

Amyloid cardiomyopathy: the different facets of a not so rare disease (RCD code III-3A.1, III-3A.2)

Ioannis Boutsikos, Maria Ntova, Aristeia Tsaroucha, Dimitrios Chatzis*

Medical School, European University Cyprus

Abstract

Amyloidosis is a rare disorder which can affect multiple organs, with cardiac amyloidosis (CA) being one of its main clinical manifestations. CA has 2 distinct subtypes, AL amyloidosis and transthyretin amyloidosis (ATTR), with different histopathological appearances and subsequently different treatment strategies. The diagnostic methods available include multiple modalities to properly detect CA, ranging from the surface electrocardiogram and simple 2D-echocardiography to more sophisticated methods such as specific biomarkers, speckle tracking echocardiography, or even bone scintigraphy with radioisotopes. However, the definitive diagnosis is reached with an endomyocardial biopsy or a biopsy from peripheral tissue. CA is a particularly challenging disorder in terms of patient management, which ranges from symptomatic treatment for heart failure symptoms to special medication and multiple drug regimens. For AL amyloidosis, a 3-drug regimen is used as a first-line therapy including cyclophosphamide, a proteasome inhibitor, and dexamethasone. For ATTR amyloidosis, specific medications are used such as Tafamidis, depending on the specific stage of the disease. Clinical trials of new drugs are pending with the ultimate goal of improving treatment rates and quality of life in patients with any type of CA. JRC D 2019; 4 (3): 34–41

Key words: rare disease, cardiac disease, electrocardiography, echocardiography, scintigraphy, endomyocardial biopsy, specific treatment, quality of life

Introduction

Amyloidosis is a serious health problem which may be associated with life-threatening multiple organ failure. It is a rare disorder characterised by the deposition of insoluble, misfolded proteins called amyloids, in various tissues and organs leading to conformational changes and subsequent dysfunction. The formation of an amyloid begins with the conversion of α -helix-rich soluble proteins to β -sheet-rich forms, the latter of which have a high propensity for forming bonds with each other as they are composed of linear polymers of amino acids. Through a nucleated-growth process this self-assembly leads to the formation of oligomers, protofibrils, and eventually highly organised macrostructures called amyloid fibrils which are deposited extracellularly in tissues. Protein fragments alone can also initiate the construction of amyloid aggregates. Amyloids have an amorphous eosinophilic appearance on hematoxylin and eosin staining, while on Congo red histological staining they produce the pathognomonic Apple – Green birefringence [1]. Accumulated data indicate that oligo-

mers and protofibrils, rather than amyloid fibrils, are responsible for the primary toxic effects on the tissues [2]. There are more than 30 different precursor proteins implicated in various amyloid diseases. Identification of the precursor protein is crucial for the selection of appropriate clinical treatment. The most important organs affected by the disease are the heart, kidneys, liver, and spleen [3].

Cardiac amyloidosis

There are approximately 30 different types of amyloidosis, each resulting from the misfolding of a unique protein. The most prominent types affecting the heart are amyloid light-chain (AL) and transthyretin (ATTR) amyloidosis.

AL amyloidosis

AL amyloidosis is a monoclonal plasma cell disorder in which the precursor protein is an antibody light chain or light chain

fragment made in the bone marrow [1]. There is evidence that AL is linked to multiple myeloma and other blood cell dyscrasias, such as monoclonal gammopathies of undetermined significance, as they seem to share similar mechanisms of pathogenesis [1]. The median age of diagnosis is 65 with 2/3 of patients being male. It affects approximately 3–12 new individuals per million person-years [4]. In the United States, AL amyloidosis is the most common type, with approximately 4 500 new cases diagnosed annually [5]. It represents a systemic disease affecting organs (heart, kidneys, gastrointestinal tract) as well as peripheral and autonomic nerves (not the brain) and soft tissues. The median survival is 6 months to 3 years and the most important prognostic factor is the grade of cardiac dysfunction [4].

Transthyretin amyloidosis (ATTR)

ATTR pathology is attributed to misfolding of the liver protein, transthyretin (previously known as prealbumin), which is a tetrameric transport protein for thyroxin and retinol [6]. The rate-limiting step for the formation of amyloid fibrils is dissociation of the tetramer into monomers [7]. This transformation can be facilitated by factors such as mutations and age, which cause instability of the tetrameric form. After dissociation, the monomers undergo conformational changes to form the fibrils [7].

According to the cause of transthyretin misfolding, ATTR is subdivided into 2 distinct subtypes: the hereditary mutant variant (ATTRmt), also known as familial amyloidosis, and the acquired wild-type variant (ATTRwt), also known as senile amyloidosis [8].

ATTRmt

ATTRmt is a familial autosomal dominant disorder and is considered to be the most common hereditary systemic form of the disease [1,9]. Over 100 single point mutations causing ATTRmt have been described [10]. The most common types are Val30Met, Thr60Ala, Val122Ile, and Ser77Tyr which may define the onset and penetrance of the disease [11]. The age of onset varies between the second and ninth decade of life depending on the subtype. Presence of the Val122Ile ATTRmt variant is associated with a worse prognosis when compared to ATTRwt, with a median survival of 2 years after the initial diagnosis [12]. However, the pathogenesis of the disease may involve other genetic and epigenetic factors [1]. Familial amyloidosis may harm the peripheral and autonomic nervous systems, the heart (familial cardiac amyloidosis [FAC]), or both. The former is attributed to the Val30Met mutation, while the latter is caused by a non-Val30Met mutation.

ATTRwt

ATTRwt is an age- and gender-related disease, predominantly affecting males close to their seventh decade of life and accounts for approximately 8–16% of cases in people over 80 years of age [1,8,13]. ATTRwt amyloidosis almost exclusively affects the heart and peripheral nerves. The clinical manifestations of carpal tunnel syndrome and spinal stenosis are strongly associated with ATTRwt and precede the development of hypertrophic restrictive cardiomyopathy and consequent heart failure by 5 to 15 years. The median survival of this subtype is 5 years after diagnosis, which is usually missed, since heart failure is a common comor-

Table 1. AL Staging according to the revised Mayo AL Staging System. One point is assigned for each of the following: cTnT ≥ 0.025 ng/mL, NT-proBNP ≥ 1800 pg/mL, and Free Light Chain-difference ≥ 18 mg/dL [17,60]

Number of abnormal laboratory tests	Stage (according to revised staging system)	Median Overall Survival (months)	5-year Survival
0	I	94.1	59%
1	II	40.3	42%
2	III	14	20%
3	IV	5.8	14%

bidity in the elderly. Its prevalence is anticipated to increase further due to the increasing number of the geriatric population [10].

Overall, amyloid heart infiltration is linked to a worse prognosis when compared to other organ involvement. Although ATTR seems to progress slowly when compared to AL, it still remains an irreversible, progressive disease which reduces the survival and quality of life in affected individuals [8].

Pathology

In cardiac amyloidosis (CA), amyloid fibrils are deposited extracellularly in cardiac tissues, primarily in the myocardium, but also in the pericardium, endocardium, and vasculature, making the heart stiff and non-compliant [14]. In AL, the deposition of light chains increases left ventricular end diastolic pressure, impeding the filling of the heart, leading to diastolic heart failure of restrictive aetiology. In severe cases, progression to systolic heart failure may also be seen. Different types of amyloidosis lead to different patterns of cardiac damage. AL amyloids are characterised by a subendocardial and diffuse deposition which also invade small coronary arteries, while ATTR amyloids accumulate in the myocardial interstitium, creating patchy areas of transmural involvement [10]. A rarer phenotype of ATTR involves the disproportionate thickening of the interventricular septum, mimicking hypertrophic cardiomyopathy (HCM) [9]. Amyloid infiltration adversely affects cellular metabolism, calcium transport, and receptor regulation, resulting in oxidative stress and cardiac remodelling [1,15]. This pathology, in combination with vascular invasion, increases the risk of diffuse ischaemia and microinfarctions.

Amyloid infiltration may involve the entire cardiac structure. The ventricular cavities are typically normal in size, however, biatrial enlargement is a very common finding. All valves, the interatrial septum, and the atria can also be affected. The latter increases the risk of atrial fibrillation (AF) (most common in ATTRwt), while the former may lead to valvular regurgitation of varying degrees. Involvement of the conduction system is associated with bundle branch block and various types of atrioventricular (AV) block (more commonly in ATTR) [10]. Moreover, pericardial involvement is common and leads to pericardial effusion [10,16]. The ac-

Table 2. Diagnostic modalities for Cardiac Amyloidosis and the advantages and disadvantages for each technique

Diagnostic modality	Advantages	Disadvantages
Electrocardiography	Easily available	No specific diagnostic signs
2-D echocardiography	Gold standard	No distinguishing features between several types of CA
Speckle-Tracking echocardiography	Differentiation between CA and hypertrophic cardiomyopathy	Not widely available
3-D Echocardiography	Visualisation of LV dyssynchrony in AL-amyloidosis	Not widely available
Nuclear Imaging (^{99m} Tc-DPD, ^{99m} Tc-PYP, ^{99m} Tc-HMDP)	Differentiates ATTR-CA from AL-CA	Mainly used in later stages, not used for early diagnosis
Cardiac MRI		
with LGE	Visualisation of microcirculatory obstructions due to amyloid deposits	Possible nephrotoxic effects of gadolinium
non-contrast T1mapping	Assessment of myocardial relaxation	Not widely available
contrast-enhanced T1 mapping	Assessment of the extracellular volume of myocardium	Possible nephrotoxic effects
Tissue Biopsy		
Endomyocardial biopsy	Actual visualisation of heart cells and amyloid deposits	Procedural difficulties and risks
Indirect biopsy of other affected organs	Less complicated procedure	Lower specificity and sensitivity
Laboratory biomarkers	Non-interventional diagnostic tools	Little prognostic value, always along with imaging

cumulation of amyloid material in the atria may lead to electromechanical dysfunction and consequently, together with the presence of AF, increases the risk of intracavitary thrombus formation.

Despite diastolic dysfunction and decreased end diastolic volume, the ejection fraction is preserved as the cardiac output is decreased as well. For this reason, patients with CA cannot usually tolerate reduced heart rates [10]. In later stages of the disease, systolic dysfunction may also ensue, leading to diminished ejection fraction. In that case, the stiffened myocardium will adversely affect mainly the systolic performance of the right ventricle.

Clinical presentation

Patients with CA usually present with signs and symptoms of a restrictive pattern of diastolic heart failure, and the majority of cases have clinical manifestations of right heart failure [14,17]. The most common complaints consist of fatigue, dyspnoea on exertion, and weakness, but patients may also present with more specific symptoms of right heart failure such as ascites, pedal oedema, hepatomegaly, as well as elevated jugular pressure. Other cardiac clinical manifestations include pulmonary oedema, angina, and thromboembolic stroke [10,14]. Arrhythmic events may also be present, such as AF, AV blocks causing syncopal episodes, and severe bundle branch blocks [16]. AF may precede the diagnosis of CA by many years and the formation of an atrial thrombus is possible, sometimes even before AF occurs [9,10]. CA can also mimic paradoxical low-flow, low-gradient aortic stenosis [18]. A high grade of suspicion should be raised for the presence of amyloidosis in previously hypertensive patients in whom autocorrection of their blood pressure has been observed (due to reduced stroke volume of the heart) or in patients with orthostatic hypotension due to autonomic neuropathy [14, 19].

The concomitant presence of other clinical manifestations related to damage of extracardiac tissues can also facilitate the diagnosis. For instance, polyneuropathy can be the result of AL and ATTRmt amyloidosis, or the patient may be diagnosed with bilateral carpal tunnel syndrome (AL, ATTRwt) or spinal stenosis (ATTRwt) [20]. In AL type, signs and symptoms of nephrotic syndrome such as macroglossia, periorbital purpura, mucocutaneous lesions, or proteinuria might be prominent [21]. Gastrointestinal symptoms and weight loss may also be caused by the disease [3].

Diagnosis of cardiac amyloidosis

An earlier diagnosis of CA is associated with better outcomes. Imaging, tissue biopsy, as well as biomarkers constitute the main tools for proper diagnosis of the disease.

Electrocardiography and imaging modalities

Electrocardiography and echocardiography

Surface Electrocardiogram (ECG) shows non-specific changes that should be accompanied with clinical suspicion and other tests in order to establish the diagnosis. The most common findings, although non-specific, may include low voltage of the QRS complex due to the infiltrative process which is correlated with the disease. Also, a QS pattern in at least two contiguous leads (“pseudoinfarction pattern”) may be observed, mimicking a previous myocardial infarction. Wide QRS complexes are observed in ATTR-amyloidosis and lower limb reduced voltages are seen in AL-amyloidosis [10]. Other findings include 1st degree atrio-

Table 3. AL treatment. *1 In 1st line therapy, we add an immunomodulator (Pomalidomide). *2 Melphalan is another alkylating agent which can be used**Three drug combination, most common 1st line therapy**

Alkylating agent	Cyclophosphamide ²
Proteasome inhibitor	bortezomib
Steroid	dexamethasone
Relapsed disease	
CD38 monoclonal antibody (if patients meet myeloma criteria)	daratumumab
New proteasome inhibitor	ixazomib
High-dose chemotherapy with autologous stem cell transplant (in patients with acceptable cardiac risk profile)	Possibly more complete and durable remission than chemotherapy alone, although controversial
Future treatment (ongoing clinical trials)	
Amyloid-directed monoclonal antibody (going clinical trials)	NEOD001 (designed to remove amyloid fibrils from affected organs)

ventricular block (21%), 2nd or 3rd degree AV block (3%) and specific arrhythmias such as AF/atrial flutter (20%) and ventricular tachycardias (5%) [22]. According to a recent study, ECG can give some clues about the type of CA. Left Bundle Branch Block has been noted in 40% of patients with ATTRwt, whereas it is found in only 4% of AL patients. [23] Lastly, a study using Holter monitoring observed supraventricular and non-sustained ventricular arrhythmias in patients with AL amyloidosis [24].

Transthoracic echocardiography (TTE) is a cost-effective and safe method which represents the gold standard for the diagnosis of CA and for further follow-up of the patient. However, it is not useful in distinguishing among the individual types of CA. The most commonly observed echocardiographic features are dilatation of the atria and biventricular wall thickening [20], and diagnosis is frequently delayed. 1 Cardiac involvement is a leading cause of morbidity and mortality, especially in primary light chain (AL Concentric hypertrophy of the left ventricle (LV) in the absence of any precipitating factor such as hypertension should raise a suspicion of CA. Additionally, the “sparkling” myocardium which is observed in CA shows a higher echogenicity than normal myocardium due to amyloid protein deposition in the myocardial cells [21]. The degree of amyloid infiltration is related to severity of the disease. In most cases, the pattern of restrictive cardiomyopathy is observed, which interferes with LV end-diastolic function. During early stages, Doppler imaging shows abnormal relaxation, followed by a pseudo-normal pattern in the intermediate stages, progressing to a restrictive pattern in the later stages [10]. Additionally, in some cases of CA, abnormal thickening of the valves may be seen (most commonly in ATTR), leading to valvular-mechanical dysfunction. In two-dimensional (2D) TTE, CA can mimic other conditions such as hypertrophic cardiomyopathy due to asymmetric hypertrophy of the interventricular septum, or myocarditis with severe fibrosis due to existence of the so called “sparkling myocardium”.

Echocardiographic technological advances may further facilitate the diagnostic process. Speckle tracking echocardiography (STE) has been used to assess the longitudinal, radial and circumferential

deformations of the myocardium that take place in CA. Recently, 2D STE has introduced a method to measure a specific mechanical property of LV motion called twisting/untwisting. It consists of an LV torsional longitudinal deformation originating from the interaction between the clockwise systolic rotation of the base and the diastolic counterclockwise rotation of the apex. Both twisting and untwisting motions of the LV are decreased in patients with CA, suggesting that early in the disease the diastolic dysfunction is compensated, but while the disease progresses this mechanism fails [25]. These parameters are notably decreased in contrast to patients with hypertrophic cardiomyopathy or hypertension-related heart disease [26]. More specifically, AL and TTR amyloidosis with preserved Ejection Fraction are characterised by impairment of the basal and mid-longitudinal strain but preserved apical longitudinal strain [27]. Some studies have revealed the ratio between GLS and EF which is impaired due to amyloidosis. The recently introduced Ejection Fraction Strain Ratio (EFSR) has become a useful tool for physicians to diagnose CA with high sensitivity and specificity (90 and 92% respectively) and provides a standardised measurement [28]. Other diagnostic tools include 3D-echocardiography and the 3D speckle tracking technique (3DST). These techniques demonstrated LV dyssynchrony in patients with AL amyloidosis by using a 16-segment index which was significantly impaired in relation to the control subjects. However, these techniques are not widely used in clinical practice, therefore, additional diagnostic measures are required [29].

Cardiac Magnetic Resonance Imaging (CMR)

CA is correlated with increased extracellular volume (ECV) of myocardial cells. Gadolinium-based contrasts rapidly extravasate and are then rapidly eliminated from the circulation. If any gadolinium is detected after the elimination phase, this suggests an ECV increase, leading to the diagnosis of CA [30].

CMR with Late Gadolinium Enhancement (LGE) imaging establishes a pattern of CA with subendocardial non-coronary territory distribution leading to correlation with microcirculatory obstruc-

Table 4. ATTR treatment

	siRNA	Patisiran
1. Block TTR synthesis	ASO (antisense oligonucleotide)	Inotersen
	Diflunisal	
2. Stabilize the TTR tetramer	Tafamidis	
	Tolcapone	
	AG10	
	Doxycycline + Tauroursodeoxycholic acid (TUDCA)	
3. Disrupt the amyloid fibril	Curcumin	
	PRX004 (anti-amyloid antibody)	

tion due to amyloid deposition both in the cardiac capillaries and in the myocardial cells [31]. The main limitation regarding LGE usage lies in the possible nephrotoxic effects of gadolinium contrast and as a result, extreme caution should be exercised, especially in patients with impaired renal function [10].

Evidently, there is a need for using novel modalities to detect amyloid deposits in the early stages of disease. The T1 mapping technique provides a useful assessment of myocardial relaxation, permitting simultaneous detection of protein deposits and fibrosis. Non-contrast T1 mapping gives valuable information regarding the composition of the myocardium, while avoiding the side effects of gadolinium. On the other hand, contrast-enhanced T1 mapping gives an estimation of the extracellular volume fraction which will be significantly increased in patients with CA, demonstrating its importance as a test which could be used to detect CA in the early stages [32,33].

Nuclear Imaging

Recent advances in CA diagnostics include the usage of radiolabelled bone tracers such as ^{99m}Tc -DPD, ^{99m}Tc -PYP, ^{99m}Tc -HMDP. The tracers are mainly used for the differentiation between ATTR-CA and AL-CA. The mechanism of myocardial uptake of these specific bone tracers is not known but is believed to be calcium mediated. Radioactive tracers are characterised by a higher diagnostic specificity in the later stages of disease. Because of this, they are not considered as a reliable tool for early CA diagnosis. In general, these radiolabelled tracers are an important diagnostic tool for CA, but there is a need for further investigation on this issue [34].

Tissue Biopsy

In addition to imaging modalities, biopsy with histopathological examination remains a crucial part of the CA diagnosis. This involves 2 aspects: direct endomyocardial biopsy (EMB) visualising the heart cells and amyloid deposits among them, or indirect biopsy of other affected organs such as abdominal fat. Obviously, EMB has the highest diagnostic specificity and sensitivity, approaching 100% in both measures [31]. EMB is required when CA is an isolated feature or when the cardiac amyloid fibril type can-

not be determined with other modalities. It should be considered in patients having a thickened LV without any known underlying pathology such as hypertension or valvular disease, especially in young patients [9].

Biomarkers

Mouselimis et al. suggested that the use of several biomarkers, along with the aforementioned diagnostic modalities, may be useful in the diagnosis of CA. In fact, there are various biomarkers which provide valuable information regarding early disease detection, risk stratification, and prognosis [35].

Independently of the subtype, patients with CA are diagnosed late in the disease course when the myocardium is already infiltrated with amyloid fibres. Thus, detection of various biomarkers reflects the symptoms associated with disease-mediated cardiac involvement. As already mentioned, the typical patient presents with symptoms of Heart Failure with preserved EF (HFpEF), which in turn leads to increased markers of cardiac responsiveness such as natriuretic peptides (proBNP, NT-proBNP) and the peptides of cardiac viability such as Troponin T and I [36].

In AL, serum free-light chains (FLC) κ and λ are elevated leading to an increased κ/λ ratio (above 1.65). An increased number of light chains which lead to accumulation of fibril deposits in the cells is the pathophysiologic mechanism underlying the increased difference of the FLC. It has been shown that an increased difference between κ and λ light chains ($\kappa > \lambda$) is related to increased cardiac involvement. This ratio, along with other clinical parameters, can have significant prognostic implications. The preferred score for the staging and prognosis of AL amyloidosis is the Mayo Amyloidosis Staging System which uses troponin T, NT-proBNP, and dFLC [37].

In the detection of mutated transthyretin, a genetic test should be included even in the absence of family history. Recently, it has been demonstrated that retinol binding protein 4 (RBP4) levels are significantly reduced in patients with ATTR amyloidosis, but only in the V122I variant. Thus, the study of RBP4 levels along with the aforementioned imaging modalities represents a significant diagnostic tool in ATTR amyloidosis [38].

Treatment

Treatment of CA focuses on relief from CA-related cardiac symptoms and treatment of the underlying cause of the disease [10].

General measures

The mainstay for management of heart failure symptoms in CA is sodium restriction and use of diuretics, including aldosterone antagonists and loop diuretics [39]. Patients with CA often present with low baseline blood pressure as a result of decreased stroke volume and may become intolerant to several heart failure therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers due to symptomatic hypotension [34,40]. These drug classes should generally be avoided in CA but if needed, they should be administered with

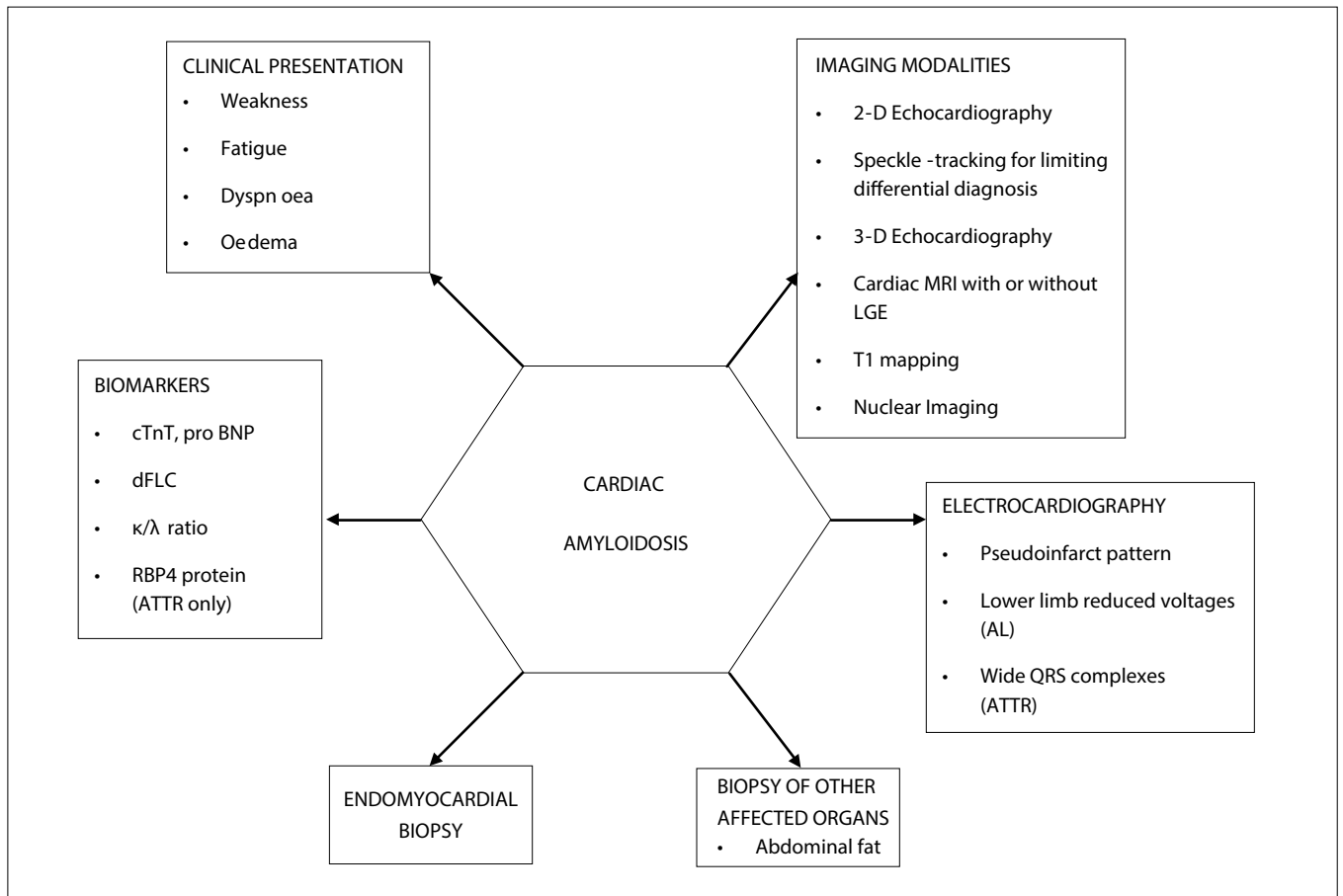


Figure 2. Proposed diagnostic algorithm. (CA: Cardiac Amyloidosis, CMR: Cardiac Magnetic Resonance, EMB: Endomyocardial Biopsy, dFLC: difference Free Light Chain, RBP4: Retinol Binding Protein 4.)

caution. Non-dihydropyridine calcium channel blockers are also contraindicated in CA because they bind to amyloid fibrils and can cause hypotension and syncope [34,40,41]. Caution with digoxin administration is also recommended, but the adverse effects of digoxin are not as severe as with non-dihydropyridine calcium channel blockers [40,41]. Lastly, anticoagulation, when compelling indications are present, is important due to the high risk of thromboembolic events [34,42].

AI treatment

Current treatment options

The first-line treatment is a 3-drug combination composed of cyclophosphamide (an alkylating agent), bortezomib (a proteasome inhibitor), and dexamethasone (a steroid), and is administered weekly [10,43,44].

For relapsed or refractory disease, the CD38 monoclonal antibody daratumumab is used when myeloma criteria are met. Likewise, newer proteasome inhibitors such as ixazomib can be used as alternatives in these patients [10,44,45]. Finally, high-dose chemotherapy with autologous stem cell transplant provides a more broad

and durable response than chemotherapy alone, although this is debatable [10,43,45].

Future treatment perspectives

NEOD001 is a humanised monoclonal antibody that binds to a light chain epitope which is exposed in misfolded but not normally-folded light chains. This antibody was shown to remove the AL amyloid fibrils from affected organs, via macrophages and neutrophils. Phase 1 and 2 clinical trials with this agent are complete and there are more ongoing related clinical trials [10,47].

Serum amyloid P component (SAP) is a glycoprotein found in all types of amyloid fibrils and is important for fibril formation. Therefore, SAP represents an attractive target for the promotion fibril degradation. A monoclonal immunoglobulin G1, **anti-SAP antibody**, facilitates amyloid removal via a complement-dependent, macrophage-mediated pathway [47].

ATTR treatment

There are 3 classes of drugs which can be used for the treatment of TTR amyloidosis based on 3 distinct mechanisms of action:

1. Block TTR synthesis. Both small-interfering RNAs (siRNAs) and antisense oligonucleotides act as “silencers” of TTR mRNA

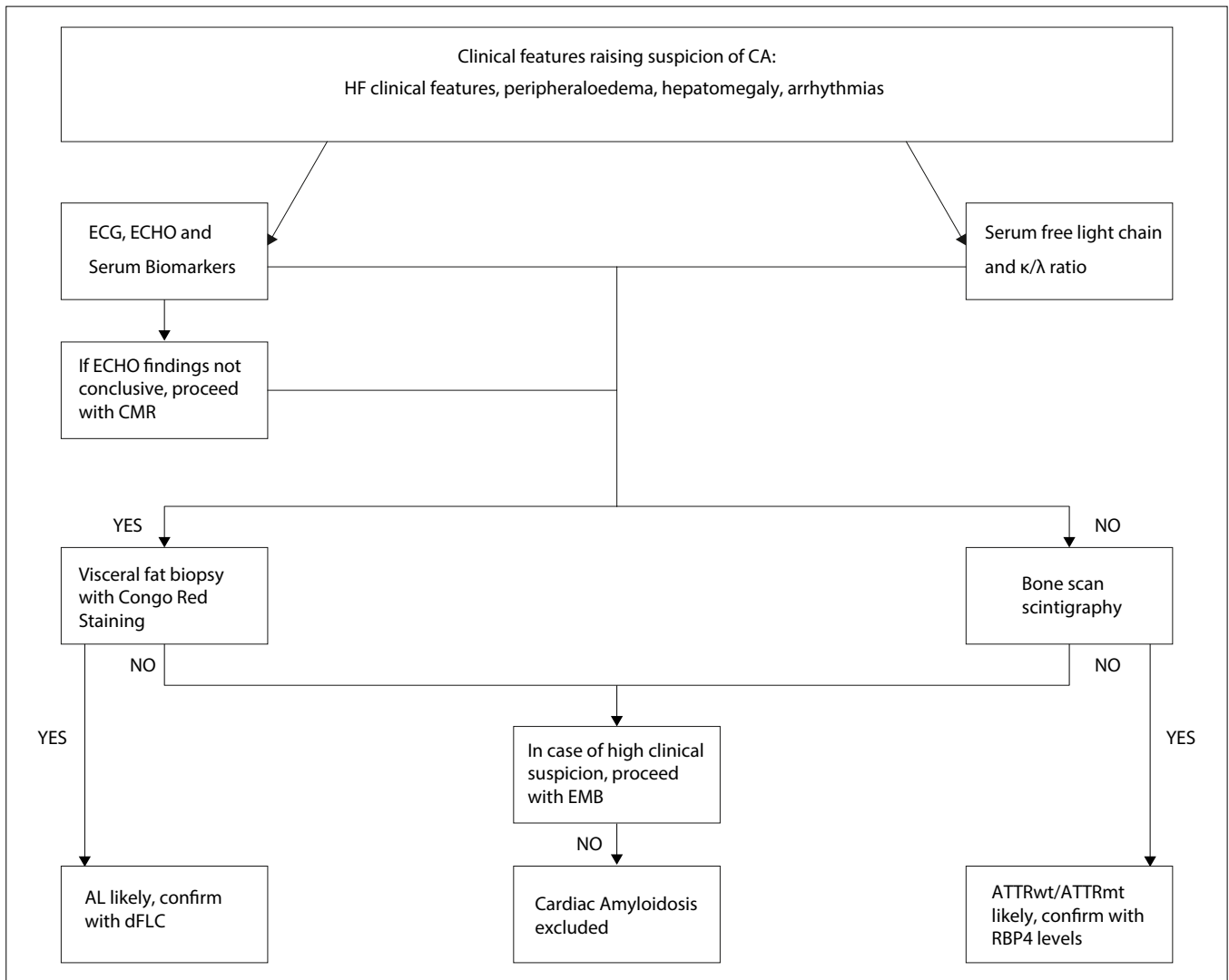


Figure 2. Proposed diagnostic algorithm. (CA: Cardiac Amyloidosis, CMR: Cardiac Magnetic Resonance, EMB: Endomyocardial Biopsy, dFLC: difference Free Light Chain, RBP4: Retinol Binding Protein 4.)

translation and consequently reduce the production of TTR protein by hepatocytes [10,48]. The siRNA, patisiran, is an IV medication, and may be beneficial in the treatment of FAP (familial amyloid polyneuropathy), as well as in both ATTRm-CA and ATTRwt-CA. The antisense oligonucleotide, inotersen, is given subcutaneously once a week [10,44,48]. This agent will likely be approved by the US Food and Drug Administration (FDA) for neuropathic indications and may also benefit patients with ATTRm-CA and ATTRwt-CA. The efficacy and safety of these agents in the treatment of ATTR-CA patients require further studies.

2. Stabilise the TTR tetramer (the TTR tetramer has 2 thyroxine binding pockets that stabilise the structure). The rate-limiting step for fibril formation in ATTR amyloidosis is dissociation of the tetramer into unstable, amyloidogenic monomers. **Diflunisal** is a non-acylated salicylate NSAID which is used to treat arthritis and musculoskeletal pain. It is used off-label in the treatment of ATTR amyloidosis in patients with preserved kidney func-

tion and no increased bleeding risk, with monitoring needed for possible signs of fluid retention and changes in renal function. [10,49]. **Tafamidis** is used for early-stage ATTR polyneuropathy but is less effective in preventing disease progression in advanced stage Val30Met TTR-FAP patients. A phase 3 ATTR-ACT study (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) was designed to determine the efficacy and safety of tafamidis in patients with hereditary and wildtype transthyretin amyloid cardiomyopathy. This was an international, multicentre, double-blind, placebo-controlled, randomised clinical trial in which 441 patients with ATTR were assigned tafamidis 80 mg, tafamidis 20 mg, or placebo. The difference in all-cause mortality and frequency of cardiovascular-related hospitalisations favoured tafamidis over placebo, except in patients with NYHA class III disease at baseline. [50] Moreover, tafamidis reduced the decline in functional capacity and quality of life as compared with placebo, and also led to a smaller increase in NT-proBNP level. In addition, tafamidis showed a favourable safety and tolerability profile

over placebo. The FDA has recently approved 2 oral formulations of the drug for the treatment of cardiomyopathy caused by transthyretin mediated amyloidosis [50]. **Tolcapone** is approved by the FDA for Parkinson's disease and has a risk of causing potentially fatal acute fulminant liver failure and is not currently used for ATTR. Moreover, tolcapone binds with higher affinity to wild-type and Val122Ile ATTR amyloidosis than tafamidis [10,44]. Unlike other known TTR stabilizers, tolcapone can cross the blood-brain barrier. Because of this, it has a crucial role in the treatment of TTR amyloidosis patients with leptomeningeal involvement. **AG10** is a promising candidate for treating patients with ATTR cardiomyopathy, particularly those with the Val122Ile mutation, and is being tested in a phase I clinical trial [10,44].

3. Disrupt and clear the ATTR amyloid fibril. This relies on the synergistic effect of co-administration of **doxycycline** (a tetracycline antibiotic) **plus tauroursodeoxycholic acid** (a bile acid used to treat cholelithiasis) [10,31]. **Curcumin** (found in the household spice, turmeric) acts as a TTR stabiliser, by binding to the thyroxine binding pocket, and as an amyloid fibril disruptor by increasing macrophage degradation activity [10,44]. **PRX004** is a synthetic antibody that is being tested in a phase I clinical trial in the setting of ATTRm [10].

Heart/liver transplantation

There appears to be a role for heart transplantation in patients with ATTR-CA. Patients with the ATTRm mutation V122I have been treated with heart transplant alone, while patients with the T60A mutation, which causes both polyneuropathy and cardiomyopathy, require combined heart and liver transplant [10].

Moreover, liver transplantation, which removes the main site of mutant TTR production, has been the only disease-modifying treatment option for TTR-FAP.

References

- Lee GK, Feng D, Grogan M, et al. Cardiac Amyloidosis: Typing, Diagnosis, Prognosis and Management. In: Intech Open, Amyloidosis, ed: DaLi Feng, 2013, 1240 – 1598.
- Reixach N, Deechongkit S, Jiang X, et al. Tissue damage in the amyloidosis: Transthyretin monomers and nonnative oligomers are the major cytotoxic species in tissue culture. *Proc Natl Acad Sci USA* 2004; 101(9): 2817–2822.
- Baker KR, Rice L. The Amyloidoses: Clinical Features, Diagnosis and Treatment. *Methodist Debaque Cardiovasc J* 2012; 8 (3): 3–7.
- McCausland KL, White MK, Guthrie SD, et al. Light Chain (AL) Amyloidosis: The Journey to Diagnosis. *Patient* 2018; 11(2): 207–216.
- Hasan SM, Ahmed NN, Ahmed Z, et al. Response of Bortezomib Chemotherapy in Hepatic Amyloidosis. *J Investig Med High Impact Case Rep* 2018; 6: 2324709618760079.
- Chen R, Chen CP, Preston JE. Effects of transthyretin on thyroxine and β -amyloid removal from cerebrospinal fluid in mice. *Clin Exp Pharmacol Physiol* 2016; 43(9): 844–850.
- Coelho T, Merlini G, Bulawa CE, et al. Mechanism of Action and Clinical Application of Tafamidis in Hereditary Transthyretin Amyloidosis. *Neurol Ther* 2016; 5(1):1–25.
- Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. *Circulation* 2012; 126 (10): 1286–1300.
- Banyersad SM, Moon JC, Whelan C, et al. Updates in cardiac amyloidosis: a review. *J Am Heart Assoc* 2012; 1(2): e000364.
- Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med* 2017; 84 (12 Suppl 3): 12–26.
- Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. *Clin Med (Lond)* 2018; 18 (Suppl 2): 30–35.
- Singh A, Geller HI, Falk RH. Val122Ile mt-ATTR Has a Worse Survival Than wt-ATTR Cardiac Amyloidosis. *J Am Coll Cardiol* 2017; 69(6): 757–758.
- Adams D, Hawkins P, Schmidt H. Abstracts from the First European Meeting for ATTR Amyloidosis for Doctors and Patients. *Orphanet J Rare Dis* 2017; 12 (Suppl 1): 165.
- Squier TC. Oxidative stress and protein aggregation during biological aging. *Exp Gerontol* 2001; 36(9): 1539–1550.
- Hassan W, Al-Sergani H, Mourad W, et al. Amyloid Heart Disease: New Frontiers and Insights in Pathophysiology, Diagnosis, and Management. *Tex Heart Inst J* 2005; 32 (2): 178–184.
- Sertac C. Cardiac amyloidosis and aortic stenosis: Great masquerader back again! *J Thorac and Cardiovasc Surg* 2018; 156 (1): 104–105.
- Metzler M, Duerr S, Granata R, et al. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. *J Neurol* 2013; 260 (9): 2212–2219.
- Bjerrum OW, Rygaard-Olsen C, Dahlerup B, et al. The carpal tunnel syndrome and amyloidosis. A clinical and histological study. *Clin Neurol Neurosurg* 1984; 86 (1): 29–32.
- Westermarck P, Westermarck GT, Suhr OB, et al. Transthyretin-derived amyloidosis: Probably a common cause of lumbar spinal stenosis. *Ups J Med Sci* 2014; 119 (3): 223–228.
- Banyersad SM, Moon JC, Whelan C, et al. Updates in cardiac amyloidosis: a review. *J Am Heart Assoc* 2012; 1(2): e000364.
- García-Pavía P, Tomé-Esteban MT, Rapezzi C. Amyloidosis. Also a heart disease. *Rev Esp Cardiol* 2011; 64 (9): 797–808.
- Murtagh B, Hammill SC, Gertz MA, et al. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. *Am J Cardiol* 2005; 95: 535–537.
- Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidosis: disease profiles and clinical courses of the 3 main types. *Circulation* 2009;120: 1203–1212.
- Pinney J GJ, Lachmann H, Wehalekar A, et al. Disturbances of Cardiac Rhythm in AL Amyloidosis. 13th International Myeloma Workshop(Abtract) 2011:426.
- Porciani MC, Cappelli F, Perfetto F, et al. Rotational mechanics of the left ventricle in AL amyloidosis. *Echocardiography* 2010; 27: 1061–1068.
- Sun JP, Stewart WJ, Yang XS, et al. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of Ventricular Wall thickening by two-dimensional strain imaging echocardiography. *Am J Cardiol*. 2009; 103 (3): 411–415.
- Quarta CC, Solomon SD, Uraizee I, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation* 2014;129 (18): 1840–1849.
- Pagourelis ED, Mirea O, Duchenne J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis A Head-to-Head Comparison of Deformation and Nondeformation Parameters. *Circ Cardiovasc Imaging* 2017; 10 (3): e005588.
- Migrino RQ, Harmann L, Woods T, et al. Intraventricular dyssynchrony in light chain amyloidosis: a new mechanism of systolic dysfunction assessed by 3-dimensional echocardiography. *Cardiovasc Ultrasound* 2008; 6:40.
- Syed IS, Glockner JF, Feng D, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2010; 3(2): 155–164.
- Izumiya Y, Takashio S, Oda S, et al. Recent advances in diagnosis and treatment of cardiac amyloidosis. *J Cardiol* 2018; 71 (2): 135–143.
- Fontana M, Banyersad SM, Treibel TA, et al. Native T1 mapping in transthyretin amyloidosis. *JACC Cardiovasc Imaging* 2014;7(2): 157–165.
- Karamitsos TD, Piechnik SK, Banyersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2013; 6 (4): 488–497.
- Bhogal S, Ladia V, Sitwala P, et al. Cardiac Amyloidosis: An Updated Review with Emphasis on Diagnosis and Future Directions. *Curr Probl Cardiol* 2018;43 (1): 10–34.
- Kyriakou P, Mouselimis D, Tsarouchas A, et al. Diagnosis of cardiac amyloidosis: a systematic review on the role of imaging and biomarkers. *BMC Cardiovasc Disord* 2018; 18: 221.
- Qian G, Wu C, Zhang Y, et al. Prognostic value of high-sensitivity cardiac troponin T in patients with endomyocardial-biopsy proven cardiac amyloidosis. *J Geriatr Cardiol* 2014;11(2): 136–140.
- Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol* 2012; 30 (36): 4541–4549.
- Arvanitis M, Simon S, Chan G, et al. Retinol binding protein 4 (RBP4) concentration identifies V122I transthyretin cardiac amyloidosis. *Amyloid* 2017; 24(sup1): 120–121.
- Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005; 112 (13): 2047–2060.
- Castaño A, Drachman BM, Judge D, et al. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev* 2015; 20 (2):163–178.
- Rubinow A, Skinner M., Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 1981; 63 (6):1285–1288.
- Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation* 2009; 119 (18): 2490–2497.
- Gertz MA. Immunoglobulin light chain amyloidosis: 2016 update on diagnosis, prognosis, and treatment. *Am J Hematol* 2016; 91 (9): 947–956.
- Alexander KM, Singh A, Falk RH. Novel pharmacotherapies for cardiac amyloidosis. *Pharmacol Ther.* 2017; 180: 129–138.
- Santhorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood* 2017; 130 (5): 597–605.
- Gertz MA, Landau H, Comenzo RL, et al. First-in-human phase I/II study of NEO001 in patients with light chain amyloidosis and persistent organ dysfunction. *J Clin Oncol* 2016; 34 (10): 1097–1103.
- Pepys MB, Herbert J, Hutchinson WL, et al. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature* 2002; 417 (6886): 254–259.
- Hanna M. Novel drugs targeting transthyretin amyloidosis. *Curr Heart Fail Rep* 2014; 11 (1): 50–57.
- Castaño A, Helmke S, Alvarez J, et al. Diflunisal for ATTR cardiac amyloidosis. *Congest Heart Fail* 2012; 18 (6): 315–319.
- Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018; 379 (11): 1007–1016.