REVIEW

Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature

Robert Daniel Adam[1,2], Daniel Coriu[2,3], Andreea Jercan[2], Sorina Bădeliţă[3], Bogdan A. Popescu[1,2], Thibaud Damy[4,5] and Ruxandra Jurcuţ[1,2]*

[1]*Department of Cardiology, Emergency Institute for Cardiovascular Diseases 'Prof. Dr. C. C. Iliescu', 3rd Cardiology Department, 258 Fundeni Street, Bucharest, 022328, Romania;* [2]*University of Medicine and Pharmacy 'Carol Davila', Bucharest, Romania;* [3]*Department of Hematology, Fundeni Clinical Institute, Bucharest, Romania;* [4]*French Referral Center for Cardiac Amyloidosis, Amyloidosis Mondor Network, Créteil, France; and* [5]*Department of Cardiology, Henri Mondor Hospital/AP-HP, Créteil, France*

Abstract

Cardiac amyloidosis is a restrictive cardiomyopathy determined by the accumulation of amyloid, which is represented by misfolded protein fragments in the cardiac extracellular space. The main classification of systemic amyloidosis is determined by the amyloid precursor proteins causing a very heterogeneous disease spectrum, but the main types of amyloidosis involving the heart are light chain (AL) and transthyretin amyloidosis (ATTR). AL, in which the amyloid precursor is represented by misfolded immunoglobulin light chains, can involve almost any system carrying the worst prognosis among amyloidosis patients. This has however dramatically improved in the last few years with the increased usage of the novel therapies such as proteasome inhibitors and haematopoietic cell transplantation, in the case of timely diagnosis and initiation of treatment. The treatment for AL is directed by the haematologist working closely with the cardiologist when there is a significant cardiac involvement. Transthyretin (TTR) is a protein that is produced by the liver and is involved in the transportation of thyroid hormones, especially thyroxine and retinol binding protein. ATTR results from the accumulation of transthyretin amyloid in the extracellular space of different organs and systems, especially the heart and the nervous system. Specific therapies for ATTR act at various levels of TTR, from synthesis to deposition: TTR tetramer stabilization, oligomer aggregation inhibition, genetic therapy, amyloid fibre degradation, antiserum amyloid P antibodies, and antiserum TTR antibodies. Treatment of systemic amyloidosis has dramatically evolved over the last few years in both AL and ATTR, improving disease prognosis. Moreover, recent studies revealed that timely treatment can lead to an improvement in clinical status and in a regression of amyloid myocardial infiltration showed by imaging, especially by cardiac magnetic resonance, in both AL and ATTR. However, treating cardiac amyloidosis is a complex task due to the frequent association between systemic congestion and low blood pressure, thrombo-embolic and haemorrhagic risk balance, patient frailty, and generally poor prognosis. The aim of this review is to describe the current state of knowledge regarding cardiac amyloidosis therapy in this constantly evolving field, classified as treatment of the cardiac complications of amyloidosis (heart failure, rhythm and conduction disturbances, and thrombo-embolic risk) and the disease-modifying therapy.

Introduction

Cardiac amyloidosis (CA) is determined by the accumulation of amyloid, which is represented by misfolded protein fragments in the cardiac extracellular space. The main classification of systemic amyloidosis is determined by the amyloid precursor proteins causing a very heterogeneous disease spectrum. Until now, there are over 36 proteins described as amyloid precursors,[1,2] but CA is mainly determined by two protein precursors: immunoglobulin light chains and transthyretin (TTR).

Light chain amyloidosis (AL), in which the amyloid precursor is represented by misfolded immunoglobulin light chains, can involve almost any system: soft tissues (bilateral carpal

tunnel syndrome, pseudohypertrophy of the muscles, and rupture of the biceps tendon), kidney (leading to nephrotic syndrome), peripheral nervous system (both somatic polyneuropathy and autonomic orthostatic hypotension, gastrointestinal and urinary dysfunction, and erectile dysfunction), liver, or lungs.[3] These patients have the worst prognosis among amyloidosis patients.[4] This has however dramatically improved in the last few years with the increased usage of the novel therapies such as proteasome inhibitors and haematopoietic cell transplantation,[5] in the case of timely diagnosis and initiation of treatment.

Transthyretin (previously known as prealbumin) is a protein that is produced by the liver and is involved in the transportation of thyroid hormones, especially thyroxine and retinol binding protein. TTR amyloidosis (ATTR) results from the accumulation of TTR amyloid in the extracellular space of different organs and systems, especially the heart and the nervous system.[6] Furthermore, ATTR can be determined by the accumulation of either variant TTR (ATTRv, also known as hereditary ATTR or mutant ATTR) or wild-type TTR (ATTRwt, previously known as senile systemic amyloidosis).[2]

ATTRv results from single base substitutions causing more than 120 recognized pathogenic mutations of the TTR gene,[7] with an autosomal dominant inheritance pattern. The clinical presentation of ATTRv is very heterogeneous, depending on the mutation: pure nervous system phenotype (polyneuropathy and autonomic dysfunction), pure cardiac phenotype (ATTR CA), or mixed phenotypes with different evolution and prognosis.[7] The variant that is most commonly associated with ATTR-CA is ATTRV122I, which is the most common mutation identified in the USA, especially in the African Americans and Afro-Caribbeans, but also in France, carrying the worst prognosis.[8,9] Prevalence of ATTRv in hypertrophic cardiomyopathy (HCM) has been underestimated, and recent studies showed that around 9.3% of 343 patients with HCM referred to tertiary centres have CA (5% ATTRwt, 3.5% ATTRv, and 0.9% AL)[10] and 5% of 298 consecutive patients diagnosed with HCM in France had, in fact, ATTRv.[11] In contrast, the most commonly spread mutation worldwide is ATTRV30M especially in endemic regions like Portugal, Scandinavia, and Japan. This mutation is responsible for either an early-onset disease neurological phenotype (in endemic regions) or a late-onset cardiac phenotype with rare neurological involvement in elderly people from non-endemic regions, carrying a better prognosis.[12] ATTRT60A is another mutation associated with cardiac involvement, but the polyneuropathy can also be a common finding, being responsible for a mixed phenotype with better prognosis than ATTRV122I but worse than ATTRV30M.[13]

Distinct from ATTRv, ATTRwt is considered to occur with ageing and is mainly affecting the heart, but it can also involve the soft tissues leading to spinal stenosis or bilateral carpal tunnel syndrome. ATTRwt commonly affects elderly men, and an autopsy study published in 2008 reported a prevalence of the disease of 25% in 256 patients aged over 85.[14] Moreover, the presence of ATTRwt was described in 13% of heart failure with preserved ejection fraction patients >60 years old and with left ventricular (LV) hypertrophy of more than 12 mm,[15] as well as in 16% of patients with severe aortic stenosis referred to transcatheter aortic valve implantation (TAVI).[16] González-López et al. showed that the clinical spectrum of ATTRwt is heterogeneous and differs from the classical phenotype.[17]

Another classification can use the MOGE(S) nosology system, which has been endorsed for the standardized classification of cardiomyopathy using the morpho-functional phenotype description (M), organ/system involvement (O), genetic inheritance pattern (G), aetiology (E), and stage (S). According to this classification, CA is denoted EA.[18]

The diagnosis of CA is based on a complex algorithm, based on cardiac and extracardiac red flags for the diagnostic suspicion, and confirmed either through identification of the amyloid deposits from endomyocardial biopsy specimens or using a non-invasive approach, which includes extracardiac identification of amyloid deposits from tissue biopsies, serum protein immunofixation, diphosphonate scintigraphy, and TTR gene sequencing[19,20] (Figure 1).
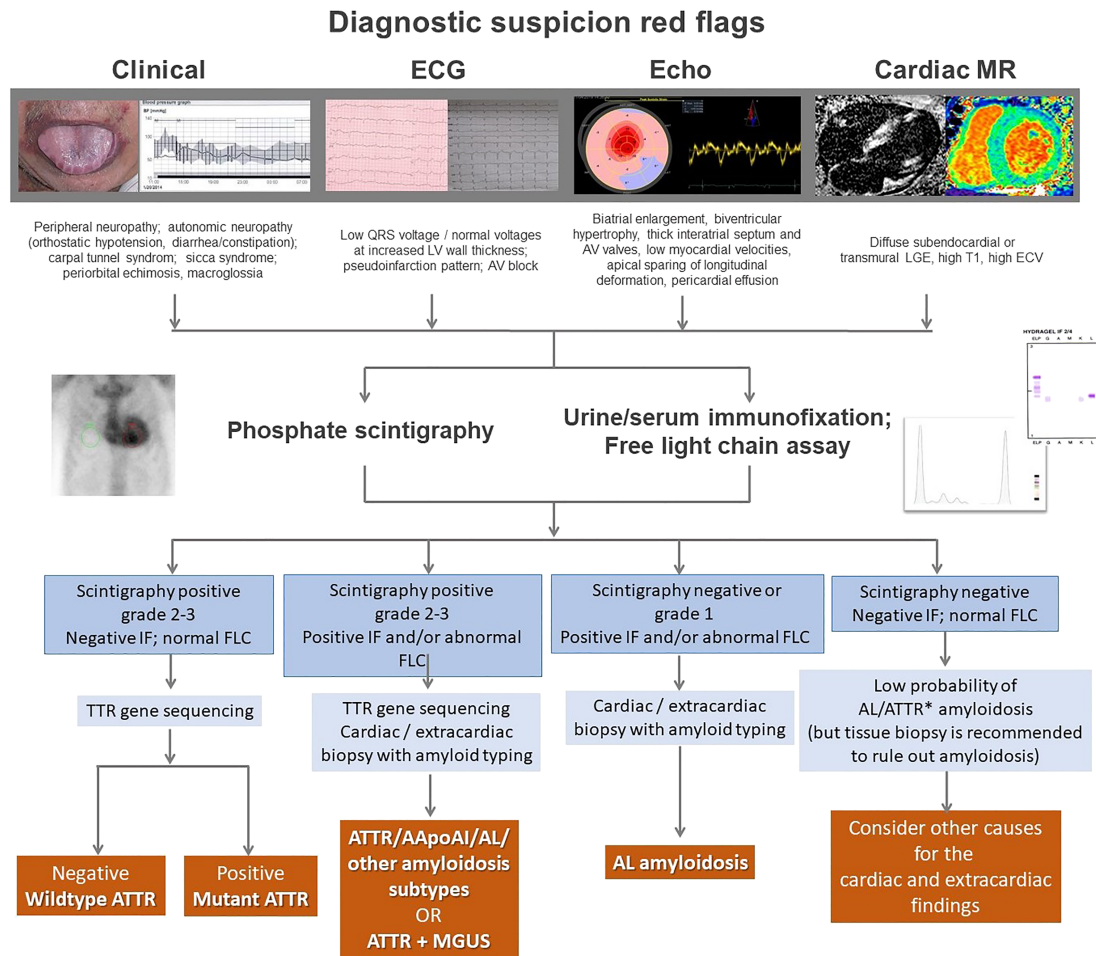
Understanding the pathophysiology of CA helps explaining specific therapeutic choices (Figure 2). Extracellular amyloid infiltration leads to thickening of ventricular walls, increased ventricular stiffness, and consequently to high ventricular filling pressure. Atrial wall infiltration also occurs, leading to functional and electrical changes [e.g. atrial fibrillation (AF) and atrial paralysis], as well as to an increased risk of atrial thrombus formation.[21] Direct amyloid fibrils toxicity and non-inflammatory oedema may be responsible for cardiac dysfunction in AL and to a lesser extent in ATTR in addition to interstitial infiltration.[22]

The treatment of systemic amyloidosis has dramatically evolved over the last few years in both AL and ATTR, improving disease prognosis. However, treating CA is a complex task due to the frequent association between systemic congestion and low blood pressure, thrombo-embolic and haemorrhagic risk balance, patient frailty, and poor prognosis. The aim of this review is to describe the current state of knowledge regarding CA therapy, classified as therapy of the cardiac complications of amyloidosis [heart failure (HF), rhythm and conduction disturbances, and thrombo-embolic risk] and the disease-modifying therapy (for AL and ATTR amyloidosis, respectively) (Figure 3).

Management of cardiac symptoms

The pathophysiology of CA leads to a restrictive phenotype associated with systemic congestion and low cardiac output. However, CA is considered a rare disease with a bad

Figure 1 Diagnostic algorithm leading from the clinical suspicion for CA to the final diagnosis. *Except in genotype positive/phenotype negative mutant ATTR relatives or specific mutations with known low myocardial uptake like TTR Phe64Leu. FLC, free light chain; MGUS, monoclonal gammapathy of unknown significance. For all other abbreviations, see text. Reproduced with permission from Jurcut *et al*.[20]

Diagnostic suspicion red flags

Clinical	ECG	Echo	Cardiac MR
Peripheral neuropathy; autonomic neuropathy (orthostatic hypotension, diarrhea/constipation); carpal tunnel syndrom; sicca syndrome; periorbital echimosis, macroglossia	Low QRS voltage / normal voltages at increased LV wall thickness; pseudoinfarction pattern; AV block	Biatrial enlargement, biventricular hypertrophy, thick interatrial septum and AV valves, low myocardial velocities, apical sparing of longitudinal deformation, pericardial effusion	Diffuse subendocardial or transmural LGE, high T1, high ECV

Phosphate scintigraphy — **Urine/serum immunofixation; Free light chain assay**

Scintigraphy positive grade 2-3 Negative IF; normal FLC	Scintigraphy positive grade 2-3 Positive IF and/or abnormal FLC	Scintigraphy negative or grade 1 Positive IF and/or abnormal FLC	Scintigraphy negative Negative IF; normal FLC
TTR gene sequencing	TTR gene sequencing Cardiac / extracardiac biopsy with amyloid typing	Cardiac / extracardiac biopsy with amyloid typing	Low probability of AL/ATTR* amyloidosis (but tissue biopsy is recommended to rule out amyloidosis)
Negative **Wildtype ATTR** / Positive **Mutant ATTR**	**ATTR/AApoAI/AL/ other amyloidosis subtypes OR ATTR + MGUS**	**AL amyloidosis**	**Consider other causes for the cardiac and extracardiac findings**

prognosis and therefore is an exclusion criterion from most randomized trials on HF therapies when diagnosed. Therefore, therapeutic decisions are usually based on a consensus of experts, personal experience, or data from small cohort studies.[22]

Diuretics

Diuretics represent the first line of medical treatment in HF and CA, being necessary for congestion relief. Often, these patients require high doses of diuretics to reduce systemic and pulmonary congestion, particularly in the population with severe diastolic dysfunction or systolic dysfunction.[23,24] The diuretic treatment should be conducted with care to avoid an excessive diuresis with important preload reduction and worsening of the renal function. Often, a loop diuretic (e.g. furosemide) is used in combination with a mineralocorticoid receptor antagonist (e.g. spironolactone). In patients

with autonomic dysfunction leading to orthostatic hypotension, mostly in AL and ATTRv diuretics must be used with caution.

Beta-blockers

While widely used in HF with reduced ejection fraction, beta-blockers (BBs) are not well tolerated in restrictive cardiomyopathies in general and CA in particular. BBs can often lead to low cardiac output, fatigue, conduction disturbances, hypotension, and even syncope in a disease with restrictive physiology where the cardiac output is very dependent on the heart rate.[25,26] Conversely, a common scenario that should raise clinical suspicion of CA is development of profound hypotension and fatigue after initiation of BBs.[22] In patients who tolerate high-dose BBs, an alternative aetiology of HF symptoms should be sought.

Figure 2 Amyloidosis pathophysiology and therapeutic implications. For abbreviations, see text.
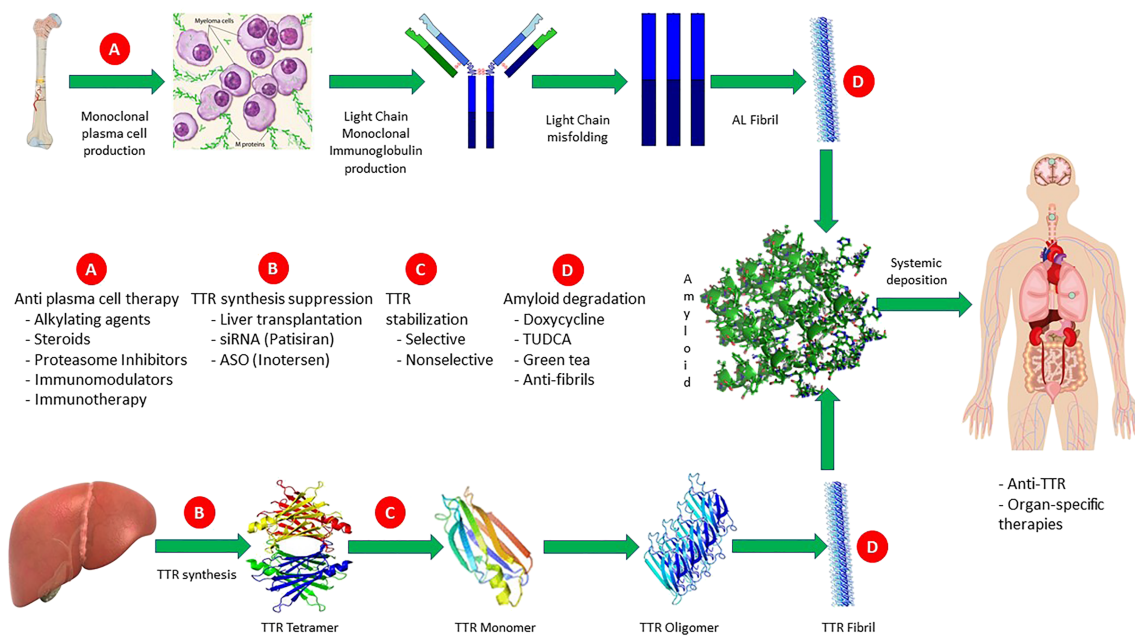
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

The use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers is primarily limited in patients with CA because of the associated autonomic dysfunction with orthostatic hypotension.

Digoxin

Traditionally, digoxin has been contraindicated in CA because of early reports demonstrating that it binds to amyloid fibrils leading to an increased toxicity in this population.[27,28] A recent study however concluded that digoxin may be cautiously used in CA.[29] Based on its findings, the authors suggested using digoxin at lower doses (0.125 mg/day or lower) and with frequent drug concentration monitoring (target digoxinemia of 0.5–0.8 ng/mL) along with close monitoring of renal function and electrolytes.

Calcium channel blockers

Non-dihydropiridine calcium channel blockers are also contraindicated in CA because they have an important negative inotropic, chronotopic, and dromotropic effect.[30] Furthermore, verapamil can bind to amyloid fibrils increasing its toxicity and may precipitate worsening HF, being therefore contraindicated in CA.[31]
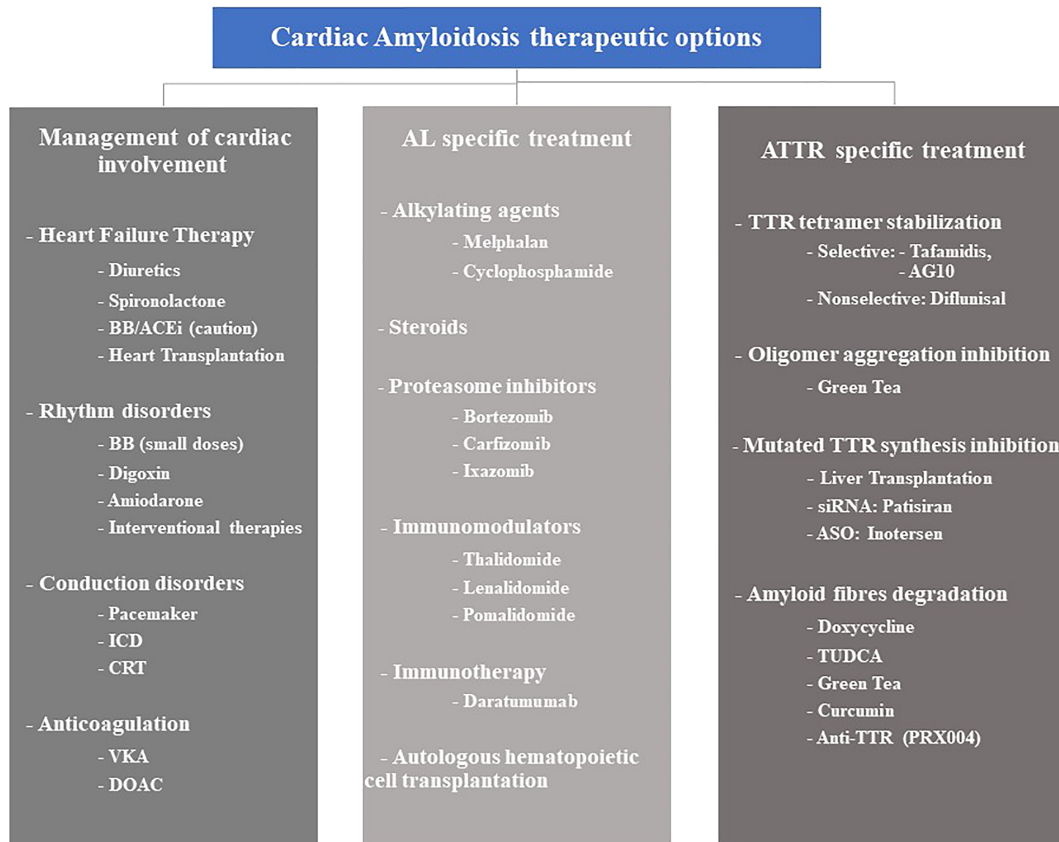
Antiarrhythmic drugs

Because of atrial dilatation and atrial wall infiltration with amyloid, atrial arrhythmias are a common finding in CA, with AF being described in up to 44% of CA patients, as compared with around 1% in the general population.[32] Rhythm and rate control can prove to be difficult in these patients. Because pharmacological rhythm control options are limited, amiodarone is the most commonly administered drug in CA with arrhythmias and is relatively well tolerated.[22,33] Other options used in clinical practice are sotalol and dofetilide, if well tolerated.

Ventricular arrhythmias also appear to be prevalent in CA, including premature ventricular contractions, and non-sustained and sustained ventricular tachycardias.[34] Moreover, they hold a prognostic role, being associated to sudden cardiac death (SCD).[34] Amiodarone is indicated for the pharmacological therapy, and consideration on the role of cardiac defibrillators and ablation is presented below.

Anticoagulant therapy

Patients with CA present a high frequency of intracardiac thrombosis, especially those with AL type, even in the presence of sinus rhythm and preserved systolic function, likely because of a poor atrial function (determined by severe LV diastolic dysfunction and direct infiltration of the left atrial wall), leading to embolic events and high mortality.[35] The same group demonstrated that a transmitral A wave velocity

Figure 3 Cardiac amyloidosis therapeutic options. ACEi, angiotensin-converting enzyme inhibitor; ASO, antisense oligonucleotide; ATTR, transthyretin amyloidosis; BB, beta-blocker; DOAC, direct anticoagulant; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; TTR, transthyretin; TUDCA, tauroursodeoxycholic acid; VKA, vitamin K antagonist.

Figure 3 — Cardiac Amyloidosis therapeutic options

Management of cardiac involvement
- Heart Failure Therapy
  - Diuretics
  - Spironolactone
  - BB/ACEi (caution)
  - Heart Transplantation
- Rhythm disorders
  - BB (small doses)
  - Digoxin
  - Amiodarone
  - Interventional therapies
- Conduction disorders
  - Pacemaker
  - ICD
  - CRT
- Anticoagulation
  - VKA
  - DOAC

AL specific treatment
- Alkylating agents
  - Melphalan
  - Cyclophosphamide
- Steroids
- Proteasome inhibitors
  - Bortezomib
  - Carfizomib
  - Ixazomib
- Immunomodulators
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- Immunotherapy
  - Daratumumab
- Autologous hematopoietic cell transplantation

ATTR specific treatment
- TTR tetramer stabilization
  - Selective: - Tafamidis,
               - AG10
  - Nonselective: Diflunisal
- Oligomer aggregation inhibition
  - Green Tea
- Mutated TTR synthesis inhibition
  - Liver Transplantation
  - siRNA: Patisiran
  - ASO: Inotersen
- Amyloid fibres degradation
  - Doxycycline
  - TUDCA
  - Green Tea
  - Curcumin
  - Anti-TTR (PRX004)

of <30 cm/s was associated with intracardiac thrombi in AL patients in the absence of AF, concluding that in the presence of atrial mechanical dysfunction (especially with coexisting restrictive LV filling), intracardiac thrombosis can be detected and anticoagulation should be carefully considered.[36]

In a cohort of ATTR-CA patients and AF, Donnellan *et al*.[37] found no association between the CHA_2DS_2-VASc score and the presence of left atrial appendage thrombus on transesophageal echocardiogram. Therefore, anticoagulation of patients with CA and AF is recommended irrespective of the CHA_2DS_2-VASc score.[38]

Moreover, in a recently published study on 58 patients with CA evaluated for direct-current cardioversion for atrial arrhythmias, there was a high cancellation rate (28%) mainly due to a high incidence of intracardiac thrombi (13 of 16 patients—81%) even among patients who receive adequate anticoagulation.[39] Consequently, even after correct anticoagulation course prior to planned cardioversion, transesophageal echocardiogram control or computed tomography scan should be performed to rule out left atrial thrombi.

When prescribing anticoagulant therapy to CA patients, especially in AL, the benefit–risk ratio should take into account the possible coexisting amyloid vasculopathy or the deficiency of factor X.[40] However, anticoagulation with either warfarin or the novel oral anticoagulants can usually be safely prescribed to patients with CA.[23]

Arrhythmia ablation

Catheter ablation for AF in CA was explored in several small recent studies, suggesting that it is a feasible strategy for appropriately selected patients, being most effective when performed earlier during the disease process.[41,42] Barbhaiya *et al*. found higher arrhythmia recurrence rates at 1 year compared with non-CA age-matched AF patients (83% vs. 25% at 1 year).[43] Among the 24 patients with ATTR-CA who underwent ablation, 5 of 14 Stage I or II ATTR-CA patients (36%) experienced recurrent arrhythmia compared with 9 of 10 (90%) with Stage III disease.[41] More data are therefore needed in order to determine the efficacy of catheter ablation of AF in CA patients.

Pacemakers and cardiac defibrillators

Amyloid fibrils infiltrating the myocardium are predisposing to conduction disturbances and bradyarrhythmias. High prevalence of conduction system disease in ATTR-CA was recently described, including wide QRS, first-degree atrioventricular (AV) block, high-degree AV block, and progressive sinus node dysfunction, with high pacemaker implantation rate during follow-up.[44] In a large series of patients with ATTRv with neuropathy (262 patients), a prophylactic pacemaker was implanted in 100 patients based on the I/IIa indication, namely, (i) prolonged HV interval (≥70 ms) or (ii) an abnormal HV interval (>55 ms) associated with a fascicular block on electrocardiogram (ECG) (right bundle branch block, left bundle branch block, left anterior haemiblock, and left posterior haemiblock), a first-degree AV block (PR interval ≥200 ms), or a Wenckebach anterograde point ≤100 b.p.m.[45] During a mean follow-up of 45 months, a high-degree AV block was discovered in 24 of the 95 patients (25%). Additionally, the risk of high-degree AV block was higher in patients with first-degree AV block or Wenckebach anterograde point under 100 b.p.m, while low voltage on surface ECG reduced the risk, suggesting that prophylactic pacemaker implantation prevented symptomatic bradycardia in these patients. Although it is not indicated by guidelines to perform screening electrophysiological studies in all CA patients, these results suggest that we should further investigate any conduction disturbance on the surface ECG with at least repeated ECG Holter monitoring.

However, recent work from Donnellan et al. including 78 ATTR-CA patients showed that a higher right ventricular pacing burden is associated with deleterious remodelling and progressive HF in patients with ATTR CA, whereas biventricular pacing is associated with functional improvement.[46] Therefore, the authors suggested that biventricular pacing should be considered in patients with ATTR-CA and an indication for pacing.

Clear recommendations for the choice between conventional pacemaker and implantable cardioverter defibrillator (ICD) are not yet released; therefore, the individual decision should be made based on available data and risk stratification. This topic has been studied predominantly in AL-related cardiomyopathy,[47] and the rates of appropriate ICD therapies are high in these patients.[48] However, the mortality after implantation remains high, the most common causes of death being demonstrated to be asystole and electromechanical dissociation.[49] There is no evidence of a survival benefit with ICD implantation for primary prevention of SCD in CA,[50] so their routine use in CA patients is not recommended.

Because of those limited and sometimes contradictory data, European and American guidelines for SCD prevention in CA have also been divergent in the past. While the 2015 European Society of Cardiology guidelines[51,52] only recommend ICD use in secondary prevention in patients with sustained ventricular arrhythmias causing haemodynamic instability and expected to survive at least 1 year, the 2013 American guidelines also mentioned some indications for ICD implantation in primary prevention.[53] The Stanford University group also recommended ICD implantation for primary prevention in patients with New York Heart Association (NYHA) class <IV, life expectancy >1 year, history of non-postural syncope, or evidence of non-sustained ventricular tachycardia on ECG monitoring.[54] However, in the updated 2017 American guidelines, these recommendations were withdrawn and an individual decision was recommended.[51,52] The recent European Society of Cardiology consensus for CA management briefly recommends ICD for primary prevention of SCD,[55] saying that ICD in primary prevention is usually not recommended.

Cardiac amyloidosis and aortic stenosis

Concomitant pathology of aortic stenosis and ATTRwt CA is common in older patients and differs from lone aortic stenosis, the association of these two diseases carrying a worse clinical presentation and prognosis unless treated.[56] Two recent studies demonstrated that TAVI significantly improves outcome in both lone aortic stenosis and aortic stenosis associated with CA, while periprocedural complications and mortality were similar to lone aortic stenosis, suggesting that TAVI should not be denied to patients with dual disease.[56,57]

Supportive therapies

Peripheral vasoconstrictors could be used for the blood pressure support of patients with autonomic dysfunction and symptomatic hypotension. One of the most effective available agents is midodrine, which acts as an α_1 agonist through its metabolites and exerts its action via activation of the α-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure.[58] Of note, in some patients, the number of daily pills can reach 16 pills a day. The anticholinergic pyridostigmine can also improve neurogenic orthostatic hypotension,[59] and some centres are also using droxidopa as a support for orthosthatic blood pressure in both neurodegenerative diseases and AL.[60,61] Fludrocortisone can be helpful in some patients who do not show a good response to midodrine but may cause or exacerbate fluid retention.

Heart transplantation

According to the 2016 International Society for Heart Lung Transplantation, there are three main recommendations regarding heart transplantation in CA.[62] Selected patients with HF due to AL amyloidosis who are not candidates for

disease-specific therapies due to cardiovascular compromise may be considered for orthotopic heart transplantation (OHT) in experienced centres with established collaborations between cardiovascular and haematology teams. Furthermore, autologous haematopoietic cell transplantation should be planned as soon as clinically feasible after recovery from OHT (Class IIA, Level of Evidence B); therefore, new chemotherapies such as bortezomib have replaced autologous haematopoietic cell transplantation in many countries.[62] Also, patients with TTR amyloidosis-related cardiomyopathy (ATTR-CM) may be considered for OHT. ATTRv patients should be considered for combined heart and liver transplantation in experienced centres with established collaboration between cardiology, hepatology, and neurology (Class IIA, Level of Evidence B).[62] Amyloid involvement of extracardiac organs must be carefully evaluated when considering AL patients for OHT. Severe cardiac amyloid organ dysfunction should be considered a contraindication to proceeding with transplantation (Class IIA, Level of Evidence B).[62]

Specific therapies in light chain amyloidosis

The treatment for AL is directed by the haematologist working closely with the cardiologist when there is a significant cardiac involvement. The main role of the cardiologist during treatment is to evaluate the initial cardiac involvement, to stabilize the heart function (diuresis, prevention of embolic events, management of arrhythmias, and conduction disorders) during the treatment, and to assess the cardiac response to treatment.[63] CA prognosis was proven to be correlated to cardiac biomarkers levels, which have been included in the Mayo staging system for AL[64] and the European staging system in ATTR.[65]

Traditionally, the cardiac response was evaluated by the clinical response (changes in NYHA class) and by echocardiographic evolution of wall thickness, and diastolic and systolic function assessed by the LV ejection fraction.[66] Because significant improvement in wall thickness or in systolic function is uncommon, there was a need to develop more subtle parameters such as global longitudinal strain (GLS), which is an independent predictor of survival in AL-CA.[67] Improvements in myocardial deformation study can appear despite the absence of a significant improvement in the classical echocardiographic parameters.[68] Cardiac magnetic resonance could also provide strong evidence for amyloid regression revealing early improvements such as reduction of myocardial oedema, mass, and T1 with improvement in late gadolinium enhancement, challenging the belief that CA may only stabilize after successful treatment of AL.[69] Misfolded light chains may have toxic effects on cardiomyocytes, so a significant reduction in the serum free light chains can lead to a significant

reduction of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and of the clinical response. Therefore, a cardiac response was defined in 2012 as a reduction in the NT-proBNP levels of more than 30% in patients with baseline NT-proBNP value >650 pg/mL.[70]

The outcome of advanced AL has shown significant improvements in the last decade due to both earlier diagnosis and the development of new drugs such as proteasome inhibitors and immunotherapy.[71] There are some reports showing that the early mortality at 6 months improved from 40% to 24%.[72] In a large study of over 1500 patients with AL, 76% of whom had cardiac involvement, the median survival of more than 10 years was achieved by approximate one-third of patients.[5]

Novel therapies—changing the light chain amyloidosis–cardiac amyloidosis treatment paradigm

Limited options for AL-CA were available before the introduction of the novel therapies as autologous stem cell transplantation was contraindicated. The first line of treatment in AL for several years has been represented by the alkylating agents, such as melphalan and cyclophosphamide in combination with a steroid (dexamethasone) in treatment regiments as melphalan–dexamethasone or cyclophosphamide–dexamethasone.[73]

The discovery of bortezomib represented a treatment revolution in achieving rapid haematological responses in patients with AL with a complete response (CR) in 42% of the patients receiving bortezomib, melphalan, and dexamethasone compared with 19% in the group without bortezomib in the treatment.[74] The most commonly used first-line treatment is represented by a combination of three drugs—cyclophosphamide, the reversible proteasome inhibitor bortezomib, and steroids such as cyclophosphamide, bortezomib, and dexamethasone (CyBorD), with weekly administration.[63] An overall haematological response rate of CyBorD treatment regimen in 230 patients with AL was 60%, 23% of patients achieving CR. CyBorD has demonstrated rapid haematological response in patients with advanced AL-CA and appears to be an effective regimen treatment, improving the survival of these patients.[75]

Carfizomib is a second-generation proteasome inhibitor approved for the treatment of relapsed or refractory multiple myeloma[76] but with significant cardiac, renal, and pulmonary toxicities and the potential to increase NT-proBNP values,[77] due to which it is considered an effective upfront treatment option only in AL patients with neurological involvement but without severe cardiac or renal involvement.[78]

Ixazomib is the first orally available second-generation proteasome inhibitor[76] administered in a Phase 1/2 study to 27 patients with relapsed or refractory AL, being effective,

especially in patients who were not exposed to other proteasome inhibitor agent and common noted adverse events being represented by nausea, skin disorders, fatigue, and diarrhoea.[79] However, there is evidence for secondary cardiac structural damage consistent with Type I chemotherapy-induced cardiotoxicity,[80] and patients should be carefully monitored during therapy with proteasome inhibitors, and development of any cardiopulmonary symptoms should be carefully evaluated.

Immunomodulators

Immunomodulatory agents, including thalidomide, lenalidomide, and pomalidomide, have shown significant benefits in patients with refractory AL amyloidosis, these drugs acting to reduce the resistance to alkylating agents.[81–83] In these studies, treatment with immunomodulatory agents showed an overall response rate of 50–70% with a small percentage of patients achieving CR. Treatment with these agents can produce significant haematological adverse events, hydrosaline overload, and an increase in cardiac biomarkers.[71] A prospective single-centre Phase 2 trial with 50 untreated patients not eligible for high-dose treatment who received lenalidomide, melphalan, and dexamethasone published in 2017 revealed an overall response rate of 48% translated into improved event-free and overall survival, but with significant haematological and cardiac toxicity.[84] Cardiac side effects in this study were mainly worsening of cardiac function (e.g. worsening of cardiac failure and AF) and hypotension.

Immunotherapy

Daratumumab is a human IgG1κ monoclonal antibody that targets CD38 surface antigen of the plasma cells and is now an important component of multiple myeloma treatment.[71] Daratumumab effectively kills clonal plasma cells using antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis via cross-linking.[76] In a small single-centre retrospective study including 25 patients with relapsed or refractory AL, daratumumab showed great and rapid overall response rates (76%) and CR rates (36%).[85] Preliminary data from the two studies evaluating the efficacy and safety of daratumumab alone were published, from both European and American studies providing information about good safety profile and significant and rapid haematolological responses in patients treated with daratumumab.[86,87]

According to the results of the Phase III ANDROMEDA study, adding subcutaneous daratumumab to CyBorD resulted in deeper and more rapid haematological responses and improved clinical outcomes, compared with CyBorD alone, in patients with newly diagnosed AL.[88] The authors also investigated organ response rates, which almost doubled with the addition of daratumumab. The 6 month cardiac response rate was 42% for the daratumumab combination compared with 22% for CyBorD alone (P = 0.0029), and the 6 month renal response rates were 54% and 27%, respectively (P < 0.0001),[88] with low treatment discontinuation rates due to adverse events (4% in both arms).

Autologous haematopoietic stem cell transplantation

Autologous haematopoietic stem cell transplantation (auto-HSCT) in AL is associated with higher morbidity and mortality when compared with multiple myeloma.[71] In a randomized trial comparing high-dose intravenous melphalan followed by auto-HSCT with standard-dose melphalan plus high-dose dexamethasone in 50 patients with AL, the authors concluded that the outcome of treatment of AL with high-dose melphalan followed by auto-HSCT was not superior to the outcome with standard-dose melphalan plus dexamethasone, with a high transplant-related mortality (24%).[89] This article has created debate, especially regarding the selection of patients to perform auto-HSCT and the experience of the centres where auto-HSCT was performed. The high mortality in the arm receiving auto-HSCT is explained by performing the procedure in patients who are not suitable for auto-HSCT, especially patients with significant cardiac involvement.[90,91]

Following these, results from analysis of 1536 patients with AL who underwent auto-HSCT in 134 centres between 1995 and 2012 showed a significant decrease in mortality at Day 100 after transplantation, concluding that post-transplantation survival in AL has improved, with a dramatic reduction in early post-transplantation mortality and excellent 5 year survival.[92]

Importantly, the outcome of patients undergoing auto-HSCT for AL amyloidosis with three or more organs involved appears to be primarily driven by the severity of cardiac involvement rather than the number of organs involved.[93] A retrospective analysis including 75 AL patients from the Mayo Clinic with at least three organs involved undergoing auto-HSCT showed that NT-proBNP ≥ 2000 pg/mL was a powerful predictor of overall survival (relative risk 4, P = 0.013).[93]

Other novel therapies for AL amyloidosis are included in the Supporting Information.

Specific therapies in transthyretin amyloidosis

Specific therapies for ATTR act at various levels of TTR from synthesis to deposition: TTR tetramer stabilization, oligomer

aggregation inhibition, genetic therapy [small-interfering ribonucleic acid (siRNA) and antisense oligonucleotides], amyloid fibre degradation, and antiserum amyloid P and TTR antibodies (*Figure 2*).

Tranthyretin tetramer stabilization

Tafamidis

Tafamidis (2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid) is a small molecule that inhibits the dissociation of TTR tetramers by binding selectively to the two normally unoccupied thyroxin-binding sites of the tetramer and kinetically stabilizes TTRwt and TTRv tetramers, inhibiting amyloidogenesis.[94] Tafamidis was the first disease-modifying drug approved in Europe but not by the American Food and Drug Administration (FDA) for treatment of Stage 1 (early stage) ATTRv with neuropathy, lacking benefits in patients with advanced disease (Stage 2–3 polyneuropathy).[95,96]

In a Phase 2, open-label, single-treatment arm study conducted by Merlini *et al.* and published in 2013, evaluating the pharmacodynamics, efficacy, and safety of tafamidis in patients with non-Val30Met ATTR (mixed cardiac and neurological phenotypes), the treatment achieved TTR stabilization in Week 6, demonstrating some worsening of neurological function but with no relevant worsening during the 12 months of treatment in the quality of life, cardiac biomarkers, and echocardiographic parameters.[97] Furthermore, another Phase 2 open-label trial conducted by Maurer *et al.* and published in 2015 evaluating the stabilization of TTR tetramers by tafamidis 20 mg daily at Week 6, Month 6, and Month 12, as well as safety and efficacy of the treatment, concluded that tafamidis treatment effectively achieved and maintained TTR stabilization and was well tolerated with absence of significant changes in most biochemical and echocardiographic parameters, suggesting that further evaluation of tafamidis in ATTR-CA is warranted.[98] Recent real-life study showed also an association with better survival in patients treated with tafamidis in patients with mostly ATTRv neuropathy and/or cardiomyopathy.[99]

More recently, in 2018, a multicentric, international, double-blind, placebo-controlled Phase 3 trial—the ATTR-ACT study[100] enrolled 441 patients with ATTR-CM who were randomly assigned in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. In the primary analysis, when comparing the all-cause mortality and rates of cardiovascular-related hospitalizations between the tafamidis group (264 patients) and the placebo group (177 patients), tafamidis showed lower all-cause mortality (29.5% vs. 42.9%) than placebo and lower rate of cardiovascular-related hospitalizations with a risk reduction of 32%.[100] Moreover, at 30 months, tafamidis was able to alleviate symptoms, being associated with a lower rate of decline in distance for the 6 min walk test and a lower rate of

decline in the quality of life assessed by the score on Kansas City Cardiomyopathy Questionnaire,[100] with no differences in adverse effect between tafamidis and placebo. Across the different subgroups of the study, including those based on TTR status (wt vs. v) and NYHA class (I or II vs. III), the difference in all-cause mortality and frequency of hospitalizations favoured tafamidis over placebo, except in patients with NYHA Class III at baseline; the authors speculated that the higher hospitalization rate observed in this subgroup is attributable to longer survival with a more severe disease.[100] After these results, tafamidis was approved by the FDA and European Medicines Agency (EMA) for treating patients with ATR-CM. With a proven benefit of the 80 mg dose over 20 mg tafamidis meglumine, the current approval includes either the larger dose (80 mg) or the equivalent tafamidis free acid 61 mg q.d. formulation. More recently, ATTR-ACT combined with its open-label long-term extension trial showed that there was a significantly greater survival benefit with tafamidis 80 mg compared with tafamidis 20 mg.[101]

Furthermore, a study, which aimed to assess the clinical characteristics of ATTR in a real-life population in comparison with the population, included in ATTR-ACT trial and the impact of tafamidis on major cardiovascular outcome-free survival time without HF decompensation, heart transplantation or death was published in 2020 by the group from the French national centre for CA.[99] This study included 648 patients (423 ATTRwt and 225 ATTRv) from which 467 (72%) matched the inclusion criteria of the ATTR-ACT trial and showed an association between tafamidis treatment and a lower occurrence of cardiovascular outcome in this large real-life population.[99]

AG10

AG10 is a selective, oral TTR stabilizer that mimics a protective TTR mutation, Thr119Met, which has been evaluated in a Phase 2 double-blind, placebo-controlled study (AG10 400 mg vs. AG10 800 mg vs. placebo in 49 patients for 28 days) investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of this drug in ATTR-CA patients with symptomatic HF.[102] In this study, the authors concluded that AG10 treatment was well tolerated and has the potential to be a safe and effective treatment for patients with ATTR-CA, inducing TTR stabilization and increased serum TTR levels.[102] Baseline serum TTR in treated subjects was below normal in 80% of ATTRv and 33% of ATTRwt subjects and AG10 treatment restored serum TTR to normal range in all subjects with an average serum TTR improvement by 36% and 51% at 400 and 800 mg, respectively (both $P < 0.0001$ vs. placebo).[102] A Phase 3 clinical trial (NCT03860935) is ongoing from May 2019 with an estimated enrolment of 510 patients and the estimated study completion in 2023.[103]

Diflunisal

Diflunisal is a non-steroidal anti-inflammatory drug that binds to the thyroxine binding sites of TTR, preventing dissociation of the TTR tetramer and amyloid fibril formation.[22] However, the use of diflunisal is controversial given the known consequences of chronic inhibition of cyclooxygenase enzymes, including gastrointestinal bleeding, renal dysfunction, fluid retention, and hypertension that may precipitate HF.[40] In 2006, a Japanese Phase 1 study revealed that diflunisal binds the T4 binding site and should ameliorate ATTR by stabilizing the TTR tetramer.[104] Data from a single-arm, open-label investigation conducted in 2013 revealed that there was no significant mean change in cardiac structure, function, or biomarkers (serum troponins and BNP) during the course of therapy suggesting that in low doses and with careful monitoring, diflunisal can be safely administered to compensated patients with ATTR-CA.[105] The authors noted renal dysfunction and fluid overload as major adverse events, which lead to study exclusion. Recent retrospective, longitudinal studies reported diflunisal treatment resulting in measurable differences in cardiac structure and function after only 1 year of administration (TTR concentration 19 vs. 33 mg/dL, $P = 0.01$; left atrial volume index +4.6 vs. -1.4 mL/m^2, $P = 0.002$; cardiac troponin I +0.03 vs. -0.01 ng/mL; and GLS +1.2% vs. +0.1%, $P = 0.03$, in patients treated with placebo compared with diflunisal),[106] being well tolerated in both patients with ATTRv and ATTRwt; withdrawal due to side effects was related to gastrointestinal complaints, but most patients had no adverse events.[107]

Oligomer aggregation inhibition

Green tea

There are some studies that revealed that the polyphenol epigallocatehin gallate, the most abundant catechin in green tea, may be used for prevention and treatment of diseases involving amyloid fibril formation because it binds to soluble TTR and inhibits oligomer aggregation and amyloid fibril formation.[108] In a single-centre observational report on the effects of green tea consumption in patients with ATTR-CM published in 2012 by Kristen *et al.*, observing 19 patients with ATTR-CM and compensated HF over 12 months while consuming green tea and their routine medication, the authors suggest an inhibitory effect of green tea on the progression of CA [no increase in the LV wall thickness or LV mass (LVM)] with no serious adverse effects.[109]

Mutated transthyretin synthesis inhibition

Liver transplantation

Most of the TTR is produced by the liver, and therefore, othotopic liver transplantation (OLT) can represent a feasible treatment option to stop the ATTRv production. OLT was proposed for the first time in 1990 as a treatment for ATTRv with neuropathy, and the largest experience has been with the ATTRV30M mutation (without cardiac involvement), being an intervention that can prevent the development of the polyneuropathy in these patients,[110] with a mean survival at 5 years after OLT of ~75%.[111] A large international report with 125 liver transplants on patients with ATTRV30M mutation and non-ATTRV30M mutations, published in 2015, showed great long-term results, OLT extending survival, with a survival rate at 20 years of 55.3% and was able to identify independent predictors of better survival: high body mass index, shorter disease, and duration Val30Met mutation.[112]

However, there are some reports that showed progressive ATTR-CA and neuropathy after OLT due to TTRwt complexing the TTRv (60% TTRv and 40% TTRwt before and 25–75% after transplantation), which is already deposited, thus limiting the adoption of this treatment.[113–115] Moreover, an increase of the interventricular septum thickness could be observed in patients with ATTRv with neuropathy with ATTRV30M mutation after liver transplantation, and the age at onset of the disease is the main predictor for increased wall thickness and for the development of ATTR-CM after liver transplantation.[116]

Genetic treatment

Patisiran

Small-interfering RNA is a class of double-stranded RNA non-coding molecules, operating with the RNA interference pathway. It interferes with the expression of specific genes with complementary nucleotide sequences by degrading the messenger RNA after transcription, preventing translation.[117]

Patisiran is a siRNA encapsulated in lipid nanoparticles, supressing both TTRv and TTRwt by targeting the liver that produces over 95% of the TTR after intravenous administration.[118] More recently, the results of a multicentre, international, randomized, double-blind, placebo-controlled, Phase 3 trial of patisiran in patients with ATTRv, the APOLLO trial, changed the paradigm of ATTRv treatment.[119] In this study, enrolling 225 patients with ATTRv with neuropathy (148 in patisiran group and 77 in the placebo group), patisiran (0.3 mg/kg every 2 weeks for 18 months) improved multiple clinical manifestations of ATTRv with neurological involvement, with a similar incidence of the significant adverse effects between the two groups (28% in the patisiran group and 36% in the placebo group). These results led to the approval of patisiran for the treatment of ATTRv with neuropathy by both the FDA (any stage of the disease) and EMA (max. moderate disease—Stages 1 and 2).

The APOLLO trial included 126 patients with cardiac involvement (56%, mean age 61 years, NYHA Classes I and II). Seven cardiac deaths occurred in the patisiran group and

none in the placebo group, and the proportion of patients with cardiac failure adverse events was higher in the patisiran group (11.1%) compared with the placebo group (5.6%). In contrast, patisiran reduced mean LV wall thickness and LVM, increased the LV end-diastolic volume, and improved the LV GLS, these patients displaying a significant ameliora-tion of the cardiac output decreasing and lower values of the NT-proBNP, these findings suggesting that patisiran may halt or possibly reverse de progression of ATTR-CA.[120] Fur-thermore, the authors looked at the association of patisiran with regional LV myocardial strain in ATTR-CA on the popula-tion from the APOLLO trial with cardiac involvement (baseline LV wall thickness of 13 or more and no history of hyperten-sion or aortic valve disease) finding no differences in regional and GLS between the two subgroups at baseline but an improvement of the absolute GLS in the patisiran group (greatest increase in the basal region and no significant differences in the apical regions), concluding that patisiran prevented the deterioration of LV GLS over 18 months and basal longitudinal strain may be a more sensitive marker of the treatment.[121]

Very recently, Fontana *et al*. demonstrated in a very small cohort of 16 patients with ATTRv treated with patisiran a significant reduction in the extracellular volume assessed by cardiac magnetic resonance, accompanied by scintigraphic, biochemical, and functional evidence of clinical benefit, which provided evidence for ATTR cardiac amyloid regression in a proportion of patients receiving patisiran comparing with 16 patients who were retrospectively matched based on cardiac magnetic resonance results and did not receive patisiran.[122]

Revusiran

Another siRNA, revusiran, was investigated in a Phase 3 multicentre clinical trial (ENDEAVOUR study), which enrolled 200 patients with ATTR-CM, assessing the symptoms (dis-tance walked in 6 min) and TTR levels between the daily sub-cutaneous administration of revusiran and placebo groups after 18 months, but the treatment was stopped after a me-dian 6.71 months because 18 patients on revusiran (12.9%) and 2 patients on placebo (3%) died during the treatment pe-riod with most deaths being adjudicated as cardiovascular due to HF.[123] Both APOLLO and ENDEAVOUR trials questioned about the efficacy of siRNA to improve outcome in patients with CA. Thus, the undergoing APOLLO-B (NCT03997383), which excluded patients with NYHA III and Stage III of the NAC staging, will bring more insights about the impact of siRNA on cardiac outcome.

Inotersen

Inotersen is an antisense oligonucleotide that inactivates the synthesis of both TTRv and TTRwt, with the first positive evi-dence in a small single-centre, investigator-initiated open-label study, which prospectively monitored changes in cardiac

parameters in 15 patients with ATTR-CA (8 ATTRv and 7 ATTRwt) and moderate to severely advanced restrictive CM while treated with inotersen for 12 months.[124] The patients showed stabilization of disease as measured by echocardio-graphic parameters (LV wall thickness and LVM), the 6 min walk test, and GLS with the treatment being well tolerated with a good safety profile. Peak reductions of TTR serum concentration on inotersen varied from 39% to 91%, mean 72%.[124]

Later, NEURO-TTR was a randomized, double-blind, pla-cebo-controlled, 15 month Phase 3 trial of inotersen in adults with Stage 1 or Stage 2 ATTRv with neuropathy.[125] One hun-dred and seventy-two patients with TTR familial amyloid polyneuropathy (63% with cardiac involvement) were ran-domized to receive subcutaneous injections of inotersen or placebo in a 2:1 ratio, and after 66 weeks, inotersen-treated patients showed a significant improvement of symptoms in-dependent of disease stage, mutation time, or the presence of the cardiac involvement, being well tolerated. These find-ings led to approval from FDA and EMA for treatment with inotersen of patients with mild to moderate (Stages 1 and 2) ATTRv with neuropathy. However, the study was under-powered for describing cardiac effects of inotersen.[125] Pa-tients who completed the NEURO-TTR trial were eligible to enrol in an ongoing open-label extension (OLE) study (NCT02175004), which evaluated the long-term efficacy and safety of inotersen. Inotersen continued to show benefit, and patients who switched from placebo to inotersen in the OLE demonstrated improvement or stabilization of neurolog-ical disease progression.[126] The most frequent serious ad-verse events in the intoresen group reported in Neuro-TTR trial were glomerulonephritis and thrombocytopenia, with one death associated with one of the cases of thrombocytopenia,[125] but routine platelet and renal safety monitoring were effective with no new safety signals observed in the OLE study.[126]

The CARDIO-TTRansform (NCT04136171) is an undergoing trial that will evaluate efficacy and safety of AKCEA-TTR-LR$_x$, an antisense drug similar to inotersen and used to inhibit pro-duction of TTR, which plans to include 750 patients with ATTR-CA, both variant and wild type, to bring more insight into the cardiac effects of this drug family.

Amyloid fibre degradation

Doxycycline and tauroursodeoxycholic acid

Evidence from animal studies suggested that tetracyclines, especially doxycycline, are capable of disrupting TTR amyloid deposits in TTRv transgenic mice models, being a potential drug in the treatment of amyloidosis.[127] Other studies showed that associating doxycyclin to tauroursodeoxycholic acid (TUDCA), a biliary acid administered to TTRv mouse

models with amyloid deposition, is more effective than either individual drug in significantly lowering TTR depositions.[128]

A small Phase 2 study evaluating the efficacy, tolerability, safety, and pharmacokinetics of orally doxycycline and TUDCA administered continuously for 12 months on 20 patients with ATTR-CM revealed that the combination of doxycycline and TUDCA stabilized the disease for at least 1 year in the majority of patients with an acceptable toxicity profile.[129] However, a small Phase 2, 18 month prospective study on 28 patients with ATTR-CM treated by intermittent administration of doxycycline–TUDCA noted a deterioration of heart function expressed by NT-proBNP, but the authors reported that the study was flawed by the extreme high dropout rate that was caused by the treatment failure, side effects, and voluntary dropouts.[130]

Antiserum antibodies direct against amyloid fibrils

Antiserum anti-transthyretin amyloidosis

To our knowledge, two anti-monoclonal antibody-targeting TTR deposits are in development: a Phase 1, open-label study (NCT03336580) of intravenous monoclonal antibody-targeting TTR[131] and another Phase 1–2, randomized, placebo-controlled, double-blind, dose escalation trial combining single-ascending dose and multiple-ascending dose phases of NI006 or placebo, followed by an open-label extension phase in subjects with ATTR-CA (NCT04360434). Results are expected for both trials in 2021.

Conclusions

To conclude, CA therapy benefits from the impressive evolution of the substrate treatment during the last decade.

However, management of the cardiac complications of amyloidosis remains complex due to patients' frailty and to the necessity of maintaining a balance between high filling pressures and low cardiac output. Because of these difficulties, referral to expert centres for CA is instrumental for a red flag-based timely diagnosis and for successful therapeutic management.

Conflict of interest

Funding

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information.

References

1. Sipe JD, Cohen AS. Review: history of the amyloid fibril. *J Struct Biol* 2000; **130**: 88–98.
2. Benson MD, Buxbaum JN, Eisenberg DS, Merlini G, Saraiva MJM, Sekijima Y, Sipe JD, Westermark P. Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. *Amyloid.* 2018; **25**: 215–219.
3. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J Am Coll Cardiol* 2016; **68**: 1323–1341.
4. Kocher F, Kaser A, Escher F, Doerler J, Zaruba MM, Messner M, Mussner-Seeber C, Mayr A, Ulmer H, Schneiderbauer-Porod S, Ebner C. Heart failure from ATTRwt amyloid cardiomyopathy is associated with poor prognosis. *ESC Heart Fail* 2020; **7**: 3919–3928.
5. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, Grogan M, Hayman SR, Kapoor P, Leung N, Fonder A, Hobbs M, Hwa YL, Gonsalves W, Warsame R, Kourelis TV, Russell S, Lust JA, Lin Y, Go RS, Zeldenrust S, Kyle RA, Rajkumar SV, Dispenzieri A. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. *Blood* 2017; **129**: 2111–2119.
6. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation* 2012; **126**: 1286–1300.
7. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, Judge DP, Lenihan DJ, Gottlieb SS, Shah SJ, Steidley DE, Ventura H, Murali S, Silver MA, Jacoby D, Fedson S, Hummel SL, Kristen AV, Damy T, Planté-Bordeneuve V, Coelho T, Mundayat R, Suhr OB, Waddington Cruz M, Rapezzi C, THAOS Investigators. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol* 2016; **68**: 161–172.

8. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African–Americans. *Amyloid.* 2015; **22**: 171–174.

9. 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; **19**: 733–742.

10. Maurizi N, Rella V, Fumagalli C, Salerno S, Castelletti S, Dagradi F, Torchio M, Marceca A, Meda M, Gasparini M, Boschi B, Girolami F, Parati G, Olivotto I, Crotti L, Cecchi F. Prevalence of cardiac amyloidosis among adult patients referred to tertiary centres with an initial diagnosis of hypertrophic cardiomyopathy. *Int J Cardiol* 2020; **300**: 191–195.

11. Damy T, Costes B, Hagège AA, Donal E, Eicher JC, Slama M, Guellich A, Rappeneau S, Gueffet JP, Logeart D, Planté-Bordeneuve V, Bouvaist H, Huttin O, Mulak G, Dubois-Randé JL, Goossens M, Canoui-Poitrine F, Buxbaum JN. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J* 2016; **37**: 1826–1834.

12. Arruda-Olson AM, Zeldenrust SR, Dispenzieri A, Gertz MA, Miller FA, Bielinski SJ, Klarich KW, Scott CG, Grogan M. Genotype, echocardiography, and survival in familial transthyretin amyloidosis. *Amyloid.* 2013; **20**: 263–268.

13. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, Berk JL, Plante-Bordeneuve V, Schmidt HHJ, Merlini G. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol* 2015; **66**: 2451–2466.

14. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in *alpha2-macroglobulin* and *tau*: a population-based autopsy study. *Ann Med* 2008; **40**: 232–239.

15. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015; **36**: 2585–2594.

16. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017; **38**: 2879–2887.

17. González-López E, Gagliardi C, Dominguez F, Quarta CC, de Haro-del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S, Alonso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017; **38**: 1895–1904.

18. Arbustini E, Narula N, Tavazzi L, Serio A, Grasso M, Favalli V, Bellazzi R, Tajik JA, Bonow RO, Fuster V, Narula J. The MOGE(S) classification of cardiomyopathy for clinicians. *J Am Coll Cardiol* 2014; **64**: 304–318.

19. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AWJM, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016; **133**: 2404–2412.

20. Jurcuţ R, Onciul S, Adam R, Stan C, Coriu D, Rapezzi C, Popescu BA. Multimodality imaging in cardiac amyloidosis: a primer for cardiologists. *Eur Heart J Cardiovasc Imaging* 2020; **21**: 833–844.

21. Nochioka K, Quarta CC, Claggett B, Roca GQ, Rapezzi C, Falk RH, Solomon SD. Left atrial structure and function in cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1128–1137.

22. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med* 2018; **28**: 10–21.

23. Emdin M, Aimo A, Rapezzi C, Fontana M, Perfetto F, Seferović PM, Barison A, Castiglione V, Vergaro G, Giannoni A, Passino C, Merlini G. Treatment of cardiac transthyretin amyloidosis: an update. *Eur Heart J* 2019; **40**: 3699–3706.

24. Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, Massie R, Narayan J, Swiggum E, Venner CP, Ducharme A, Galant NJ, Hahn C, Howlett JG, Mielniczuk L, Parent MC, Reece D, Royal V, Toma M, Virani SA, Zieroth S. Canadian Cardiovascular Society/Canadian Heart Failure Society joint position statement on the evaluation and management of patients with cardiac amyloidosis. *Can J Cardiol* 2020; **36**: 322–334.

25. Milani P, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R, Lacy MQ, Buadi FK, Kumar S, Maurer MS, Merlini G, Hayman SR, Leung N, Dingli D, Klarich KW, Lust JA, Lin Y, Kapoor P, Go RS, Pellikka PA, Hwa YL, Zeldenrust SR, Kyle RA, Rajkumar SV, Grogan M. Independent prognostic value of stroke volume index in patients with immunoglobulin light chain amyloidosis. *Circ Cardiovasc Imaging* 2018; **11**: e006588.

26. Chapelle DFA, Chabiniak R, Guellich A, Deux JF, Damy T. Patient-specific biomechanical modeling of cardiac amyloidosis—a case study. Lecture Notes in Computer Science. 2015;8th International Conference, FIMH 2015:295–303.

27. Cassidy JT. Cardiac amyloidosis: two cases with digitalis sensitivity. *Ann Intern Med* 1961; **55**: 989–994.

28. Rubinow ASA, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 1981; **63**: 1285–1288.

29. Muchtar E, Gertz MA, Kumar SK, Lin G, Boilson B, Clavell A, Lacy MQ, Buadi FK, Hayman SR, Kapoor P, Dingli D, Rajkumar SV, Dispenzieri A, Grogan M. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? *Amyloid.* 2018; **25**: 86–92.

30. Gertz MA, Falk RH, Skinner M, Cohen AS, Kyle RA. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. *Am J Cardiol* 1985; **55**: 1645.

31. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest* 1993; **104**: 618–620.

32. Sanchis K, Cariou E, Colombat M, Ribes D, Huart A, Cintas P, Fournier P, Rollin A, Carrié D, Galinier M, Maury P, Duparc A, Lairez O, Toulouse Amyloidosis Research Network collaborators. Atrial fibrillation and subtype of atrial fibrillation in cardiac amyloidosis: clinical and echocardiographic features, impact on mortality. *Amyloid.* 2019; **26**: 128–138.

33. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL, American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation* 2020; **142**: e7–e22.

34. Palladini GMG, Co F, Pistorio A, Recusani F, Anesi E, Garini P, Merlini G. Holter monitoring in AL amyloidosis: prognostic implications. *Journal of Pacing and Clinical Electrophysiology* 2001; **24**: 1228–1233.

35. Feng D, Edwards WD, Oh JK, Chandrasekaran K, Grogan M, Martinez MW, Syed II, Hughes DA, Lust JA, Jaffe AS, Gertz MA, Klarich KW. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation* 2007; **116**: 2420–2426.

36. Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, Edwards WD,

Gertz MA, Klarich KW. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation* 2009; **119**: 2490–2497.

37. Donnellan E, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, Hanna M, Baranowski B, Saliba W, Jaber W. No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *JACC Clin Electrophysiol* 2019; **5**: 1473–1474.

38. Giancaterino S, Urey MA, Darden D, Hsu JC. Management of arrhythmias in cardiac amyloidosis. *JACC Clin Electrophysiol.* 2020; **6**: 351–361.

39. el-Am EA, Dispenzieri A, Melduni RM, Ammash NM, White RD, Hodge DO, Noseworthy PA, Lin G, Pislaru SV, Egbe AC, Grogan M, Nkomo VT. Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. *J Am Coll Cardiol* 2019; **73**: 589–597.

40. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation* 2017; **135**: 1357–1377.

41. Donnellan E, Wazni O, Kanj M, Elshazly MB, Hussein A, Baranowski B, Hanna M, Patel D, Trulock K, Martyn M, Menon V, Saliba W, Jaber WA. Atrial fibrillation ablation in patients with transthyretin cardiac amyloidosis. *Europace* 2020; **22**: 259–264.

42. Black-Maier E, Rehorn M, Loungani R, Friedman DJ, Alenezi F, Geurink K, Pokorney SD, Daubert JP, Sun AY, Atwater BD, Jackson KP, Hegland DD, Thomas KL, Bahnson TD, Khouri MG, Piccini JP. Catheter ablation of atrial fibrillation in cardiac amyloidosis. *Pacing Clin Electrophysiol* 2020; **43**: 913–921.

43. Barbhaiya CR, Kumar S, Baldinger SH, Michaud GF, Stevenson WG, Falk R, John RM. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm* 2016; **13**: 383–390.

44. Donnellan E, Wazni OM, Saliba WI, Hanna M, Kanj M, Patel DR, Wilner B, Kochar A, Jaber WA. Prevalence, incidence, and impact on mortality of conduction system disease in transthyretin cardiac amyloidosis. *Am J Cardiol* 2020; **128**: 140–146.

45. Algalarrondo V, Dinanian S, Juin C, Chemla D, Bennani SL, Sebag C, Planté V, le Guludec D, Samuel D, Adams D, Slama MS. Prophylactic pacemaker implantation in familial amyloid polyneuropathy. *Heart Rhythm* 2012; **9**: 1069–1075.

46. Donnellan E, Wazni OM, Saliba WI, Baranowski B, Hanna M, Martyn M, Patel D, Trulock K, Menon V, Hussein A, Aagaard P, Jaber W, Kanj M. Cardiac devices in patients with transthyretin amyloidosis: impact on functional class, left ventricular function, mitral regurgitation, and mortality. *J Cardiovasc Electrophysiol* 2019; **30**: 2427–2432.

47. Kristen AV, Dengler TJ, Hegenbart U, Schonland SO, Goldschmidt H, Sack FU, Voss F, Becker R, Katus HA, Bauer A. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. *Heart Rhythm* 2008; **5**: 235–240.

48. Hamon D, Algalarrondo V, Gandjbakhch E, Extramiana F, Marijon E, Elbaz N, Selhane D, Dubois-Rande JL, Teiger E, Plante-Bordeneuve V, Damy T, Lellouche N. Outcome and incidence of appropriate implantable cardioverter-defibrillator therapy in patients with cardiac amyloidosis. *Int J Cardiol* 2016; **222**: 562–568.

49. Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HJ, Fontana M, Mahmood S, Sachchithanantham S, Patel K, Hawkins PN, Whelan CJ, Gillmore JD. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. *Eur Heart J* 2014; **36**: 1098–1105.

50. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol* 2013; **24**: 793–798.

51. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, van Veldhuisen D, ESC Scientific Document Group. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793–2867.

52. al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2018; **138**: e272–e391.

53. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD, Stevenson LW. ACCF/HRS/AHA/ASE/ HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2013; **61**: 1318–1368.

54. Varr BC, Zarafshar S, Coakley T, Liedtke M, Lafayette RA, Arai S, Schrier SL, Witteles RM. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. *Heart Rhythm* 2014; **11**: 158–162.

55. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, Pantazis A, Pankuweit S, Rigopoulos AG, Linhart A. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail* 2021.

56. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, Wollenweber T, Ahmed N, Thornton GD, Kelion AD, Sabharwal N, Newton JD, Ozkor M, Kennon S, Mullen M, Lloyd G, Fontana M, Hawkins PN, Pugliese F, Menezes LJ, Moon JC, Mascherbauer J, Treibel TA. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol* 2021; **77**: 128–139.

57. Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, Katsoulis M, Hartman N, Fontana M, Pugliese F, Sabharwal N, Newton JD, Kelion A, Ozkor M, Kennon S, Mullen M, Lloyd G, Menezes LJ, Hawkins PN, Moon JC. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur Heart J* 2020; **41**: 2759–2767.

58. Wechalekar AD, Gillmore JD, Bird J, Cavenagh J, Hawkins S, Kazmi M, Lachmann HJ, Hawkins PN, Pratt G, the BCSH Committee. Guidelines on the management of AL amyloidosis. *Br J Haematol* 2015; **168**: 186–206.

59. Dispenzieri A, Buadi F, Kumar SK, Reeder CB, Sher T, Lacy MQ, Kyle RA, Mikhael JR, Roy V, Leung N, Grogan M, Kapoor P, Lust JA, Dingli D, Go RS, Hwa YL, Hayman SR, Fonseca R, Ailawadhi S, Bergsagel PL, Chanan-Khan A, Rajkumar SV, Russell SJ, Stewart K, Zeldenrust SR, Gertz MA. Treatment of immunoglobulin light chain amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy

(mSMART) consensus statement. *Mayo Clin Proc* 2015; **90**: 1054–1081.

60. Perez-Lloret S, Quarracino C, Otero-Losada M, Rascol O. Droxidopa for the treatment of neurogenic orthostatic hypotension in neurodegenerative diseases. *Expert Opin Pharmacother* 2019; **20**: 635–645.

61. Ho AH, Kinter CW, Wight J, Neelam AR, Krakow D. Droxidopa as an effective treatment for refractory neurogenic orthostatic hypotension and reflex bradycardia in amyloid light-chain amyloidosis: a case report. *J Med Case Reports* 2020; **14**: 73.

62. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EAM, Zuckermann A, International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases, Pediatric and Heart Failure and Transplantation Councils. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016; **35**: 1–23.

63. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med* 2017; **84**: 12–26.

64. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, Zeldenrust SR, Leung N, Dingli D, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Gertz MA. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012; **30**: 989–995.

65. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018; **39**: 2799–2806.

66. Vranian MN, Sperry BW, Valent J, Hanna M. Emerging advances in the management of cardiac amyloidosis. *Curr Cardiol Rep* 2015; **17**: 100.

67. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, Schellberg D, Zugck C, Galuschky C, Giannitsis E, Hegenbart U, Ho AD, Katus HA, Schonland SO, Hardt SE. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. *J Am Coll Cardiol* 2012; **60**: 1067–1076.

68. Salinaro F, Meier-Ewert HK, Miller EJ, Pandey S, Sanchorawala V, Berk JL, Seldin DC, Ruberg FL. Longitudinal systolic strain, cardiac function improvement, and survival following treatment of light-chain (AL) cardiac

amyloidosis. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1057–1064.

69. Martinez-Naharro A, Abdel-Gadir A, Treibel TA, Zumbo G, Knight DS, Rosmini S, Lane T, Mahmood S, Sachchithanantham S, Whelan CJ, Lachmann HJ, Wechalekar AD, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. CMR-verified regression of cardiac AL amyloid after chemotherapy. *JACC Cardiovasc Imaging* 2018; **11**: 152–154.

70. Madan S, Kumar SK, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Rajkumar SV, Hogan WJ, Leung N, Grogan M, Gertz MA. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. *Blood* 2012; **119**: 1117–1122.

71. Badar T, D'Souza A, Hari P. Recent advances in understanding and treating immunoglobulin light chain amyloidosis. *F1000Res* 2018; **7**: 1348.

72. Kumar SK, Gertz MA, Lacy MQ, Dingli D, Hayman SR, Buadi FK, Short-Detweiler K, Zeldenrust SR, Leung N, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Dispenzieri A. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. *Mayo Clin Proc* 2011; **86**: 12–18.

73. Palladini G, Russo P, Nuvolone M, Lavatelli F, Perfetti V, Obici L, Merlini G. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood* 2007; **110**: 787–788.

74. Palladini G, Milani P, Foli A, Vidus Rosin M, Basset M, Lavatelli F, Nuvolone M, Obici L, Perlini S, Merlini G. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case–control study on 174 patients. *Leukemia* 2014; **28**: 2311–2316.

75. Jaccard A, Comenzo RL, Hari P, Hawkins PN, Roussel M, Morel P, Macro M, Pellegrin JL, Lazaro E, Mohty D, Mercie P, Decaux O, Gillmore J, Lavergne D, Bridoux F, Wechalekar AD, Venner CP. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naive patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). *Haematologica* 2014; **99**: 1479–1485.

76. Varga C, Titus SE, Toskic D, Comenzo RL. Use of novel therapies in the treatment of light chain amyloidosis. *Blood Rev* 2019; **37**: 100581.

77. Cohen AD, Landau H, Scott EC, Liedtke M, Kaufman JL, Rosenzweig M, Gasparetto C, Vesole DH, Sanchorawala V, Lentzsch S, Gomes CL, Comenzo RL, Durie BGM. Safety and efficacy of carfilzomib (CFZ) in previously-treated systemic light-chain (AL) amyloidosis. *Blood* 2016; **128**: 645.

78. Manwani R, Mahmood S, Sachchithanantham S, Lachmann HJ,

Gillmore JD, Yong K, Rabin N, Popat R, Kyriakou C, Worthington S, Sharpley F, Smith M, Shah R, Cheesman S, Hawkins PN, Wechalekar AD. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with peripheral and autonomic neuropathy. *Br J Haematol* 2019; **187**: 638–641.

79. Sanchorawala V, Palladini G, Kukreti V, Zonder JA, Cohen AD, Seldin DC, Dispenzieri A, Jaccard A, Schönland SO, Berg D, Yang H, Gupta N, Hui AM, Comenzo RL, Merlini G. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood* 2017; **130**: 597–605.

80. Jouni H, Aubry MC, Lacy MQ, Vincent Rajkumar S, Kumar SK, Frye RL, Herrmann J. Ixazomib cardiotoxicity: a possible class effect of proteasome inhibitors. *Am J Hematol* 2017; **92**: 220–221.

81. Wechalekar AD, Goodman HJ, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109**: 457–464.

82. Palladini G, Russo P, Foli A, Milani P, Lavatelli F, Obici L, Nuvolone M, Brugnatelli S, Invernizzi R, Merlini G. Salvage therapy with lenalidomide and dexamethasone in patients with advanced AL amyloidosis refractory to melphalan, bortezomib, and thalidomide. *Ann Hematol* 2012; **91**: 89–92.

83. Palladini G, Milani P, Foli A, Basset M, Russo F, Perlini S, Merlini G. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. *Blood* 2017; **129**: 2120–2123.

84. Hegenbart U, Bochtler T, Benner A, Becker N, Kimmich C, Kristen AV, Beimler J, Hund E, Zorn M, Freiberger A, Gawlik M, Goldschmidt H, Hose D, Jauch A, Ho AD, Schönland SO. Lenalidomide/melphalan/dexamethasone in newly diagnosed patients with immunoglobulin light chain amyloidosis: results of a prospective phase 2 study with long-term follow up. *Haematologica* 2017; **102**: 1424–1431.

85. Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood* 2017; **130**: 900–902.

86. Roussel M, Arnulf B, Stoppa A-M, Karlin L, Perrot A, Macro M, Huart A, Frenzel L, Morel P, Manier S, Dorvaux V, Merlini G, Palladini G, lavergne D, Royer B, Bridoux F, Jaccard A. A prospective phase II of daratumumab in previously treated systemic light-chain (AL) amyloidosis: updated results. *Clinical Lymphoma Myeloma and Leukemia* 2019; **19**: e40–e41.

87. Sanchorawala V, Sarosiek S, Schulman A, Mistark M, Migre ME, Cruz R, Sloan JM, Brauneis D, Shelton AC. Safety, tolerability, and response rates of daratumumab in relapsed AL amyloidosis: results of a phase 2 study. *Blood* 2020; **135**: 1541–1547.

88. Palladini G, Kastritis E, Maurer MS, Zonder J, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, Bumma N, Kaufman JL, Medvedova E, Kovacsovics T, Rosenzweig M, Sanchorawala V, Qin X, Vasey SY, Weiss BM, Vermeulen J, Merlini G, Comenzo RL. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. *Blood* 2020; **136**: 71–80.

89. Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, Recher C, Asli B, Lioure B, Royer B, Jardin F, Bridoux F, Grosbois B, Jaubert J, Piette JC, Ronco P, Quet F, Cogne M, Fermand JP. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; **357**: 1083–1093.

90. Varga C, Comenzo RL. High-dose melphalan and stem cell transplantation in systemic AL amyloidosis in the era of novel anti-plasma cell therapy: a comprehensive review. *Bone Marrow Transplant* 2019; **54**: 508–518.

91. Sanchorawala V. High-dose melphalan and autologous peripheral blood stem cell transplantation in AL amyloidosis. *Acta Haematol* 2020; **143**: 381–387.

92. D'Souza A, Dispenzieri A, Wirk B, Zhang MJ, Huang J, Gertz MA, Kyle RA, Kumar S, Comenzo RL, Peter Gale R, Lazarus HM, Savani BN, Cornell RF, Weiss BM, Vogl DT, Freytes CO, Scott EC, Landau HJ, Moreb JS, Costa LJ, Ramanathan M, Callander NS, Kamble RT, Olsson RF, Ganguly S, Nishihori T, Kindwall-Keller TL, Wood WA, Mark TM, Hari P. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: a center for International Blood and Marrow Transplant Research Study. *J Clin Oncol* 2015; **33**: 3741–3749.

93. al Saleh AS, Sidiqi MH, Muchtar E, Dispenzieri A, Buadi FK, Dingli D, Lacy MQ, Warsame RM, Gonsalves WI, Kourelis TV, Hogan WJ, Hayman SR, Kapoor P, Kumar SK, Gertz MA. Outcomes of patients with light chain amyloidosis who had autologous stem cell transplantation with 3 or more organs involved. *Biol Blood Marrow Transplant* 2019; **25**: 1520–1525.

94. Bulawa CE, Connelly S, DeVit M, Wang L, Weigel C, Fleming JA, Packman J, Powers ET, Wiseman RL, Foss TR, Wilson IA, Kelly JW, Labaudiniere R. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. *Proc Natl Acad Sci U S A* 2012; **109**: 9629–9634.

95. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Plante-Bordeneuve V, Lozeron P, Suhr OB, Campistol JM, Conceicao IM, Schmidt HHJ, Trigo P, Kelly JW, Labaudiniere R, Chan J, Packman J, Wilson A, Grogan DR. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* 2012; **79**: 785–792.

96. Lozeron P, Théaudin M, Mincheva Z, Ducot B, Lacroix C, Adams D, French Network for FAP (CORNAMYL). Effect on disability and safety of Tafamidis in late onset of Met30 transthyretin familial amyloid polyneuropathy. *Eur J Neurol* 2013; **20**: 1539–1545.

97. Merlini G, Planté-Bordeneuve V, Judge DP, Schmidt H, Obici L, Perlini S, Packman J, Tripp T, Grogan DR. Effects of tafamidis on transthyretin stabilization and clinical outcomes in patients with non-Val30Met transthyretin amyloidosis. *J Cardiovasc Transl Res* 2013; **6**: 1011–1020.

98. Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, Quyyumi AA, Aarts J, Falk RH. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. *Circ Heart Fail* 2015; **8**: 519–526.

99. Bézard M, Kharoubi M, Galat A, Poullot E, Guendouz S, Fanen P, Funalot B, Moktefi A, Lefaucheur JP, Abulizi M, Deux JF, Gendre T, Audard V, Karoui K, Canoui-Poitrine F, Zaroui A, Itti E, Teiger E, Planté-Bordeneuve V, Oghina S, Damy T. Natural history and impact of treatment with tafamidis on major cardiovascular outcome-free survival time in a cohort of patients with transthyretin amyloidosis. *Eur J Heart Fail* 2021; **23**: 264–274.

100. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018; **379**: 1007–1016.

101. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail* 2021; **23**: 277–285.

102. Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, Grogan M, Selby VN, Jacoby D, Hanna M, Nativi-Nicolau J, Patel J, Rao S, Sinha U, Turtle CW, Fox JC. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol* 2019; **74**: 285–295.

103. https://clinicaltrials.gov/ct2/show/ NCT03860935 (15 Nov 2020).

104. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. *Amyloid.* 2006; **13**: 236–249.

105. Castano A, Helmke S, Alvarez J, Delisle S, Maurer MS. Diflunisal for ATTR cardiac amyloidosis. *Congest Heart Fail* 2012; **18**: 315–319.

106. Lohrmann G, Pipilas A, Mussinelli R, Gopal DM, Berk JL, Connors LH, Vellanki N, Hellawell J, Siddiqi OK, Fox J, Maurer MS, Ruberg FL. Stabilization of cardiac function with diflunisal in transthyretin (ATTR) cardiac amyloidosis. *J Card Fail* 2020; **26**: 753–759.

107. Ikram A, Donnelly JP, Sperry BW, Samaras C, Valent J, Hanna M. Diflunisal tolerability in transthyretin cardiac amyloidosis: a single center's experience. *Amyloid.* 2018; **25**: 197–202.

108. Ferreira N, Cardoso I, Domingues MR, Vitorino R, Bastos M, Bai G, Saraiva MJ, Almeida MR. Binding of epigallocatechin-3-gallate to transthyretin modulates its amyloidogenicity. *FEBS Lett* 2009; **583**: 3569–3576.

109. Kristen AV, Lehrke S, Buss S, Mereles D, Steen H, Ehlermann P, Hardt S, Giannitsis E, Schreiner R, Haberkorn U, Schnabel PA, Linke RP, Röcken C, Wanker EE, Dengler TJ, Altland K, Katus HA. Green tea halts progression of cardiac transthyretin amyloidosis: an observational report. *Clin Res Cardiol* 2012; **101**: 805–813.

110. Holmgren G, Steen L, Suhr O, Ericzon BG, Groth CG, Andersen O, Wallin BG, Seymour A, Richardson S, Hawkins PN, Pepys MB. Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. *Lancet* 1993; **341**: 1113–1116.

111. Suhr OB, Herlenius G, Friman S, Ericzon BG. Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; **6**: 263–276.

112. Ericzon BG, Wilczek HE, Larsson M, Wijayatunga P, Stangou A, Pena JR, Furtado E, Barroso E, Daniel J, Samuel D, Adam R, Karam V, Poterucha J, Lewis D, Ferraz-Neto BH, Cruz MW, Munar-Ques M, Fabregat J, Ikeda SI, Ando Y, Heaton N, Otto G, Suhr O. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation* 2015; **99**: 1847–1854.

113. Liepnieks JJ, Zhang LQ, Benson MD. Progression of transthyretin amyloid neuropathy after liver transplantation. *Neurology* 2010; **75**: 324–327.

114. Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl* 2015; **21**: 282–292.

115. Yazaki M, Mitsuhashi S, Tokuda T, Kametani F, Takei YI, Koyama J, Kawamorita A, Kanno H, Ikeda SI. Progressive wild-type transthyretin deposition after liver transplantation preferentially occurs onto myocardium in FAP patients. *Am J Transplant* 2007; **7**: 235–242.

116. Okamoto S, Zhao Y, Lindqvist P, Backman C, Ericzon BG, Wijayatunga P, Henein MY, Suhr OB. Development of cardiomyopathy after liver transplantation in Swedish hereditary transthyretin amyloidosis (ATTR) patients. *Amyloid.* 2011; **18**: 200–205.

117. Laganà A, Veneziano D, Russo F, Pulvirenti A, Giugno R, Croce CM, Ferro A. Computational design of artificial RNA molecules for gene regulation. *Methods Mol Biol* 2015; **1269**: 393–412.

118. Coelho T, Adams D, Silva A, Lozeron P, Hawkins PN, Mant T, Perez J, Chiesa J, Warrington S, Tranter E, Munisamy M, Falzone R, Harrop J, Cehelsky J, Bettencourt BR, Geissler M, Butler JS, Sehgal A, Meyers RE, Chen Q, Borland T, Hutabarat RM, Clausen VA, Alvarez R, Fitzgerald K, Gamba-Vitalo C, Nochur SV, Vaishnaw AK, Sah DWY, Gollob JA, Suhr OB. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med* 2013; **369**: 819–829.

119. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Planté-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH III, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 2018; **379**: 11–21.

120. Solomon SD, Adams D, Kristen A, Grogan M, González-Duarte A, Maurer MS, Merlini G, Damy T, Slama MS, Brannagan TH III, Dispenzieri A, Berk JL, Shah AM, Garg P, Vaishnaw A, Karsten V, Chen J, Gollob J, Vest J, Suhr O. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. *Circulation* 2019; **139**: 431–443.

121. Minamisawa M, Claggett B, Adams D, Kristen AV, Merlini G, Slama MS, Dispenzieri A, Shah AM, Falk RH, Karsten V, Sweetser MT, Chen J, Riese R, Vest J, Solomon SD. Association of patisiran, an RNA interference therapeutic, with regional left ventricular myocardial strain in hereditary transthyretin amyloidosis: the APOLLO study. *JAMA Cardiol* 2019; **4**: 466–472.

122. Fontana M, Martinez-Naharro A, Chacko L, Rowczenio D, Gilbertson JA, Whelan CJ, Strehina S, Lane T, Moon J, Hutt DF, Kellman P, Petrie A, Hawkins PN, Gillmore JD. Reduction in CMR derived extracellular volume with patisiran indicates cardiac amyloid regression. *JACC Cardiovasc Imaging* 2021; **14**: 189–199.

123. Judge DP, Kristen AV, Grogan M, Maurer MS, Falk RH, Hanna M, Gillmore J, Garg P, Vaishnaw AK, Harrop J, Powell C. Phase 3 multicenter study of revusiran in patients with hereditary transthyretin-mediated (hATTR) amyloidosis with cardiomyopathy (ENDEAVOUR). *Cardiovasc Drugs Ther* 2020: 1–4.

124. Benson MD, Dasgupta NR, Rissing SM, Smith J, Feigenbaum H. Safety and efficacy of a TTR specific antisense oligonucleotide in patients with transthyretin amyloid cardiomyopathy. *Amyloid.* 2017; **24**: 219–225.

125. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH III, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceição I, Schmidt HH, Vita G, Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med* 2018; **379**: 22–31.

126. Brannagan TH, Wang AK, Coelho T, Waddington Cruz M, Polydefkis MJ, Dyck PJ, Plante-Bordeneuve V, Berk JL, Barroso F, Merlini G, Conceição I, Hughes SG, Kwoh J, Jung SW, Guthrie S, Pollock M, Benson MD, Gertz M, for the NEURO-TTR open-label extension investigators, Drachman B, Gorevic P, Heitner S, Scheinberg M, Schmidt H, Whelan C, Adams D, Campistol Plana JM, Gamez J, Gane E, Kristen A, Obici L, Salvi F, Souza Bulle Oliveira A, Vita G. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. *Eur J Neurol* 2020; **27**: 1374–1381.

127. Cardoso I, Saraiva MJ. Doxycycline disrupts transthyretin amyloid: evidence from studies in a FAP transgenic mice model. *FASEB J* 2006; **20**: 234–239.

128. Cardoso I, Martins D, Ribeiro T, Merlini G, Saraiva MJ. Synergy of combined doxycycline/TUDCA treatment in lowering transthyretin deposition and associated biomarkers: studies in FAP mouse models. *J Transl Med* 2010; **8**: 74.

129. Obici L, Cortese A, Lozza A, Lucchetti J, Gobbi M, Palladini G, Perlini S, Saraiva MJ, Merlini G. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid* 2012; **19**: 34–36.

130. Wixner J, Pilebro B, Lundgren HE, Olsson M, Anan I. Effect of doxycycline and ursodeoxycholic acid on transthyretin amyloidosis. *Amyloid* 2017; **24**: 78–79.

131. https://clinicaltrials.gov/ct2/show/study/NCT03336580 (15 Nov 2020).