Amyloidosis and Cardiovascular diseases: a clinical insight

Running Head: Cardiac Amyloidosis

Renier A.B. Visser[a], Céline Gravenor[b], Sennia Ahmed[c], Amer Harky MRCS, MSc[d,e,f*]

[a]School of Medicine, University of Central Lancashire, Preston, United Kingdom.

[b]School of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.

[c]School of Medicine, University of Liverpool, Liverpool, United Kingdom.

[d]Department of Cardiothoracic Surgery, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom.

[e]Department of Integrative Biology, University of Liverpool, Liverpool, United Kingdom.

[f]Liverpool Centre of Cardiovascular Science, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom.

***Corresponding Author**

Amer Harky

MRCS, MSc

Department of Cardiothoracic Surgery

Liverpool Heart and Chest Hospital

Liverpool, United Kingdom

E-mail: aaharky@gmail.com

Phone: +44-151-600-1616

Funding: none obtained

Conflict of Interest: none to be declared

Key Words: Protein, disease pathology, Cardiac outcomes

Authors Contribution: All authors contributed to the paper and have approved the final version.

Abstract

Systemic amyloidosis is caused by deposition of amyloid proteins in varying organ systems throughout the body, leading to dysfunction within those systems. The development of cardiac amyloidosis is one of the main indicators for a poor prognosis for patients. Cardiac amyloidosis is most commonly caused by the Immunoglobulin light chain amyloidosis and the transthyretin amyloidosis. Both have poor prognoses when associated with cardiac amyloidosis, however, the patients with the former subtype fair far worse than those with the later. Despite amyloidosis having a history of being underdiagnosed, recent epidemiological data indicates that the rate of diagnosis has increased which has coincided with an improved in patient median survival rates. It is of great importance that patients are diagnosed with the correct subtype as the main treatment strategy is to treat the underlying cause of the amyloidosis. If a misdiagnosis is made patients can receive treatment that might be ineffective or even harmful.

There is a great of progress being made in the pharmacological treatments being made for treating the underlying causes, however, many of the proposed treatments still need more evidence to support its use.

1. Introduction

Systemic amyloidosis is a rare group of diseases caused by the extracellular deposition of amyloid proteins in various tissues throughout the body[1]. As of yet more than 30 proteins have been found that can aggregate as an amyloid protein, however, with the use of mass spectrometry it is suspected that there are many more of these precursor proteins[2].

In the majority of the cases, cardiac amyloidosis (CA) is caused by two common subtypes of these proteins, immunoglobulin light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis, together accounting for approximately 98% of all cases of CA[1,3-4]. Not only do AL and ATTR amyloidosis have markedly different prognoses, with a median survival of 6-12 months and 2-6 years respectively, they also have significantly different treatments which is why there is a great emphasis on specifying the subtype of amyloidosis[3-5].

The main focus of this review will revolve around CA as it is the leading cause of morbidity and mortality in systemic amyloidosis regardless of the subtype[1]. As it has been shown that the prevalence of CA increases with age, this is of ever greater importance due to the expanding aging population[6]. However, amyloidosis is probably still underdiagnosed and even when diagnosed, the different subtypes with their own specific treatments go unrecognized, which can lead to mismanagement of patients[7]. This emphasises the need of an updated review on CA to familiarise clinicians with the specifics of amyloidosis towards improved patient care[2].

2. Pathophysiology

Amyloidosis is characterised by infiltrative deposits of ‘amyloid proteins’, which are typically waxy, starch-like deformed protein fibrils[7]. Many different types of causative proteins have been identified, some causing systemic amyloidosis, with deposits in multiple organ systems, and others showing more localised pathology in a specific organ[8]. Some well-known diseases are caused by localised misfolded protein deposits (i.e. localised amyloidosis), such as Alzheimer’s

disease (Amyloid-β precursor protein), Creutzfeld-Jakob disease (Prion protein) and familial dementias[8]. Proteins may misfold and form amyloid fibrils if mutations occur in the genetic coding for that protein, causing amino acid substitutions, or if the protein stability is compromised[5]. As with most diseases, factors are hereditary as well as environmental (chemical, electrical, and mechanical stimuli)[7]. This review focuses on the amyloidosis types that are most prominent in causing cardiac complications: immunoglobulin amyloidosis (AL), ATTRwt amyloidosis (formerly called senile systemic amyloidosis [SSA]), ATTRv amyloidosis (formerly called familial amyloid polyneuropathy [FAP]), Table 1 provides a summary of each of the above mentioned subtypes[8].

2.1 Immunoglobulin light chain (AL) amyloidosis:

AL amyloidosis is characterised by a malignant plasma cell clone with a resulting excess of a particular misfolded light- or heavy-chain immunoglobulin (Ig) which is then systemically deposited[8]. The AL subtype is present in about 15% of patients with multiple myeloma (MM), however isolated AL amyloidosis (primary AL) has a different pattern of disease and is therefore an alone standing diagnosis[8]. Public Health England classifies primary AL amyloidosis as a cancer, and according to one report, it accounts for 65% of 5-20 per million cases of amyloidosis in the UK[9]. AL amyloidosis can affect multiple organs, or only a single organ, usually the kidney, heart, liver, gut, and peripheral nervous system[7-8]. The onset is rapid and treatment is targeted at the monoclonal immunoglobulin-producing cells[8]. Treatment that reduces the circulating free light chains (FLC) has better outcomes for heart failure, because FLC seems to be toxic to myocardial cells[10]. This suggests that Cardiac-related AL amyloidosis (AL-CA) is “not simply an infiltrative cardiomyopathy but rather a toxic infiltrative disorder”[10].

2.2 Transthyretin (ATTR) Amyloidosis:

ATTR Amyloidosis caused by misfolded or destabilised transthyretin (TTR)[7]. TTR is produced predominantly by the liver, retinal pigment epithelium and choroid plexus[8]. Two main types of TTR cause CA: a wild-type (AATRwt) and variant-type (ATTRv)[7-8]. ATTRwt amyloidosis is

associated with advancing age (hence the former name 'systemic senile amyloidosis'). The hypothesised mechanism of disease is that TTR, a cyclic tetramer protein in circulation, becomes unstable in elderly patients, and is deposited as pathologic amylaceous (starchy) fibrils[8]. The ATTRv subtype is caused by a 'variant' TTR with altered genetic mutation, inherited in an autosomal dominant pattern[8]. The onset may be early, with gradually increasing severity of symptoms over several decades[8]. There are multiple types of mutations, with varying degrees of resultant instability of the TTR tetramer[11]. The resulting amyloid fibrils are deposited in various systems depending on the mutant type; in peripheral and autonomic nerves, heart, gut, kidney, eyes and brain[8]. It was found that mutations associated with greater instability in TTR affected the peripheral nervous and oculo-leptomeningeal systems more frequently, whereas more stable TTR variants showed greater affinity for the cardiac system [12].

3. Cardiac Amyloidosis (CA):

Clinical manifestation is dependent upon the type of amyloidosis and the site of its occurrence (Figure 1). The complexity tends to develop due cardiac involvement either as part of a systemic process or a local phenomenon. Surprisingly, it is not the quantity of organ systems affected, but the deposition of amyloid fibrils in the heart that decrees a poor prognosis[10].

CA is thought to be underdiagnosed[13]. Early recognition and diagnosis are needed to delay the progression of the disease and increase suitability for surgical interventions[13]. CA should be considered as an important differential in patients with heart failure particularly if ejection fraction is preserved (HFpEF)[13].

Amyloid deposits may be found in one or all of the heart layers: endo-, myo- and pericardium[13]. The endo-myocardium will be the focus of this literature review and refers to the lining of the four chambers as well as the valves, and the cardiac muscle itself[13]. Though nodular deposits of

amyloid may be found on the pericardium[13], this will not be discussed any further in this review as it is not discussed at great length in the existing literature.

3.1 Diagnosing:

At first glance, diagnosing CA seems relatively straight forward. However, some of the difficulties in reaching a timely diagnosis include the rarity of the disease, late presentation of diverse clinical symptoms and the existence of various subtypes[14]. CA is also often mistaken for hypertrophic cardiomyopathy with left ventricular outflow tract obstruction (LVOTO)[7]. Thus, a surprise encounter on the operating table is not uncommon but significant advancements in diagnostic methods should decrease such scenarios moving forward[14].

3.1.1 Clinical:

Each subtype of amyloidosis has specific symptoms associated with it which are presented in Figure 2. CA classically presents as a rapidly progressive congestive heart failure in the absence of ischaemic pathology, which may be accompanied by conduction system disturbances such as arrhythmias and heart blocks[15].

Congestive heart failure due to restrictive cardiomyopathy should be met with high clinical suspicion[15]. The amyloidotic heart is firm, rubbery and less compliant due to the replacement of myocytes with amyloid deposits[15]. Subsequently cardiac relaxation is impaired, causing an increase in right sided filling pressures. Increased jugular venous pressure, hepatomegaly and peripheral oedema are not uncommon[15].

Patients may complain of exertional dyspnoea, fatigue, and chest discomfort. In severe cases cardiac cachexia may also be present[13,15].

Extra cardiac manifestations can be varied depending on the type of amyloid precursor in question. For instance, in AL periorbital purpura is highly characteristic of CA and should prompt

a tissue biopsy[7]. A comprehensive history and examination may also suggest leg/jaw claudication, macroglossia and proteinuria[7].

3.1.2 Echocardiogram:

An echocardiogram (ECHO) is very useful in illustrating the morphological changes that occur over time in an amyloidotic heart and has 87% sensitivity for CA[14], however the reliability may vary with the practitioner's familiarity with CA on ECHO. There is an increase in bi-ventricular and bi-atrial wall thickness, with no change in chamber size and dilatation respectively[14]. The atria undergo dilatation to withstand filling pressures[14]. Septal infiltration and valvular thickening as well as pericardial effusions are also common[14]. The abnormal texture of the infiltrated endo-myocardium appears as 'granular and sparkling', due to the discrepancy between the normal myocytes and the shimmering amyloid protein[14].

3.1.3 Electrocardiograph:

Low voltage QRS complexes on an ECG, in combination with the aforementioned positive ECHO findings is highly indicative of CA and is found in 50% of patients with CA. This is because CA associated ventricular hypertrophy is due to an infiltrative process and not true myocyte hypertrophy as seen in hypertrophic cardiomyopathy[16]. Amyloid deposits are insulative resulting in reduced QRS amplitudes[7].

Combining the clinical history, ECHO findings and a discordant ECG underlines the difficulties in diagnosing CA. CA is nothing short of a masquerade and mimics heart failure, hypertrophic cardiomyopathy and ischaemic changes (non-Q wave infarction).

3.1.4 Biopsy and staining:

Endomyocardial biopsy is not the only means by which tissue can be obtained for immuno-characterisation of amyloid precursors. Extra-cardiac sites, in particular, the abdominal fat pad, are also viable possibilities[7,16]. Aspiration of the subcutaneous fat has successfully helped diagnose CA in 85% of patients[16].

The gold standard for diagnosing amyloidosis subtypes remains histological staining and immunophenotyping of tissue biopsies[7]. Stains such as methyl violet, thioflavin, and haematoxylin and eosin (H&E) can be used[7]. The most selected stain is the Congo red which under polarised light, produces an apple-green birefringence[7]. However, it should be noted that abundant collagen on aortic valves can produce a false positive Congo stain, leading to possibly an incorrect diagnosis of CA[14]. Gertz et al. suggest using mass spectrometry in addition to staining to better guide clinical decisions[16].

3.1.5 Magnetic resonance imaging (MRI):

The new MRI “late gadolinium enhancement” technique has been shown to be effective in diagnosing amyloidosis[6]. This is done by identifying a characteristic pattern of increased myocardial enhancement with other morphological findings such as increased left ventricle wall thickening and abnormal myocardial and blood pool kinetics[6]. Other MRI imaging techniques such as long axis strain and myocardial contraction fraction have been shown to have great prognostic value, as well as determining morphological and functional markers of disease[17]. However, more evidence is needed to support the two latter techniques before they become more commonly used[17].

3.2 Staging

The revised Mayo Clinic amyloidosis staging system, in addition to the New York Heart Association (NYHA) four stage system for congestive HF, can be used to determine progression

and severity of AL amyloidosis[5,8]. In Mayo Clinic staging system patient are assigned a score of 1 for each difference in FLC (difference between involved and uninvolved FLC) ≥18mg/dL (180mg/L), cTnT ≥0.025ng/mL, and NT-proBNP ≥1,800pg/mL, creating stages I to IV with scores of 0 to 3 points[8]. Patients diagnosed with the Mayo Clinic staging system had rapidly decreasing survival rates with higher stages, and in a cohort treated for CA, those treated earlier on (in stage I-II of NYHA staging) had better responses to treatment[18].

3.3 Diagnostic epidemiological data

As stated above, it is important to diagnose CA early on, and that clinicians are aware of the cardiac and systemic signs, as well as the up-to-date diagnostic techniques for improved patient outcomes. A 2018 epidemiological study in the United States showed an increasing proportion of the population being diagnosed with amyloidosis each year[19], which suggests increasing awareness of the disease amongst medical professionals. This study also noted increased survival rates, which is reflected by the trends observed by a UK-based epidemiological study in 2017[20]. This shows significant development in management of amyloidosis, and advancement in general management of complex chronic disease in elderly patients.

4. Vascular amyloidosis

The current literature has a small number of case reports on the presence of amyloid deposits in vasculature. Although some attempt is made to understand vascular amyloidosis (VA), there is no transparency regarding the frequency and extent of vascular involvement [21-22].

Amyloidosis affecting the vasculature can present as myopathy, jaw claudication and/or angina[21]. Microvascular involvement is common and often results in increased serum troponin leading to a misdiagnosis of ‘non-Q wave’ infarction in the absence of true coronary artery disease[13]. Myocardial flow reserve becomes impaired in VA leading to myocyte necrosis[13].

Amyloid deposits can affect the morphology of the vessel and/or the functionality. The dependent variables are frequently reported as carotid artery intimal thickness (IMT) and brachial artery flow mediated dilatation (FMD)[21].

4.1 Coronary vessels

In a cohort study conducted by Sharma et al. AL amyloidosis was associated with a transmural deposition of amyloid whereas ATTRwt amyloidosis was found mainly in the adventitia and external media[22]. This implies that there is also a distinction to be made on location of deposits and not just the frequency and extent. Coronary vessels were affected in all but one in the patient group. However, it was noted that vessel lumen was significantly affected in AL amyloidosis, likely due to transmural deposit pattern[22].

Smith et al. measured the frequency of vascular involvement (as well as other morphologic markers) in AL amyloidosis compared to ATTRwt amyloidosis[23]. A total of 47 autopsy proven amyloidotic hearts were analysed, AL amyloidosis showed higher inclination for vasculature (90 %) whereas this figure was 4% for ATTRwt amyloidosis[23]. Crotty et al found the percentages to be 88% and 26% for the AL and ATTRwt subtypes respectively[24].

Dorbala et al. proposed that coronary artery flow can be impeded via three different pathways: A) Deposits in the vessel wall causing stenosis of lumen (structural), B) extrinsic compression due to interstitial deposits and C) endothelial dysfunction[25]. A comparison was made between patients with amyloidosis versus those with hypertrophic cardiomyopathy in relation to coronary perfusion[25]. MBF (myocardial blood flow) and CRF (coronary flow reserve) were reduced in the amyloidosis group suggesting microvascular involvement[25].

4.2 Aorta

Amyloidosis of the aorta is more likely to be found in the ATTRwt subtype[26-28]. It is associated with an increase in age and is thus a manifestation of senile amyloidosis[26-28]. Iwata et al. investigated 224 ATTRwt amyloidosis autopsy cases and found aortic amyloidosis to an average incidence of 79%[27]. They found that the media of the aorta was affected by amyloidosis, which presented multiple minute deposits and having no relation to atherosclerosis[27]. ATTRwt amyloidosis in the aorta has been suspected of one of the possible cause of aortic aneurysms but this claim still needs to be investigated further[28]. There have been no comprehensive studies to suggest that aortic amyloidosis is solely limited to the ATTRwt subtype, however no studies show a significant occurrence of aortic involvement in AL amyloidosis[26-28].

5. Management and Prognosis

Management of amyloidosis varies with each subtype; therefore, correct diagnosis is imperative[7]. If incorrectly diagnosed, the prognosis can be far poorer because amyloidosis has varying causes that do not respond to the same treatment[7]. One of the two main strategies used for managing CA is to address cardiac symptoms and signs and improve stability[8]. Flow and conduction abnormalities are common in CA, and traditional pharmacological treatments are generally advised, however they may have adverse effects that are not properly investigated in patients presenting with CA-related HF[8]. More evidence is needed to show the potential benefit of surgical interventions and device therapy. The second strategy is to address the underlying cause of cardiac symptoms by slowing the progression of amyloid deposition and is currently considered the primary approach for managing CA[8] and will therefore be the main focus of this section.

5.1 Treating the cause of CA

5.1.1 AL amyloidosis management and prognosis:

Patients with AL have a poor prognosis, and untreated median survival is 13 months[7]. Patients with AL and cardiac involvement have a very poor prognosis of 6-12 months after onset of congestive cardiac failure[5]. Syncope, right ventricular dilatation, left ventricular wall thickness, and elevated troponin I and T levels are all indicators of poor prognosis[5].

Once diagnosed, AL can be treated with chemotherapeutic agents in combination with steroids[7]. Standard treatment is cyclic oral melphalan and prednisone or dexamethasone, and the prognosis is shown to be extended to 17 months[7]. The 2015 British Committee for Standards in Haematology Guideline recommends cyclophosphamide (CPA), bortezomib (BOR), and dexamethasone (DEX) (together known as CyBorD or CVD), however treatment toxicity is greater[8]. Recently, autologous peripheral blood stem-cell transplantation is suggested for far better systemic outcomes, 40% haematologic remission within a year, and prognosis extended to 4.6 years[7]. However, outcomes for patients with cardiac involvement remain low, with median survival at 1.6 years, versus 5 months for the untreated patients[7]. The efficacy of thalidomide combined with bortezomib has been shown and is expected to become more widely used in the future[8].

Peri-transplant mortality rate has remained high for these patients, at 13%. In patients with HF due to CA, heart transplant remains the only option alongside palliative care[29]. Heart donations are limited, and typically patients have a low chance of meeting the recipient criteria due to systemic organ involvement of amyloidosis[7]. In a small cohort of 8 heart transplant recipients, 5 patients had evidence of amyloid deposits 5 months after transplantation[7]. This suggests that in severe CA, the progression of the disease is not halted by only replacing the damaged organ. In more recent data, heart transplants either with or without stem cell transplant, coupled with aggressive chemotherapy to reduce the light chain replication, resulted in 100% one-year survival[5]. Heart transplant remains a promising therapeutic option for cardiac amyloidosis, particularly when systemic deposits are limited post-surgery with chemotherapy[14]. However, 5-

year survival for patients undergoing heart transplant for cardiac amyloidosis was about half the survival rate for patients undergoing heart transplant for other indications[14].

The most effective treatment of AL-CA remains early diagnosis and early drug treatment with a chemotherapeutic-steroidal combination.

5.1.2 ATTR amyloidosis management and prognosis:

The two main subtypes of ATTR (variant and wild-type), will be addressed together because of very similar pathogenesis and treatment[8]. Prognosis for cardiac-related ATTR amyloidosis (ATTR-CA) is better than for AL-CA, with median survival typically 2–6 years compared with 5-6 months[7]. Increasing amounts of evidence point to ATTR amyloidosis as a significant underlying cause of HF[5-6,8][5.6]. High rates of misdiagnosis lead to harmful treatments, as many traditional treatments for cardiac disease are contra-indicated or of unknown or little benefit.

Treatment for AL-CA is not indicated in ATTR-CA, therefore correct diagnosis is necessary to avoid inappropriate chemotherapy[30]. The most effective treatment for ATTR amyloidosis remains liver transplant, as the liver produces the tetramers that misfold into amyloid proteins[7-8]. However, liver donations are not always available and some patients do not qualify for recipient criteria[7]. Furthermore, cardiac symptoms due to ATTR amyloidosis continue to progress after liver transplant, as well as retinal and cerebral deposits due to TTR production in the retinal epithelium and choroid plexus[8].

Alternative or simultaneous (to liver transplant) treatment for ATTR amyloidosis includes drugs that inhibit liver TTR production, that stabilise TTR, and that increase excretion of TTR amyloid[5]. In 2012, Coehlo et al showed the efficacy of Tafamidis, a TTR stabiliser, for reducing all-cause mortality, cardiovascular disease hospitalisations and for improving quality of life[8]. Tafamidis has been shown to be beneficial for both ATTR-CA subtypes. Diflunisal is a non-steroidal anti-

inflammatory drug (NSAID) with tetramer-stabilising properties, but further trials are needed to prove its efficacy in light of typical NSAID adverse effects[5]. Other therapeutic agents recently investigated are nucleic acids, which were effective in limiting the production of TTR[8]. Patisiran, a small interfering RNA (siRNA) targeting TTR mRNA, reduced serum TTR by 80% after 18 months, and limited progression of cardiac signs[8]. Inotersen, an antisense oligonucleotide, was also effective but had serious adverse effects[7-8]. Tafamidis and Patisiran are both recommended as being potentially viable treatment options, but more trials are needed to prove their combined efficacy or non-maleficence[8]. Doxycycline and (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) have been suggested due to their TTR amyloid-clearing properties but further human trials are needed to prove efficacy[5].

5.2 Aortic Stenosis (AS) in CA and its Prognosis:

CA may be more prevalent in elderly men with AS and is associated with far greater mortality. The signs of TTR CA overlap considerably with low-flow AS from other causes, and 25% of post-mortem hearts of octogenarians had amyloidosis (ATTRwt) deposits[5]. This suggests a great proportion of undiagnosed CA, particularly in elderly patients. In another two studies, patients with severe AS and treated with aortic valve replacement (AVR) were biopsied for amyloid deposits - 16% of which had CA in both studies, and in one study, 32% amongst the men only[17,31]. CA-AS had a 3-fold greater mortality rate than AS alone in patients treated with AVR (56% vs 20%)[6]. According to Java et al, AVR for other indications is not harmful in patients with amyloidosis, and provides symptom relief in the mid-term[32]. However, prior evidence - which is mostly on a handful of case studies - shows that prognosis of AVR in patients with amyloidosis is a mixed picture [32-33]. There are particularly poor outcomes for entry at the apical site and better outcomes for trans-femoral AVR[32]. Evidence analysed by Çiçek et al. suggests that AVR make no improvement to the overall mortality of patients with CA[33]. Limitations to the study by Java et al. is that due the small cohort of patients (n=16), with possible selection bias, and that these

patients have various subtypes of amyloidosis, therefore, the quality of this evidence is insufficient for a reliable recommendation for effective and sustainable treatment with AVR in patients with amyloidosis[32]. In another paper, AVR as well as other cardiac surgery including remodelling, are strongly advised against based on the poor prognosis observed[14], probably due to the surgery being non-curative for CA. Clinicians need to be wary of misdiagnosis of more common cardiac diseases in the presence of the ambiguous cardiac amyloidosis symptoms and signs[14], or "probably vastly underrecognised concomitant amyloidosis"[33].

Therefore, aortic valve replacement alone is not a suitable treatment for patients with AS caused by CA. Thorough investigation is needed to confirm and appropriately treat the underlying cause of heart disease, which is more commonly due to amyloidosis in older patients. Appropriate treatment of amyloidosis will result in better survival outcomes, as opposed to cardiac surgery alone.

6. Future research

There is need for evidence regarding the specific efficacy and potential adverse effects of traditional HF medication, surgery and device therapy in relation to the management of symptoms in patients with CA[8]. Additional further research also needs to be conducted in regard to developing more accurate, non-invasive diagnostic techniques.

As mentioned above, Diflunisal has potential to be used in future treatment regimes, however, randomised trials are needed to solidify its efficacy and especially weighing up its benefits compared to common NSAID adverse effects that may be associated with its use[5]. Phase 3 trials of Tafamidis have been completed further supporting its efficacy but despite this there is still a need for a randomised-control trial to further consolidate the evidence supporting it[34]. As human trials for both Doxycycline and CPHPC are in their infancy there is still a great need for further research to be done on its use[5]. Focused research to further improve our understanding of the

specific mechanism and factors of misfolding is necessary in order to develop more targeted therapies.

7. Conclusion

Despite the rarity of amyloidosis and that it is still being underdiagnosed, the epidemiological data infers that the rate of diagnosis is improving most likely due to increased awareness of the disease and the development of more diagnostic techniques. The improvements in the diagnostic process should hopefully lead to earlier and more accurate detection of the disease which have shown to dramatically improve the management and prognosis of patients. Even with all these improvements there is still lack of evidence in our understanding of the cause of the disease as well as not enough evidence to support potential use of many of the proposed treatments. By addressing this dearth of evidence regarding amyloidosis, marked further improvements can be made towards better patient outcomes and their care.

References

1. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. *Clin Med (Lond)*. 2018;18(Suppl 2):s30-s35. doi:10.7861/clinmedicine.18-2-s30
2. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet.* 2016 Jun 25;387(10038):2641-2654. doi: 10.1016/S0140-6736(15)01274-X.
3. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21. doi:10.1016/j.tcm.2017.07.004
4. Maleszewski JJ. Cardiac amyloidosis: pathology, nomenclature, and typing. *Cardiovasc Pathol*. 2015 Nov-Dec;24(6):343-50. doi: 10.1016/j.carpath.2015.07.008.
5. Dungu JN. Cardiac Amyloid - An Update. *Eur Cardiol*. 2015;10(2):113-117. doi:10.15420/ecr.2015.10.2.113
6. Cavalcante JL, Rijal S, Abdelkarim I, et al. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. *J Cardiovasc Magn Reson*. 2017;19(1):98. Published 2017 Dec 7. doi:10.1186/s12968-017-0415-x
7. Hassan W, Al-Sergani H, Mourad W, Tabbaa R. Amyloid heart disease. New frontiers and insights in pathophysiology, diagnosis, and management. *Tex Heart Inst J*. 2005;32(2):178-184.
8. Kitaoka H, Izumi C, Izumiya Y, Inomata T, Ueda M, Kubo T, Koyama J, Sano M, Sekijima Y, Tahara N, Tsukada N, Tsujita K, Tsutsui H, Tomita T, Amano M, Endo J, Okada A, Oda S, Takashio S, Baba Y, Misumi Y, Yazaki M, Anzai T, Ando Y, Isobe M, Kimura T, Fukuda K; Japanese Circulation Society Joint Working Group. JCS 2020

Guideline on Diagnosis and Treatment of Cardiac Amyloidosis. *Circ J*. 2020 Aug 25;84(9):1610-1671. doi: 10.1253/circj.CJ-20-0110

9. Nienhuis HL, Bijzet J, Hazenberg BP. The Prevalence and Management of Systemic Amyloidosis in Western Countries. *Kidney Dis (Basel)*. 2016;2(1):10-19. doi:10.1159/000444206
10. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation*. 2005;112(13):2047-2060. doi:10.1161/CIRCULATIONAHA.104.489187
11. Rowczenio DM, Noor I, Gillmore JD, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. *Hum Mutat*. 2014;35(9):E2403-E2412. doi:10.1002/humu.22619
12. Sekijima Y, Wiseman RL, Matteson J, et al. The biological and chemical basis for tissue-selective amyloid disease. *Cell*. 2005;121(1):73-85. doi:10.1016/j.cell.2005.01.018
13. Falk RH, Dubrey SW. Amyloid heart disease [published correction appears in Prog Cardiovasc Dis. 2010 Mar-Apr;52(5):445-7]. *Prog Cardiovasc Dis*. 2010;52(4):347-361. doi:10.1016/j.pcad.2009.11.007
14. Zacek P, Harrer J. Amyloidosis and Cardiac Surgery. In: Narin C, editor. Perioperative Considerations in Cardiac Surgery [Internet]. InTech; 2012 [cited 2020 Sep 26]. Available from: http://www.intechopen.com/books/perioperative-considerations-in-cardiac-surgery/cardiac-amyloidosis-versus-cardiac-surgery
15. Manolis AS, Manolis AA, Manolis TA, Melita H. Cardiac amyloidosis: An underdiagnosed/underappreciated disease. *Eur J Intern Med*. 2019;67:1-13. doi:10.1016/j.ejim.2019.07.022
16. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and treatment of cardiac amyloidosis. *Nat Rev Cardiol*. 2015;12(2):91-102. doi:10.1038/nrcardio.2014.165
17. Arenja N, Andre F, Riffel JH, Siepen FAD, Hegenbart U, Schönland S, Kristen AV, Katus HA, Buss SJ. Prognostic value of novel imaging parameters derived from standard cardiovascular magnetic resonance in high risk patients with systemic light chain amyloidosis. *J Cardiovasc Magn Reson*. 2019 Aug 22;21(1):53. doi: 10.1186/s12968-019-0564-1
18. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol*. 2004;22(18):3751-3757. doi:10.1200/JCO.2004.03.029
19. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. *Blood Adv*. 2018 May 22;2(10):1046-1053. doi: 10.1182/bloodadvances.2018016402.
20. Lane T, Pinney JH, Gilbertson JA, et al. Changing epidemiology of AA amyloidosis: clinical observations over 25 years at a single national referral centre. *Amyloid*. 2017;24(3):162-166. doi:10.1080/13506129.2017.1342235
21. Modesto KM, Dispenzieri A, Gertz M, et al. Vascular abnormalities in primary amyloidosis. *Eur Heart J*. 2007;28(8):1019-1024. doi:10.1093/eurheartj/ehm066
22. Sharma PP, Payvar S, Litovsky SH. Histomorphometric analysis of intramyocardial vessels in primary and senile amyloidosis: epicardium versus endocardium. *Cardiovasc Pathol*. 2008;17(2):65-71. doi:10.1016/j.carpath.2007.05.008
23. Smith TJ, Kyle RA, Lie JT. Clinical significance of histopathologic patterns of cardiac amyloidosis. *Mayo Clin Proc*. 1984;59(8):547-555. doi:10.1016/s0025-6196(12)61493-1
24. Crotty TB, Li CY, Edwards WD, Suman VJ. Amyloidosis and endomyocardial biopsy: Correlation of extent and pattern of deposition with amyloid immunophenotype in 100 cases. *Cardiovasc Pathol*. 1995;4(1):39-42. doi:10.1016/1054-8807(94)00023-k
25. Dorbala S, Vangala D, Bruyere J Jr, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. *JACC Heart Fail*. 2014;2(4):358-367. doi:10.1016/j.jchf.2014.03.009

26. Miura Y, Tsumoto H, Iwamoto M, et al. Age-associated proteomic alterations in human aortic media. *Geriatr Gerontol Int*. 2019;19(10):1054-1062. doi:10.1111/ggi.13757
27. Iwata T, Kamei T, Uchino F, Mimaya H, Yanagaki T, Etoh H. Pathological study on amyloidosis--relationship of amyloid deposits in the aorta to aging. *Acta Pathol Jpn*. 1978;28(2):193-203. doi:10.1111/j.1440-1827.1978.tb00531.x
28. Enqvist S, Peng S, Persson A, Westermark P. Senile amyloidoses--diseases of increasing importance. *Acta Histochem*. 2003;105(4):377-378. doi:10.1078/0065-1281-00727
29. Yoon DW, Park BJ, Kim IS, Jeong DS. Isolated Tricuspid Regurgitation: Initial Manifestation of Cardiac Amyloidosis. *Korean J Thorac Cardiovasc Surg*. 2015;48(6):422-425. doi:10.5090/kjtcs.2015.48.6.422
30. O'Meara E, McDonald M, Chan M, et al. CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis. *Can J Cardiol*. 2020;36(2):159-169. doi:10.1016/j.cjca.2019.11.036
31. Castaño A, Narotsky DL, Hamid N, 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):2879-2887. doi:10.1093/eurheartj/ehx350
32. Java AP, Greason KL, Dispenzieri A, et al. Aortic valve replacement in patients with amyloidosis. *J Thorac Cardiovasc Surg*. 2018;156(1):98-103. doi:10.1016/j.jtcvs.2017.12.048
33. Çiçek S. Cardiac amyloidosis and aortic stenosis: Great masquerader back again!. *J Thorac Cardiovasc Surg*. 2018;156(1):104-105. doi:10.1016/j.jtcvs.2018.01.080
34. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689