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ARE WE UNDERDIAGNOSING CARDIAC AMYLOIDOSIS IN OLDER PATIENTS?

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Abstract

Cardiac amyloidosis (CA) is a relatively common cause of heart failure (HF) with preserved ejection fraction in older adults, particularly those of African-American and Afro-Caribbean descent. Despite its prevalence it continues to be underdiagnosed. There are clinical findings that should increase the suspicion for cardiac amyloidosis; however, their absence does not rule out the diagnosis. Specialized cardiac MRI and nuclear imaging techniques are now allowing for non-invasive early-stage diagnosis of CA. Novel disease-modifying therapies may drastically improve patient outcomes, but they are most effective in early-stage disease, making early diagnosis of paramount importance.

This article has been peer reviewed.

Conflict of Interest: None

This article was published in July 2019.

Key words:
cardiovascular diseases, haematological disorders

Introduction

Heart failure (HF) is common in the aged population and has many underlying etiologies. Until recently, the significance of cardiac amyloidosis (CA) as a cause for HF in older patients has been under-appreciated.[1] The accumulation of misfolded proteins in the cardiac interstitium can result in the loss of normal cardiac architecture and eventually cardiac dysfunction.[2] At least 30 different proteins can form amyloid fibrils and deposit in the heart; however, most CA (Table 1)[2] results from either monoclonal light-chain amyloidosis (AL), or a transthyretin-related amyloidosis (ATTR). ATTR is further classified into mutant ATTR (ATTRm) and wild-type ATTR (ATTRwt), the latter of which occurs most commonly in older adults and was previously termed "senile" amyloidosis.[3] Regardless of the protein responsible, CA can result in the development of HF in the aging population.

Table 1. The 3 Most Common Types of Cardiac Amyloidosis[2]

	Light Chain Amyloidosis (AL)	Transthyretin-related Amyloidosis (ATTR)	
Protein	Monoclonal immunoglobulin light chain	Wild-type transthyretin (ATTRwt)	Inherited mutant transthyretin (ATTRm)
Etiology	Plasma cell dyscrasia results in over-production of monoclonal light chain (either kappa or lambda), which aggregate and deposit in tissues	Transthyretin is intrinsically unstable, has propensity to misfold, aggregate and deposit as individuals age	Amino acid substitutions result in highly unstable transthyretin monomers prone to aggregation and deposition

Due to improved diagnostic techniques and increased comorbidities associated with aging, diagnoses of CA in older patients presenting with HF have surged in the last five years.[4] In the past, the prevalence of CA was estimated to be 1/100,000, but recent literature suggests these figures were significantly under-estimates.[5] New studies suggest 13-18% of all patients hospitalized for HF with preserved ejection fraction (HFpEF) are attributable to ATTRwt and 30% of patients with HFpEF have cardiac amyloid deposits on autopsy.[6] Interestingly, 3-4% of African-American and Afro-Caribbean individuals also carry a mutant ATTR,[7] and an age-dependent autosomal dominant amyloid cardiomyopathy can be a cause of significant heart disease in older African Americans.[8]

The recent development of disease-modifying medical therapies is beginning to transform the landscape of CA management, although early diagnosis remains critical in achieving the best outcomes.[9,10]
It is imperative that clinicians recognize that CA is a common illness, and that they are educated on early diagnosis and intervention.[1] Our aim with this review is to promote a higher index of suspicion for CA in the context of HF in aged patients and to provide a framework for CA work-up and management. To gather our information, we searched PubMed and Medline from 2005 to 2018 using key words and MeSH terms associated with cardiac amyloidosis as a cause of HF in elderly patients. We included all study types and systematic reviews within our search. We also hand-picked the most recent and highly significant research articles on newly developed treatments published in *The New England Journal of Medicine*.

Clinical Diagnosis

The diagnosis of CA should be entertained in any older adult with unexplained HF. In addition, recent findings suggest increased suspicion of CA is particularly warranted in hypertensive patients whose pressures spontaneously normalize and require medication discontinuation, and in HF patients who are unable to tolerate standard cardiac medications.[11]

The prevalence of AL among specific ethnic groups is varied (Table 2).[12-14] AL is the result of a clonal plasma cell disorder whereby aberrant free light chains (FLCs) are secreted from monoclonal plasma cells in the bone marrow. It can occur in the context of multiple myeloma, albeit in the minority of cases (10-15%).[13] It occurs equally in male and female patients, but the onset most commonly occurs after the age of 60.[13] HF due to AL is usually rapidly progressive and often accompanied by multi-organ dysfunction (primarily kidney, liver and nervous system).[12,13] In the context of an older patient with HF, detection of macroglossia, periorbital purpura and recurrent petechial lesions on the eyelids are highly suggestive of AL; however, they are not seen in the majority of patients.[13,14] More commonly, patients with HF due to AL may have nephrotic range albuminuria, peripheral neuropathy and/or autonomic dysfunction. Without treatment, AL is rapidly fatal following symptom onset, which highlights the importance of early diagnosis and discrimination from other types of CA.[12]

In contrast, HF due to misfolded tissue transthyretin (ATTR) often presents with non-specific findings such as insidious HF symptoms or dyspnea, atrial arrhythmias and occasionally syncope or angina.[4,15] Hereditary ATTR (ATTRm) commonly presents with other systemic symptoms such as peripheral or autonomic neuropathy, gastrointestinal dysfunction or renal failure, whereas age-related ATTR (ATTRw) most commonly presents with isolated HF symptoms. Therefore, the most important factors in identifying ATTR as a cause of HF is a high index of suspicion and exploring a cardiomyopathy-sensitive history and physical exam. History of ruptured distal biceps tendon, carpal tunnel syndrome (especially if bilateral) and spinal stenosis should serve as red flags when distinguishing ATTR from other causes of HF.[16-18]

ATTRm presents in younger patients, usually in the 4th-6th decade, and is more likely to have multiple organs involved.[1,3] There are many associated mutations each specific to different populations with varying degrees of penetrance, making it difficult to use family history or ethnicity as reliable diagnostic tools for ATTRm. However, the most common ATTRm-causing mutation (V122I) is carried by 3-4% of Africans and Afro-Caribbeans, therefore, increasing the index of suspicion for CA when faced with HF in these populations.[7]

Table 2. Maintaining a High Index of Suspicion for Cardiac Amyloidosis[12-14]

Criteria	AL[a]	ATTRwt[b]	ATTRm[c]
Demographic	>60 years, Men = women, ethnicity variable	>70 years, Mostly men (90-97%) Women present later Caucasian (90%)	>60 years, Mostly men, Ethnicity variable; most common is V122I mutation in African, Afro-Caribbean
Associated signs and symptoms	Rapid onset HF, multi-system damage, macroglossia, periorbital purpura and petechial lesions on the eyelids or periorbita	Often: Insidious HF, dyspnea, and/or atrial arrhythmias Occasionally: syncope, angina and neuropathy (mostly ATTRm) Ruptured distal biceps tendon Carpal tunnel syndrome (especially bilateral) Spinal stenosis	
	Spontaneously normalized HTN requiring medication discontinuation or unable to tolerate standard HF medications (ACEi/ARB, Beta-blocker)		

[a] Light chain amyloidosis (AL), [b] wild-type transthyretin-related amyloidosis (ATTRwt), [c] hereditary Transthyretin-related Amyloidosis (ATTRm).

Clinical Investigation

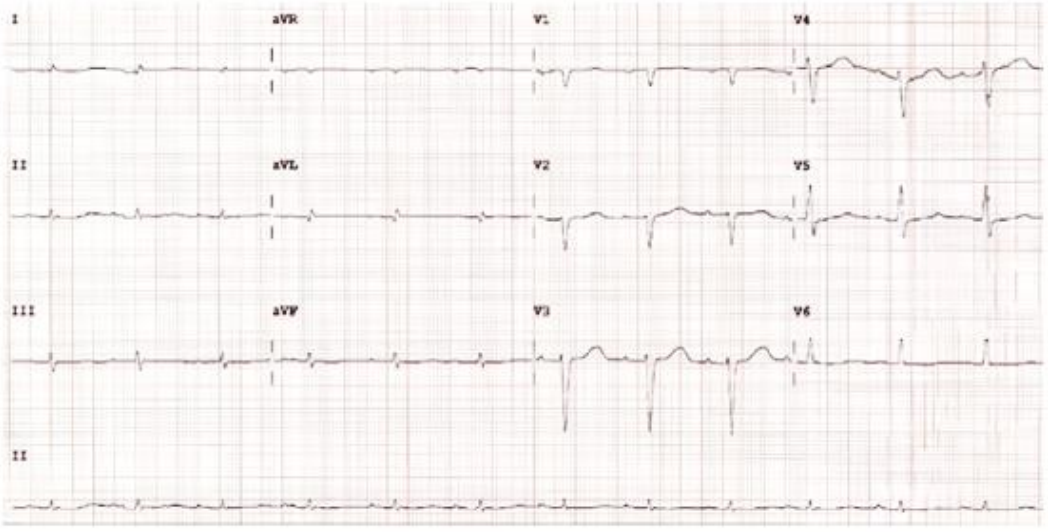
AL results from a plasma cell dyscrasia originating in the bone marrow in the vast majority of cases, thus any suspected case of CA requires serum and urine protein electrophoresis and immunofixation, as well as a serum FLC assay to establish the presence of a monoclonal gammopathy.[14] Very rarely, AL amyloidosis can present without a systemic monoclonal protein, and it can occasionally occur in other lympho-proliferative disorders. Therefore, the absence of a monoclonal protein does not definitively rule out his type of amyloidosis. These tests should be performed and interpreted in an experienced laboratory, as the interpretation can be challenging (Table 3).[19-28] For example, FLCs in the serum are renally excreted, and the normal range for a serum FLC assay is wider in patients with chronic kidney disease (CKD).[19] In borderline cases, the most useful marker can be the difference between involved and uninvolved FLCs (dFLC), which determines the monoclonal component and remains unaltered in CKD.[14] Unfortunately, since FLC and dFLC both increase in monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma, these markers cannot differentiate AL from ATTR with concurrent MGUS.[14] This concept is important, as both of these conditions are exceedingly common in the older population.

Although not diagnostic, concentrations of N-terminal pro-B type natriuretic peptide (NT-proBNP) and cardiac troponin T (cTnT) are both elevated in CA and are useful in staging and prognostication of AL and ATTR.[20] Elevated NT-proBNP, elevated cTnT or disproportionate to cardiac strain in an older HF patient should increase suspicion of CA.[21]

Electrocardiograph:

A pseudo-infarction pattern (anterior leads), atrial arrhythmias, AV or bundle-branch blocks and low QRS voltage is the most common ECG abnormality in CA; however, ECG may also be normal.[11] Nevertheless, low QRS voltage tends to be a late-stage finding of CA.[22]

Figure 1: EKG for a Patient with Cardiac Amyloidosis Featuring Low Voltage in Limb Leads and Pseudoinfarct Pattern



Echocardiograph:

Morphological echocardiographic findings suggestive of CA include LV hypertrophy (LVH>12 mm, and symmetric in 75% of CA), AV-valve thickening and atrial dilation.[23] Depressed global longitudinal strain with relative apical sparing is the most sensitive and specific echocardiographic finding of CA, and helps differentiate CA from other causes of LVH.[24]

Specialized Imaging:

Cardiac MRI provides detailed information on cardiac morphology and function but also allows for visualization via late gadolinium enhancement (LGE) and quantification via T1 mapping and extracellular volume (ECV) of amyloid infiltration.[25] Recently, native T1, LGE and ECV have been validated as diagnostic tools capable of detecting even early-stage CA.[26] ECV also has prognostic value. Although cardiac MRI is a very sensitive measure of CA and results may suggest either AL or ATTR, it is not diagnostic, and cannot definitively type the amyloid fibril.[27] Given that treatment differs significantly between AL and ATTR, further investigations are required including a tissue biopsy.

Bone scintigraphy is 99% sensitive for ATTR with false positives arising from low-grade (grade 1) radiotracer uptake in AL.[28] In the absence of MGUS, high-grade (grade 2-3) uptake on scintigraphy is 100% specific to ATTR and allows for diagnosis of ATTR without histopathological confirmation.[28] Currently, 99mTechnetium (99mTc)-pyrophosphate and 99mTc-3,3-diphosphono-1,2-propanodicarboxylic are the only validated radiotracers for ATTR diagnosis, but preliminary data also shows other 99mTc-labelled radiotracers may be equivalent. These techniques remove the need for endo-myocardial biopsy (EMB) in most cases of ATTR, thus reducing risk of procedural harm in a frail population. Unfortunately, they are early in clinical use and not routinely available in most centres.

Biopsy:

All suspected cases that cannot be definitively identified with scintigraphy require biopsy for diagnosis.[29-31] The highest yield is a biopsy of the affected organ. However, given the risks of cardiac or renal biopsy, less invasive alternatives are preferred. In AL amyloidosis, an abdominal fat pad aspiration or biopsy is 80% sensitive, a bone marrow biopsy is 50% sensitive and, combined, they are about 90% sensitive. The combination is considered the standard of care when suspecting AL amyloidosis. Abdominal fat pad aspiration is significantly less sensitive in the case of ATTR, and therefore, a biopsy of the affected organ is usually necessary to confirm the diagnosis.

Accurate amyloid typing is absolutely crucial given the differences in treatments varying with subtype. The gold standard for tissue typing is mass spectrometry-based proteomic analysis, which identifies all amyloid fibril types with close to 100% specificity.[32] Traditionally, immunohistochemistry was used for both AL and ATTR, but the stains are notoriously unreliable, lack sensitivity and specificity, and are considered inadequate in the era of mass spectrometry.[32]

Table 3. Clinical Investigations Useful in the Identification of Cardiac Amyloidosis[19-28]

Investigation	Result Characteristic of Cardiac Amyloidosis
Laboratory	*Monoclonal gammopathy on serum or urine electrophoresis and immunofixation and/or increased dFLC[a] (>50 mg/L) Elevated NT-proBNP[b], cTnT[c] disproportionate to cardiac strain
Electrocardiogram	Pseudo-infarction pattern (anterior leads), Atrial arrhythmias, AV or bundle-branch blocks Low QRS; using a modified Sokolow index (cut-off <0.5 mV)
Echocardiogram	Depressed global longitudinal strain with relative apical sparing LVH >12 mm (symmetrical or asymmetrical), AV-valve thickening, atrial dilation
Cardiac MRI	Diffuse late gadolinium enhancement, Increased T1 native and extracellular volume

[a] Difference between involved and uninvolved free light chains (dFLC), [b]N-terminal pro-B type natriuretic peptide (NT-proBNP), [c] cardiac troponin T (cTnT). *AL occurs in the context of plasma cell dyscrasia, but free light chains (FLCs) and the difference between involved and uninvolved FLCs (dFLC) both increase in monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma (MM). Thus, these markers cannot differentiate AL from ATTR with a concurrent MGUS or MM.

Clinical Management:

Management of HF caused by CA is difficult due to poor tolerance of traditional HF medications such as ACEi/ARBs and beta-blockers,[12] due to the underlying pathophysiology of the disease.
The hypertrophied walls of the ventricles do not allow for adequate filling in diastole, resulting in decreased preload. These patients are therefore dependent on being able to raise their heart rates to maintain stroke volume/blood pressure. They are also afterload dependent to maintain blood pressure, and this compensatory mechanism can become compromised should they also have autonomic instability. Therefore, if beta-blockers are added and the heart rate is slowed or afterload reducers (ACEI/CCB) reduce blood pressure, the patients often experience profound fatigue, postural hypotension, presyncope/syncope and falls.[33] Furthermore, standard HF management using ACEi and beta-blockers, which demonstrate evidence of benefit in patients with other forms of cardiomyopathy, has not shown to improve outcomes or cardiac remodelling in patients with amyloidosis, likely due to the underlying infiltrating proteins.

Symptom management is best achieved with loop diuretics +/- spironolactone.[12,33] If atrial fibrillation is present, beta-blockers for rate control can be used cautiously, and anticoagulation is indicated regardless of risk score. It should be noted that patients with AL amyloid can have Factor X deficiency as well, and a coagulation profile and Factor X level should be performed in patients starting on anticoagulation. While symptom management is paramount, the most important factor in ameliorating CA-related HF is reducing further amyloid formation and deposition.

Current treatment of AL is aimed at decreasing FLC production and serum concentration, ultimately reducing amyloid deposition and hopefully minimizing cardio-myo-toxic effects of FLCs themselves.[12] Unfortunately, tissue involvement is not necessarily reversed. The therapeutic agents of choice depend on the fitness of the patient and degree of organ involvement, but commonly include combinations of Bortezomib, Alkylators (Melphalan or Cyclophosphamide) and dexamethasone. Autologous stem cell transplantation is performed in select patients with minimal cardiac involvement and limited comorbidities.[34,35] Response to treatment is monitored by both hematologic response (reductions in dFLC), as well as organ response (reductions in NT-proBNP, and cTnT to below previously established cut-off values).[36]

Table 4. Emerging Disease-modifying Therapies for Cardiac Amyloidosis[9,10,37]

Class	Drug	Mechanism
Transthyretin gene silencers	Patisiran[9]	Suppress expression of the transthyretin gene whether mutated or wild-type
Transthyretin stabilizers	Tafamidis[10]	Stabilizes misfolded transthyretin monomers, preventing aggregation and deposition in tissues
Amyloid clearance by antibodies[37]	1) CPHPC[a]: small molecule followed by, 2) Anti-SAP[b] IgG: humanized monoclonal antibody	1) CPHPC complexes with SAP in serum, complex is cleared by liver 2)Anti-SAP IgG binds SAP in tissue amyloid deposits triggering immune clearance
[a] (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC), [b] Serum amyloid P component (SAP)		

Recent breakthroughs (Table 4)[9-10] in ATTR therapy including Transthyretin gene silencers (Patisiran)[9] and stabilizers (Tafamidis)[10] have demonstrated potential benefit in the treatment of ATTR. Patisiran, an investigational RNA interference therapeutic agent, specifically inhibits hepatic synthesis of transthyretin and has shown improvement in multiple clinical manifestations of hereditary transthyretin amyloidosis.[9] A Phase 3 clinical trial by Maurer, et al. showed treatment with Tafamidis was associated with a decrease in all-cause mortality at 30 months compared to placebo (29.5% vs. 42.9%) and a 22% reduction in cardiac-related hospitalizations.[10] Therapeutic clearance of amyloid by antibodies and targeting serum amyloid P component (SAP), a protein essential to amyloid deposit stabilization, is also emerging.[37]
For individuals with ATTRm who meet transplant criteria, the most effective treatment may still be liver transplantation.[38] TTR is produced in the liver, and therefore, liver transplant effectively removes the source of abnormal TTR, drastically slowing disease progression resulting in >50% survival at 20 years.

Conclusion

In summary, amyloidosis needs to be considered as a cause of HF in older adults. Therapy and prognosis of this illness differs from other forms of HF in this population, and the landscape of CA management is rapidly changing. Diagnostic techniques are increasingly sensitive and specific, and therapies are increasingly more effective and better tolerated by patients, particularly those with early-stage disease. Fortunately, new cardiac

MRI and nuclear imaging techniques are beginning to open the door to non-invasive identification and diagnosis of early-stage CA. Further work is required to increase awareness of this condition in the elderly population and to promote its optimal management.

REFERENCES

1. Rapezzi C, Lorenzini M, Longhi S, et al. Cardiac amyloidosis: the great pretender. Heart Fail Rev. 2015 Mar 11;20(2):117-24.

2. Chiti F, Dobson CM. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu Rev Biochem. 2017 Jun 20;86(1):27-68.

3. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc 2013 Apr 22;2(2):e000098. Available from: www.ncbi.nlm.nih.gov/pubmed/23608605

4. Maurer MS, Hanna M, Grogan M, et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol. 2016 Jul [cited 2018 Jun 21]; 68(2):161-72.

5. Pinney JH, Smith CJ, Taube JB, et al. Systemic Amyloidosis in England: an epidemiological study. Br J Haematol. 2013 May 161(4):525-32.

6. 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 Oct 7;36(38):2585-94.

7. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African–Americans. Amyloid. 2015 Jul 3 Jun 6];22(3):171-4.

8. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. Genet Med. 2017 Jul 19;19(7):733-42.

9. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang C-C, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):11-21.

10. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-16.

11. González-López E, Gagliardi C, Dominguez F, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. Eur Heart J. 2017 Jun 21;38(24):1895-904.

12. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. Heart Fail Rev. 2015 Mar 2;20(2):155-62.

13. Dubrey SW, Hawkins PN, Falk RH. Amyloid diseases of the heart: assessment, diagnosis, and referral. Heart. 2011 Jan 1;97(1):75-84.

14. Gillmore JD, Wechalekar A, Bird J, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. Br J Haematol. 2015 Jan;168(2):207-18.

15. Connors LH, Sam F, Skinner M, et al. Heart Failure Resulting from Age-Related Cardiac Amyloid Disease Associated with Wild-Type Transthyretin: A Prospective, Observational Cohort Study. Circulation 2016;133(3):282-90.

16. Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016 Jan 2;23(1):58-63.

17. Geller HI, Singh A, Alexander KM, et al. Association Between Ruptured Distal Biceps Tendon and Wild-Type Transthyretin Cardiac Amyloidosis. JAMA. 2017 Sep 12;318(10):962.
18. Westermark P, Westermark GT, et al. Transthyretin-derived amyloidosis: Probably a common cause of lumbar spinal stenosis. Ups J Med Sci. 2014 Aug 12;119(3):223-8.

19. Hutchison CA, Harding S, Hewins P, et al. Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2008 Nov 1;3(6):1684-90.

20. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements. J Clin Oncol. 2012;30:989-95.

21. Palladini G, Foli A, Milani P, et al. Best use of cardiac biomarkers in patients with AL amyloidosis and renal failure. Am J Hematol. 2012 May;87(5):465-71.

22. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. Am J Cardiol. 2014 Oct 1;114(7):1089-93.

23. Koyama J, Ikeda S, Ikeda U. Echocardiographic Assessment of the Cardiac Amyloidoses. Circ J. 2015 Mar 25;79(4):721-34.

24. Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012 Oct 1;98(19):1442-8.

25. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017 Jul;70(4):466-77.

26. Pozo E, Castellano JM, Kanwar A, Deochand R, et al. Myocardial Amyloid Quantification with Look-Locker Magnetic Resonance Sequence in Cardiac Amyloidosis. Diagnostic Accuracy in Clinical Practice and Histological Validation. J Card Fail. 2018 Feb;24(2):78-86.

27. Dungu JN, Valencia O, Pinney JH, et al. CMR-Based Differentiation of AL and ATTR Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2014 Feb;7(2):133-42.

28. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016 Jun 14;133(24):2404-12.

29. Sławek S, Araszkiewicz A, Gaczkowska A, et al. Endomyocardial biopsy via the femoral access – still safe and valuable diagnostic tool. BMC Cardiovasc Disord. 2016 Dec 15;16(1):222.

30. Halloush RA, Lavrovskaya E, Mody DR, Lager D, Truong L. Diagnosis and typing of systemic amyloidosis: The role of abdominal fat pad fine needle aspiration biopsy. Cytojournal. 2010 Jan 15;6:24.

31. Fine NM, Arruda-Olson AM, Dispenzieri A, RA, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol. 2014 May 15;113(10):1723-7.

32. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009 Dec 3;114(24):4957-9.

33. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and Management of the Cardiac Amyloidosis. J Am Coll Cardiol. 2007 Nov 27;50(22):2101-10.

34. Gatt ME, Hardan I, Chubar E, et al. Outcomes of light-chain amyloidosis patients treated with first-line bortezomib: a collaborative retrospective multicenter assessment. Eur J Haematol. 2016 Feb;96(2):136-43.

35. Sperry BW, Ikram A, Hachamovitch R, et al. Efficacy of Chemotherapy for Light-Chain Amyloidosis in Patients Presenting With Symptomatic Heart Failure. J Am Coll Cardiol. 2016 Jun;67(25):2941-8.

36. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012 Dec 20;30(36):4541-9.

37. Richards DB, Cookson LM, Berges AC, et al. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. N Engl J Med. 2015 Sep 17;373(12):1106-14.

38. Ericzon B-G, Wilczek HE, Larsson M, et al. Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative? Transplantation. 2015 Sep;99(9):1847-54.