Amyloid Cardiomyopathy: An Update

Roy S. Small, M.D.
The Heart Group of Lancaster General Health

THE TYPES OF HEART FAILURE

The syndrome of chronic congestive heart failure can be defined simply as the inability of the heart to provide adequate blood and oxygen to satisfy the metabolic needs of the body. Broadly speaking, there are two distinct phenotypes of left heart failure (HF), each characterized by the state of left ventricular (LV) systolic function as defined by ejection fraction:

1. Heart failure with preserved ejection fraction (HFpEF), formerly called "diastolic" dysfunction;
2. Heart failure with reduced ejection fraction (HFrEF), previously referred to as "systolic" dysfunction.

The new nomenclature recognizes the fact that although it is clinically and therapeutically useful to distinguish the two types of heart failure, both involve systolic *and* diastolic dysfunction. HFpEF is usually defined as an ejection fraction (EF) greater than 50%, while HFrEF refers to patients with an EF less than 40%.

Patients with mid-range EF (40-50%) are a diverse group that includes those with HFrEF and partial recovery; those in the process of developing more significant LV dysfunction; and those with mixed physiology (such as patients with an ischemic cardiomyopathy in addition to hypertensive heart disease). Although oftentimes clinically indistinguishable, HFpEF and HFrEF should be considered as different disease entities with dissimilar etiologies, treatment regimens, and prognosis.

Right ventricular (RV) dysfunction and right-sided heart failure are usually a secondary consequence of LV dysfunction. However, a number of disease entities impact RV function primarily, and – depending upon their pathophysiology – may be amenable to specific treatments. These factors that can cause RV dysfunction may be intrinsic (e.g. RV dysplasia) or extrinsic (e.g. pulmonary and pulmonary arterial disease). Fortunately, there have been major advances in the treatment of RV dysfunction, particularly in the setting of pulmonary artery hypertension. [1]

A comprehensive general review of our current understanding of HF and the optimal treatment regimens is available in the 2013 ACCF/AHA Guideline for the Management of HF,[2] and the 2017 ACC/AHA/HFSA Focused Update on the 2013 Guidelines.[3] This article will focus on cardiac amyloidosis as a specific example of HFpEF.

CLINICAL SIGNIFICANCE AND SUB-TYPES OF CARDIAC AMYLOIDOSIS

It has been estimated that 10% to 20% of HFpEF patients have cardiac amyloid as a fundamental cause of the restrictive physiology which accompanies HFpEF. So, while the management of HFpEF remains focused on the treatment of co-morbid conditions (obesity, hypertension, sleep apnea, diabetes, and atrial arrhythmias), the recognition that amyloid cardiomyopathy (amyloid CM) is a frequent underlying cause of the restrictive physiology has changed the diagnostic and therapeutic approaches to these patients. Less frequently, amyloid CM can present as HFrEF. It has been estimated that up to 20% of patients with low flow/low gradient severe aortic stenosis referred for TAVR have amyloid CM.

There are two general types of amyloid in western societies (AL amyloid and transthyretin or ATTR), and they must be distinguished, as their prognoses and treatments are radically different.

PATHOPHYSIOLOGY

1. *AL amyloid* is due to an overproduction of free immunoglobulin light chains, most commonly the lambda type. These pathological partial antibodies are produced by clonal hematopoietic plasma cells which are sometimes associated with multiple myeloma (5-10%). The pathologic light chains may have direct cardiac and renal toxicity, but the primary cardiac pathophysiology is due to the deposition of fibrils of amyloid in the cardiac extracellular matrix causing a restrictive cardiomyopathy. It is a systemic disease frequently associated with nephropathy (causing nephrotic syndrome), neuropathy (peripheral and autonomic nervous systems), and – less frequently – gastrointestinal involvement.[4]

Untreated and undiagnosed, AL amyloid CM is rapidly progressive with a median survival of 6 months. A high index of suspicion, with rapid diagnosis and treatment, can extend survival for years.

2. *TTR amyloid* (ATTR) is a consequence of the tissue

deposition of disassociated tetramers of transthyretin, the transport protein for thyroid hormone and retinol (Vitamin A) which is produced in the liver. These misfolded amyloidogenic monomers aggregate into amyloid fibrils which are then deposited in various tissues and organs. Accumulation of amyloid deposits may result in nephropathy, peripheral neuropathy, soft tissue accumulations, and gastrointestinal dysfunction. A history of bilateral carpal tunnel or spinal stenosis may precede the clinical cardiac manifestations by years, and should prompt a consideration of amyloid.

Cardiac involvement is due to the aggregation of the misassembled proteins in the cardiac extracellular matrix and within cardiac myocytes. It manifests as a restrictive cardiomyopathy, sometimes with associated conduction system abnormalities and arrhythmias (specifically atrial fibrillation). Amyloid deposition in the atria lead to atrial dysfunction and an increased risk of thromboembolic events. Left atrial thrombi may develop even in the absence of atrial fibrillation.[5]

Most ATTR amyloid is due to age-degraded normal or "wild type" transthyretin (ATTRwt), for which there is no associated pathologic genetic mutation. It is a disease of the elderly in whom the primary manifestation is often cardiac dysfunction. Autopsy studies have shown cardiac amyloid deposits in up to 25% of adults 80 years old or older.

In addition to ATTRwt, more than 120 mutations have been associated with "mutant" (also referred to as familial or hereditary) TTR (ATTRm). The various mutations have different disease manifestations. The most common mutation in the United States is Val122Ile, found in 3.4% of the black population. Median survival for untreated ATTRm (Val122Ile mutation) is 2.5 years in patients diagnosed with HF, compared with 3.6 years for ATTRwt. Death is usually related to cardiac complications with ATTR. In patients with primarily neurologic findings (polyneuropathy) without HF, the median survival for ATTRm is 8-10 years. ATTRm is more commonly associated with peripheral and autonomic neuropathy than is ATTRwt.

Once ATTR is identified, genetic testing for specific mutations is essential; it may direct therapy, and is of course important for genetic counseling of family members.

DIAGNOSIS

Traditionally, cardiac amyloidosis has been thought to be a rare disease. It is not. This misconception combined with the previous lack of any specific treatment has led to a reluctance to pursue the diagnosis. The situation is analogous to developments in pulmonary hypertension: once rarely diagnosed, it is frequently recognized now that there are several effective treatments. Early diagnosis of ATTR-CM is crucial, as the disease is relentlessly progressive without treatment and results in progressive organ dysfunction. Unlike AL amyloid, which is rapidly progressive, ATTR CM is characteristically associated with years of clinical stability prior to progression to intractable HF.

Physical Findings

Two physical findings are specifically associated with amyloidosis; spontaneous periorbital hemorrhage and macroglossia. Either finding in a HF patient is virtually pathognomonic of amyloid CM. These patients will frequently have an elevated jugular venous pressure (JVP) and Kussmaul's sign (paradoxical increase in JVP with inspiration) due to the restrictive physiology.

Imaging

The first clue of cardiac amyloid is often an abnormal echocardiogram performed for the evaluation of shortness of breath. Although the classic pattern of myocardial "speckling" is often absent, the finding of concentric left ventricular hypertrophy (frequently with RV hypertrophy) in a heart failure patient with no history of hypertension should prompt an evaluation for amyloid. Strain imaging, if performed, will usually show global impairment, with more normal apical contraction (apical sparing). This pattern is highly suggestive of amyloid cardiomyopathy. Diastolic function will be abnormal, and atrial dysfunction is common. While AL amyloid is generally associated with more profound ventricular thickening than ATTR amyloid, the echocardiogram cannot distinguish between the two types.

"Low voltage" on an EKG is a common finding (more so in patients with AL amyloid), but it is not specific, and its absence should not deter further evaluation. A discordance between the EKG (low voltage) and echocardiogram (concentric left ventricular hypertrophy) should arouse concern for amyloid CM. Cardiac MR (CMR) will usually show changes of an infiltrative process with delayed gadolinium uptake and a failure to "null" the myocardium. However, as with the echocardiogram, CMR cannot reliably differentiate AL from ATTR amyloid.

Isotope scanning

Technetium pyrophosphate (^{99m}TcPYP) scanning is a simple noninvasive test that is commonly used to screen for ATTR cardiac amyloidosis. Intense myocardial uptake of ^{99m}TcPYP is extremely sensitive (> 99%) and highly specific (86%) for ATTR amyloid, but is nearly always negative in AL amyloid patients. A positive ^{99m}TcPYP scan may obviate the need for a tissue biopsy for ATTR cardiac amyloidosis,

in the absence of an abnormal monoclonal protein or abnormal free light chain ratio.[6]

Laboratory testing

For AL amyloid, laboratory testing is essential to establish the diagnosis. Serum free light chains and serum and urine immunofixation should be performed to detect the dysfunctional free light chains. Unlike multiple myeloma, free light chain levels may be low, so the free light chain kappa/lambda ratio is particularly useful. An abnormal ratio should prompt consideration of a tissue biopsy even if immunofixation shows minimal elevation of kappa or lambda chains. There is no longer any role for serum protein electrophoresis (SPEP) in AL amyloid as the immunofixation of serum and urine is a much more sensitive test.

With ATTR amyloid, there are no specific laboratory findings. Troponin and NT-proBNP levels are usually persistently elevated with both ATTR and AL amyloid CM. If there is renal involvement there may be laboratory findings of nephrotic syndrome.

Tissue biopsy

Confirmation of AL amyloid necessitates a tissue biopsy. For ATTR amyloid, diagnosis will also sometimes require a tissue biopsy, because 25% of ATTR patients have a monoclonal gammopathy of unknown significance (MGUS), some with an abnormal kappa/lambda ratio. Endomyocardial biopsy, if performed with multiple samples and interpreted correctly, has nearly 100% sensitivity and specificity.

For AL disease, a subcutaneous fat aspirate is frequently diagnostic (80%), but is much less so with ATTR (15% sensitivity). All patients with confirmed AL amyloid require a referral to hematology and a bone marrow biopsy to rule out multiple myeloma (present in 5%-10% of AL amyloid CM patients), or less commonly, lymphoma or Waldenstrom macroglobulinemia.

TREATMENT OF AMYLOID CM

Treatment of both types of cardiac amyloid disease requires diuretics for volume control, but management is often complicated by hypotension due to volume sensitivity. Although patients with amyloid CM may present with impaired LV function (HFrEF), neurohormonal blockade is characteristically poorly tolerated and generally has no management role. Similarly, calcium channel blockers and digoxin should be avoided.

Atrial fibrillation is a common consequence of both types of cardiac amyloidosis, and adds to the likelihood of hypotension. There is a narrow therapeutic window for rate control due to the accompanying autonomic polyneuropathy, and the small ventricular cavity. Most importantly, systemic anticoagulation should be considered regardless of the CHADs-VASc score, due to the atrial dysfunction, and the propensity for atrial thrombi. Amiodarone is usually the antiarrhythmic of choice for rhythm control.

AV block may result from deposition of amyloid fibrils in the conduction system. A Holter monitor should be performed in patients with syncope or near syncope. Standard ACC/AHA/HRS pacing guidelines apply. Insertion of ICDs for primary prevention in amyloid patients with LV dysfunction is controversial, but it is reasonable for secondary prevention. Resynchronization pacing (CRT P or D) may be beneficial when the usual criteria are satisfied.

The treatment of non-cardiac aspects of AL amyloidosis is beyond the scope of this discussion, but involves chemotherapy for the plasma cell dyscrasia and sometimes autologous stem cell transplant. There have been major advances in chemotherapy recently, with improved response rates and prolonged survival.

For ATTRwt and ATTRm amyloid there are currently three pharmacologic treatment strategies: mRNA inhibition (TTR silencers), TTR stabilization, and fibrillar disruption.

Tafamidis meglumine is a TTR stabilizer that slows the dissociation of transthyretin and thus the creation and tissue deposition of the pathogenic monomers and oligomers. It has been shown to slow the progression of the polyneuropathy and cardiomyopathy associated with ATTR amyloid.

The ATTR-ACT Trial [7] was a multicenter, double-blind placebo-controlled trial of tafamidis (80 and 20 mg doses) vs. placebo in patients with ATTR (24% ATTRm and 75% ATTRwt) and NYHA Class I-III HF. Tafamidis had an all-cause mortality benefit in both types of ATTR. There was also a decrease in cardiovascular-related admissions in the tafamidis treated groups, except for those with advanced symptoms (NYHA III), who had a higher rate of hospitalization with tafamidis. This finding underscores the importance of early treatment for disease stabilization prior to the development of irreversible cardiac dysfunction.

Tafamidis is well tolerated with few significant adverse reactions. The cost of treatment had been a serious early concern and the initial estimates were astronomical for a drug that would be taken daily for an extended period. However, in practice most patients have received the drug at a reasonable cost through manufacturer-sponsored support programs.

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) that kinetically stabilizes TTR tetramers by binding with the thyroxine receptor and inhibiting the formation

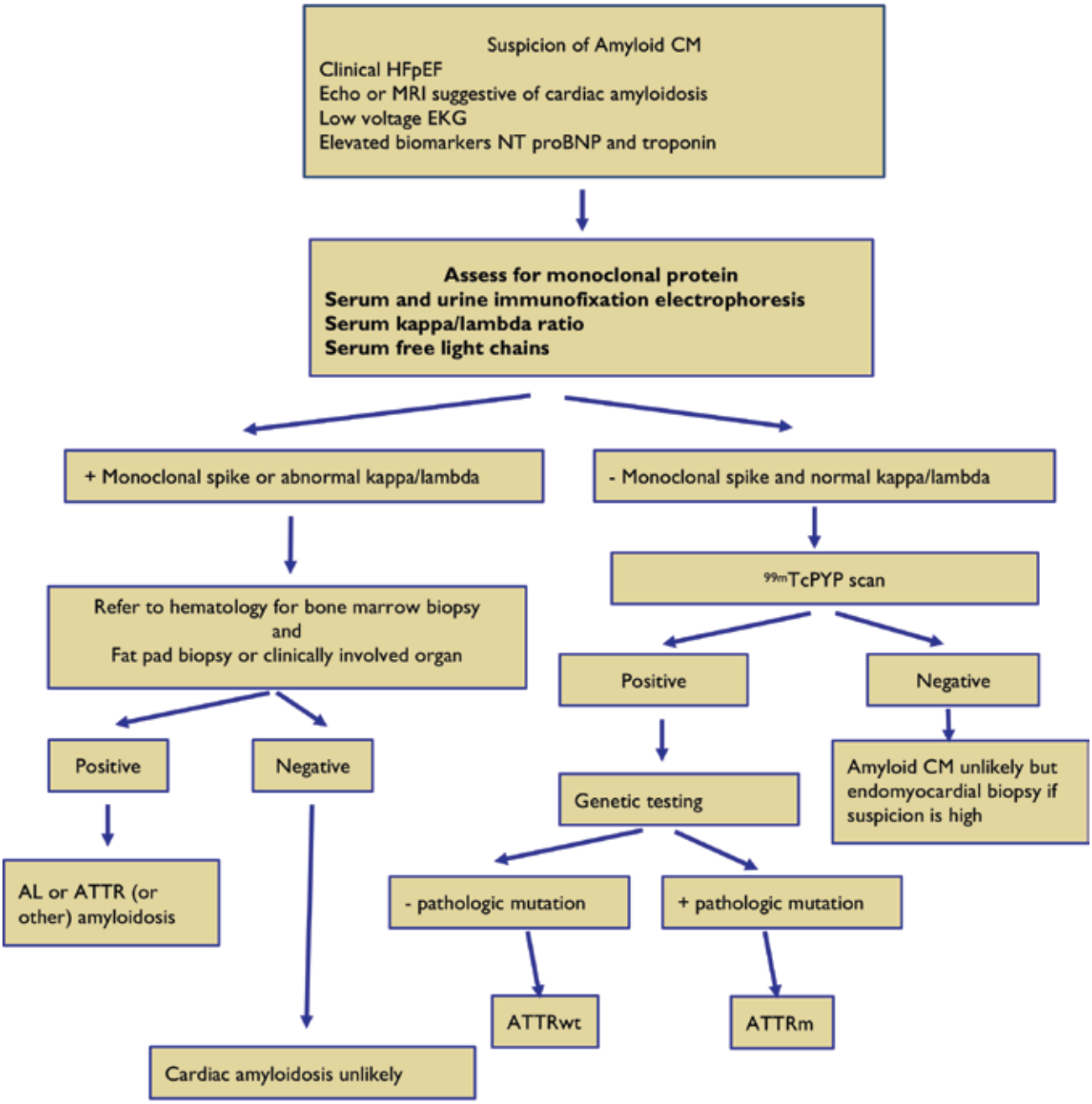

Fig. 1. **Algorithm for Management of Amyloid Cardiomyopathy.** Adapted from: Ruberg, FL et al. Transthyretin Amyloid Cardiomyopathy, JACC State of the art review. *J Am Coll. Card.* 2019; 73:2872-91 and Rodney, FH et al. AL (Light-Chain) Cardiac Amyloidosis, A Review of Diagnosis and Therapy. *J Am Coll. Card.*; 68:1323-41.

of amyloid TTR monomers. A small (130 patients randomized), placebo controlled trial of diflunisal (250 mg twice daily) in ATTRm patients reduced the rate of progression of the polyneuropathy and improved the quality of life.[8] Diflunisal is not FDA approved for treatment of ATTR, but the benefit appears similar to tafamidis. Though inexpensive, it is not frequently utilized because of concerns about potential renal toxicity in patients who may have renal involvement due to their underlying disease.

The combination of the antibiotic doxycycline and an over-the-counter dietary supplement, tauroursodeoxycholic acid (TUDCA), can disrupt amyloid fibrils and potentially stabilize or diminish TTR deposits. There is one small study[9] which showed potential benefit, although the

combination is not FDA approved for use in amyloid cardiomyopathy. Nonetheless, prior to the availability of tafamidis it was one of the few therapeutic options available outside of clinical trials. Some practitioners continue to use these drugs in combination with tafamidis with the goal of decreasing the production of amyloid fibrils and disrupting existing deposits.

Patisiran is a small interfering mRNA (RNAi) which disrupts transthyreton mRNA leading to a reduction of TTR levels in both ATTRwt and ATTRm amyloid, and is classified as a TTR silencer. It is administered intravenously every three weeks. Common side effects include peripheral edema and infusion-related reactions. It has been approved for the treatment of ATTRm with polyneuropathy with or without cardiac involvement.

The APOLLO Trial [10] was a prospective, randomized, placebo controlled trial that compared patisiran to placebo in ATTRm patients with peripheral neuropathy, with or without cardiac involvement. The patisiran treated cohort showed a sustained reduction in TTR levels throughout the 18-month study period, associated with improvement in neurologic function (the primary endpoint). In the cardiac subpopulation, there was a significant reduction in NT-proBNP in the patisiran treated group, accompanied by better parameters of cardiac function (global longitudinal strain) and structure (LV wall thickness).

Inotersen, a TTR silencer, is an antisense oligodeoxynucleotide that interferes with hepatic production of TTR and is approved for ATTRm with polyneuropathy. It is administered as a weekly subcutaneous injection. The most common side effects are glomerulonephritis and thrombocytopenia, and the drug requires careful routine monitoring.

The NEURO-TTR study[11] was a multinational, randomized, placebo-controlled study that showed reduction in neurological progression in the group receiving Inotersen, and a sustained reduction in circulating transthyretin levels throughout the intervention period. Subgroup analysis showed stabilization of LV wall thickness, 6-minute walk test and global systolic strain. Studies with primarily cardiac endpoints are ongoing. There are currently no comparison studies of TTR silencers.

To recap the options for treatment (Fig. 1), the TTR stabilizer tafamidis is approved for TTR patients (both ATTRwt and ATTRm) with primarily cardiac involvement and NYHA class I-III symptoms. Early treatment may slow disease progression, and benefits were not observed in patients with more advanced disease (NYHA III). The TTR silencers inotersen and patisiran should be considered in patients with ATTRm and neurologic symptoms. Neither drug is currently approved for TTR cardiomyopathy in the absence of neuropathy. Combination therapy with diflusinal or doxycycline/TUDCA may be a consideration.[12]

SUMMARY

Cardiac amyloidosis is a common cause of heart failure with preserved ejection fraction (HFpEF). There are novel specific treatment regimens which may dramatically delay clinical deterioration and prolong life. It is crucial to differentiate AL from ATTR amyloid. ATTR patients should be genetically tested to distinguish ATTRm from ATTRwt.

REFERENCES

1. Konstam MA, Kiernan MS, Bernstein D, et al. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circ.* 2018; 137:e578-e627.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circ.* 2013; 128:1810-1852.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. *Circ.* 2017; 136: e137-e161. doi: 10.1161/CIR.0000000000000509.
4. Falk RH, Alexander KM, Liao R, et al. AL (Light-Chain) cardiac amyloidosis a review of diagnosis and therapy. *J Am Coll Cardiol.* 2016; 68:1323-1341.
5. Ruberg FL. Grogan M, Hanna M, et al. Transthyretin amyloid cardiomyopathy; JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2019; 73:2872-2891.
6. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *J Am Coll Cardiol: Heart Failure.* 2019; 7:709-716. doi: 10.1016/j.jchf.2019.04.010.
7. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med.* 2018; 379:1007-1016. doi: 10.1056/NEJMoa1805689
8. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy a randomized clinical trial. *J Am Med Assoc.* 2013; 310:2658-2667. doi:10.1001/jama.2013.283815
9. Wixner J, Pilebro B, Lundgren HE, et al. Effect of doxycycline and ursodeoxycholic acid on transthyretin amyloidosis. *Amyloid* 2017; 24(sup 1):78-79. doi: 10.1080/13506129.2016.1269739
10. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018; 379:11-21. doi: 10.1056/NEJMoa1716153
11. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018; 379:22-31. doi: 10.1056/NEJMoa1716793
12. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management. *Circ.* 2020; 141:e1-e22