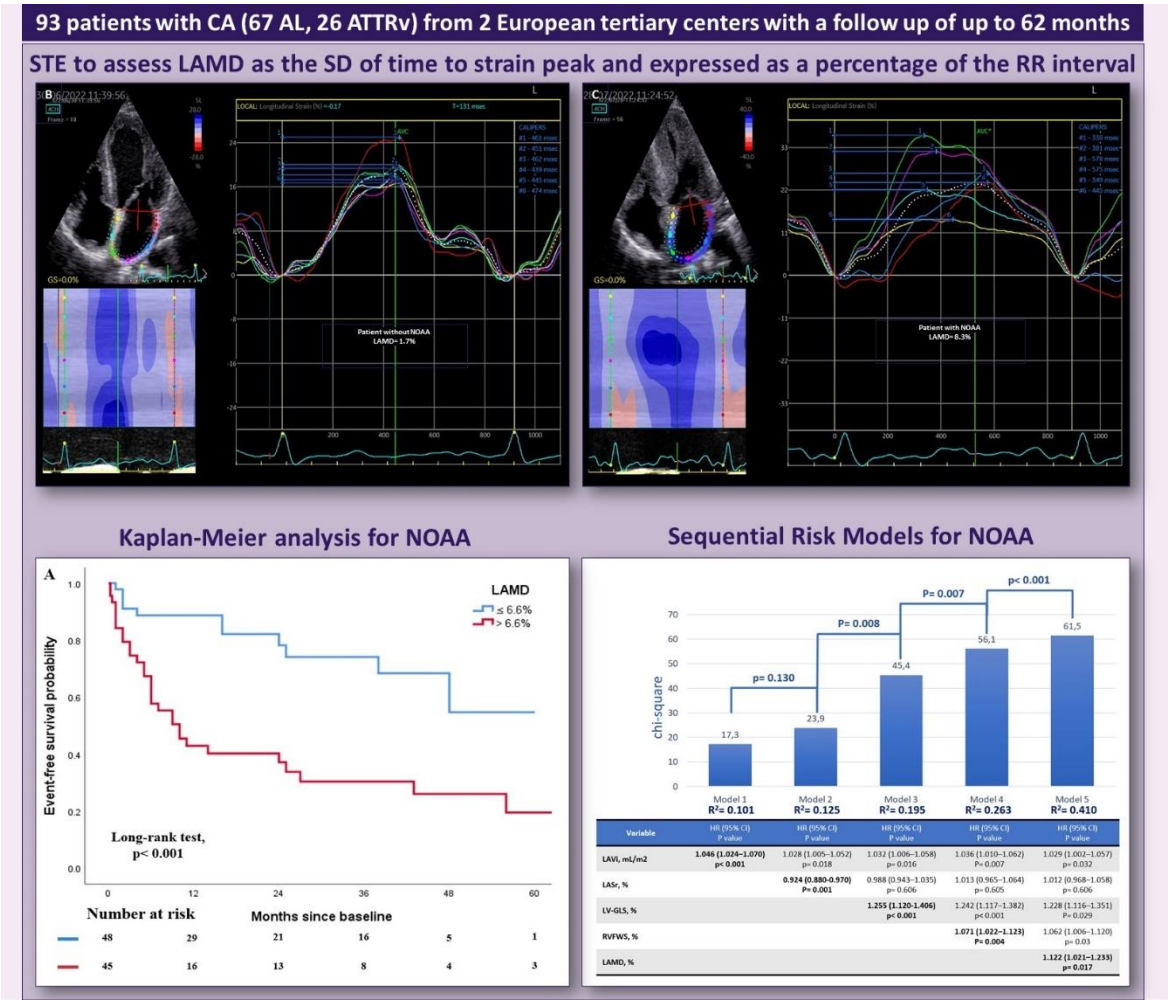


Figure 4. Central figure of the study. *AL, light-chain amyloidosis; ATTRv, variant transthyretin amyloidosis; CA, cardiac amyloidosis; LAMD, left atrium mechanical dispersion; LASr, left atrium strain during the reservoir phase; LV-GLS, left ventricular global longitudinal strain; LAVi, left atrium volume index; NOAA, new onset atrial arrhythmias; RVFWS, right ventricular free wall strain*

In the multivariate analysis adjusting for confounding factors, a lower LAMD was independently associated with higher risk for NOAA (HR: 1.182, 95% CI: 1.033-1.351, p= 0.015). Using ROC curves the optimal cut-off value of LAMD for predicting NOAA was 6.6%. patients with LAMD> 6.6% had a higher risk for NOAA than those with LAMD≤

6.6% (P<0.001 by log-rank test). Furthermore, LAMD> 6.6% as a categorical variable remained an independent predictor for NOAA in both univariate [HR 3.561 (1.778-7.134), p< 0.001] and multivariate [HR 2.432 (0.932-6.343, p= 0.047)] analysis.

Five models were created to demonstrate the incremental value of using sequential Cox models for NOAA prediction and the model based on LA volume was significantly improved by adding LV-GLS, RV free wall strain and finally, LAMD ($\chi 2$= 61.5, p< 0.001), but it was not significantly improved by adding the LASr ($\chi 2$= 23.9, p= 0.130).

Discussions:

Clinical relevance of LAMD: The study demonstrates that LAMD can be used to identify patients at increased risk of atrial arrhythmias, providing an opportunity for preventive interventions.

Comparison with other biomarkers: LAMD was compared with other traditional biomarkers, showing superior predictive value.

Study limitations: The limitations include the relatively small number of patients and variability in echocardiographic measurements.

Conclusions: LAMD assessed by speckle-tracking echocardiography is a novel, reproducible and independent predictor of NOAA in patients with CA, being superior and incremental to other imaging predictors such as LA dilatation or dysfunction, or LV or RV deformation.

Conclusions and personal contributions

Cardiac amyloidosis, a complex and devastating pathology, requires a multidisciplinary approach for effective diagnosis and treatment. In this thesis, the research objectives were achieved through a series of detailed studies that investigated the clinical and imaging characteristics of the disease, early diagnostic methods, and new therapies.

The extent to which the scientific research objectives have been achieved:

Identification of specific clinical and imaging characteristics: Studies have demonstrated that speckle tracking echocardiography and cardiac magnetic resonance imaging provide detailed information about ventricular hypertrophy and diastolic dysfunction, contributing to the early diagnosis of cardiac amyloidosis.

Evaluation of the effectiveness of early diagnostic methods: The utility of echocardiography and cardiac magnetic resonance imaging in the diagnosis of amyloidosis has been confirmed, and bone scintigraphy with bisphosphonates has proven to be an effective method for differentiating between AL and ATTR types.

Arrhythmic risk stratification: Studies have validated the use of specific biomarkers and risk scores for stratifying arrhythmic risk in patients with cardiac amyloidosis, allowing for personalized treatment.

Technical and economic advantages and disadvantages:

Advantages: New diagnostic and treatment methods enable more efficient identification and management of cardiac amyloidosis, reducing costs and the burden associated with severe complications of the disease.

Disadvantages: The initial costs for implementing advanced imaging technologies and innovative therapies can be high, potentially limiting access for patients in certain regions.

Unsolved problems:

Early diagnosis: Although advancements in diagnostics are significant, early identification of the disease remains a challenge, particularly in the absence of specific

symptoms in the early stages.

Treatment accessibility: Limited access to new therapies and their high costs still represent a major obstacle.

Risk of arrhythmias and intracardiac thrombosis: There is still no thorough stratification of arrhythmic risk or for thromboembolic events.

Future Research Directions:

Development of More Accessible Diagnostic Methods: There is a need for the development and validation of diagnostic methods that are less costly and more accessible to larger populations;

Expansion of Clinical Research: Further studies are needed to validate the long-term efficacy of new therapies and to discover new predictive biomarkers;

Integration of Advanced Technologies: Future research should explore the integration of artificial intelligence and other advanced technologies to improve the diagnosis and management of cardiac amyloidosis.

Personal contributions:

Identification of Specific Clinical and Imaging Characteristics

We conducted a detailed study of patients with cardiac amyloidosis, identifying distinctive signs and symptoms that can aid in the early diagnosis of the disease;

Speckle tracking echocardiography and cardiac magnetic resonance imaging were used to highlight the phenotypic characteristics specific to amyloidosis.

Evaluation of the Efficiency of Early Diagnostic Methods

Our study demonstrated that echocardiography and cardiac magnetic resonance imaging are essential tools in the early diagnosis of cardiac amyloidosis;

We developed and validated the use of a non-invasive diagnostic score that does not rely on scintigraphy or cardiac magnetic resonance imaging to differentiate between the two main forms of the disease.

Arrhythmic Risk Stratification

We developed and validated arrhythmic risk stratification models based on specific imaging biomarkers and risk scores;

These models allow for personalized treatment and improved prognosis for patients with cardiac amyloidosis.

Contribution to Raising Awareness and Educating Romanian Cardiologists, Following the Survey Which Highlighted Knowledge Gaps Among Respondents:

We organized workshops and conferences to further educate Romanian cardiologists on the diagnosis and treatment of cardiac amyloidosis;

We published articles and practical guides that were distributed within the medical community to improve the knowledge and skills of practitioners in managing this disease.

Development of an International Collaboration Network:

We initiated collaborations with centers of excellence across Europe, facilitating the exchange of knowledge and participation in multicenter clinical studies;

This collaboration network has provided access to international resources and expertise, enhancing the quality of our research and contributing to global progress in the field of cardiac amyloidosis.

Selective references

1. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. Vol. 28, Trends in Cardiovascular Medicine. Elsevier Inc.; 2018. p. 10–21.
2. Adam R, Munteanu A, Mititelu R, Onciul S, Deleanu D, Iliescu VA, et al. Severe aortic stenosis and attrwt amyloidosis – beware in the aging: A case report and review of the literature. Clin Interv Aging. 2020;15:1863–72.
3. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. Vol. 68, Journal of the American College of Cardiology. Elsevier USA; 2016. p. 1323–41.
4. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Vol. 126, Circulation. 2012. p. 1286–300.
5. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: Disease profiles and clinical courses of the 3 main types. Circulation. 2009 Sep;120(13):1203–12.
6. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail. 2021 Apr 1;23(4):512–26.
7. Kittleson MM, Maurer MS, Ambardekar A V., Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. Circulation. 2020 Jul 7;142(1):E7–22.
8. Kittleson MM, Ruberg FL, Ambardekar A V., Brannagan TH, Cheng RK, Clarke JO, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023 Mar 21;81(11):1076–126.
9. Jurcuţ R, Onciul S, Adam R, Stan C, Coriu D, Rapezzi C, et al. Multimodality imaging in cardiac amyloidosis: A primer for cardiologists. Vol. 21, European Heart Journal Cardiovascular Imaging. Oxford University Press; 2020. p. 833–44.
10. Adam RD, Coriu D, Jercan A, Bădeliţă S, Popescu BA, Damy T, et al. Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. Vol. 8, ESC Heart Failure. John Wiley and Sons Inc; 2021. p. 2380–96.
11. Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. Circ Heart Fail. 2022 Jan 1;15(1):E008193.
12. Röcken C, Peters B, Juenemann G, Saeger W, Klein HU, Huth C, et al. Atrial amyloidosis: An arrhythmogenic substrate for persistent atrial fibrillation. Circulation. 2002 Oct 15;106(16):2091–7.
13. Nochioka K, Quarta CC, Claggett B, Roca GQ, Rapezzi C, Falk RH, et al. Left atrial structure and function in cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2017 Oct 1;18(10):1128–37.
14. El-Am EA, Dispenzieri A, Melduni RM, Ammash NM, White RD, Hodge DO, et al.

Direct Current Cardioversion of Atrial Arrhythmias in Adults With Cardiac Amyloidosis. J Am Coll Cardiol. 2019 Feb 12;73(5):589–97.
15. Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G, et al. Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation. Amyloid. 2021;28(1):12–8.
16. Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, Mirelis JG, Baksi AJ, Moon JC, et al. High Prevalence of Intracardiac Thrombi in Cardiac Amyloidosis. Vol. 73, Journal of the American College of Cardiology. Elsevier USA; 2019. p. 1733–4.
17. Lohrmann G, Patel MA, Brauneis D, Sanchorawala V, Sarosiek S, Vellanki N, et al. Left Atrial Mechanics Associates With Paroxysmal Atrial Fibrillation in Light-Chain Amyloidosis Following Stem Cell Transplantation. JACC CardioOncol. 2020 Dec 1;2(5):721–31.
18. Henein MY, Suhr OB, Arvidsson S, Pilebro B, Westermark P, Hörnsten R, et al. Reduced left atrial myocardial deformation irrespective of cavity size: a potential cause for atrial arrhythmia in hereditary transthyretin amyloidosis. Amyloid. 2018 Jan 2;25(1):46–53.
19. Choi YJ, Kim D, Rhee TM, Lee HJ, Park JB, Lee SP, et al. Left atrial reservoir strain as a novel predictor of new-onset atrial fibrillation in light-chain-type cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2023 Jun 1;24(6):751–8.
20. Akintoye E, Majid M, Klein AL, Hanna M. Prognostic Utility of Left Atrial Strain to Predict Thrombotic Events and Mortality in Amyloid Cardiomyopathy. JACC Cardiovasc Imaging. 2023;
21. Adam R, Neculae G, Stan C, Jurcut R. Current challenges of cardiac amyloidosis awareness among romanian cardiologists. Diagnostics. 2021 May 6;11(5).
22. Jercan A, Ene A, Jurcut R, Draghici M, Badelita S, Dragomir M, et al. Clinical characteristics in patients with hereditary amyloidosis with Glu54Gln transthyretin identified in the Romanian population. Orphanet J Rare Dis. 2020 Jan 30;15(1).
23. Neculae G, Adam R, Jercan A, Bădeliță S, Tjahjadi C, Draghici M, et al. Cardiac amyloidosis is not a single disease: a multiparametric comparison between the light chain and transthyretin forms. ESC Heart Fail. 2024;