



Transthyretin amyloid cardiomyopathy : evolution in 2020

Yannick Mbaki Mampuya

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THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1
sous le sceau de l'Université Bretagne Loire

Thèse en vue du
DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

présentée par
YANNICK MBAKI MAMPUYA

Né le 01/07/1986 à KINSHASA

**Cardiopathie amyloïde à
Transthyrétine:
Evolution en 2020**

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le 29/10/2020 devant le jury composé de :
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Figure 3. Amyloid fibril Bulawa and *al*, PNAS, 2012

Figure 4. ECG from a patient with CA, sinusual, low voltage, q-waves

Figure 5. 2D TTE from a patient with CA

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Figure 12. Flowcharts

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The figure displays Kaplan–Meier curves of readmission for ALL CAUSES, readmission for HF, death for all causes, death for cardiovascular reason

Figure 19. Average ages of the population (baseline and follow-up)

Title

Transthyretin amyloid cardiomyopathy: Evolution in 2020

ABSTRACT

Introduction: Cardiac amyloidosis remained ignored for a long time because of a lack of an effective treatment and because it was supposed to develop only in the elderly. New data on the epidemiology and the treatments have been recently published and lead to a specific involvement of cardiologists in the management of this disease. We sought to describe the characteristics of the patients diagnosed in Rennes University Hospital for a better understanding of the strengths and weaknesses of our management.

Methods: We retrospectively looked at a group of consecutive patients diagnosed and treated or not with Tafamidis. We looked at the characteristics of our population and assessed the evolution of biological and TTE parameters after one-year follow-up.

Results: Out of 500 hypertrophic cardiomyopathy diagnosed in the competence center of the Rennes University Hospital, 91 had a TTR amyloidosis. 70 patients were included in the study, 63 men with the mean age of 81.4 years. The death rate after one year is 20%, the percentage of hospitalization after one year was 37.9%. The NtproBNP level decreased significantly at 1 year of follow up in both groups and even more in the group treated by Tafamidis. Deaths and cardiovascular hospitalizations occurred less under Tafamidis. Furthermore, these patients have similar EF (55% vs 48.9% $p = 0.52$), GLS (-9.2 vs -9.5 $p=0.847$) and renal function (CrCl 58.89 vs 49.03 $p= 0.034$) but a lower age in the tafamidis group (80,9 years vs 83.4 years $p=0.04$)

Conclusion: TTR amyloidosis is a frequent disease that required specific management and treatment. We describe who these patients are and how treatment especially using Tafamidis tends to impact ATTR-CM prognosis.

Keywords: Cardiac amyloidosis, transthyretin related amyloidosis, transthyretin, Tafamidis, ATTR-ACT study

ABBREVIATIONS

AL: Amyloid Light Chain

AL-CM: AL Amyloid Cardiomyopathy

ATTR-CM: Transthyretin Amyloid Cardiomyopathy

ATTRm: Mutated Transthyretin Amyloid Cardiomyopathy

ATTRwt: Wild-Type Transthyretin Amyloid Cardiomyopathy

CA: Cardiac Amyloidosis

CHF: Chronic Heart Failure

CV: Cardiovascular

EF: Ejection Fraction

GLS: Global Longitudinal Strain

HF: Heart Failure

HF_rEF: Heart Failure with reduced Ejection Fraction

HF_pEF: Heart Failure with Preserved Ejection Fraction

IFE: Immunofixation Electrophoresis

LVEF: Left Ventricular Ejection Fraction

LVH: Left Ventricular Hypertrophy

LVM: Left Ventricular Mass

MGUS: Monoclonal Gammopathy of Undetermined Significance

RV: Right Ventricular

RV FW-GLS: Right Ventricular Free Wall - Global Longitudinal Strain

TAPSE: Tricuspid Annulus Plane Systolic Excursion

TTR: Transthyretin

Before starting the report of our own work and taking into account the lack of knowledge that might exist about this disease and its recent development, we start our document by some key messages about the disease, its diagnostic and its management.

2-INTRODUCTION

2-1 Amyloidosis: Definition, General Mechanism and Classification

Amyloidosis is a large group of protein folding disorders. They have in common a multifactorial pathogenesis characterized by the deposition of insoluble proteinaceous amorphous material in various organs, mainly in parenchymal organs (kidney, heart, brain, liver, nerves, etc.). Under certain conditions (oxidative stress, genetic mutation, heat, decrease in pH, etc.)^{1,2}, these proteins misfold into amyloid fibrils also known as β -pleated sheet and accumulate in organs and alters their normal function.

The rest of the deposits are made of glycosaminoglycans and serum amyloid P component that stabilize old fibrils and help to create new ones. By electron microscopy, amyloid fibrils appear rigid, are non-branching, and typically measure 8–12 nm in diameter³. Many of these proteins circulate as constituents of plasma. There are more than 30 different type of these proteins that can form amyloid deposits in vivo, according to the Nomenclature Committee of the International Society of Amyloidosis⁴.

Classification

Amyloidosis can be classified into two groups depending on the anatomical distribution of the amyloid fibrils:

- Systemic amyloidosis, with deposits of amyloid protein in multiple organs and tissues
- Localized amyloidosis, in which amyloid proteins are deposited in specific organs

In the 1990s, Husby *and al*, proposed another classification of the different types of amyloidosis based on the nature of the precursor protein, and the clinical form that is systemic or localized with the different target organs⁵.

Nomenclature for amyloid subunit proteins includes the letter "A", followed by the abbreviation of the name of the precursor protein.

Systemic amyloidosis occurs in more than 10 per million person-years in the USA. It accounts for 1 in 1000 deaths in the British population and is probably underdiagnosed in the elderly population. Systemic amyloidosis is the most serious and commonly diagnosed form, with 2000–2500 new cases annually in the USA⁶. Multi-systemic, also known as primary amyloidosis forms are the most frequent observed, whereas localized forms are rarer. Systemic amyloidosis can be acquired.

The following are the most common types of amyloidosis with cardiac involvement.

Systemic Amyloid Light Chain Amyloidosis

Systemic Amyloid Light Chain Amyloidosis is the most common type of cardiac amyloidosis represented by amyloid light chain or AL (or sometimes amyloid heavy chain in 1/3 of cases), caused by monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, plasmacytoma or malignant non-Hodgkin B lymphoma, which produce and increase the number of circulating light or heavy chain fragments in the blood (lambda or kappa fragments). Multiorgan infiltration is classic; the organs most commonly involved are the kidney and the heart. The heart is affected in up to 90% of systemic AL amyloidosis patients, which represents the most important clinical manifestation and prognostic determinant.

The diagnosis of AL requires demonstrations and should lead to an immediate and aggressive treatment that often gives satisfying results.

TTR-Related Amyloidosis

There are 2 distinct types of TTR-related amyloidosis, systemic senile amyloidosis, also referred to as a wild-type amyloidosis (ATTRwt), and hereditary amyloidosis or mutated (ATTRm).

TTR is a 127 amino acid protein, which forms a tetrameric, 55 kDa transport protein primarily synthesized in the liver. This protein is a carrier of thyroxine and retinol (vitamin A) binding protein complex. It is the tertiary carrier of thyroxine in plasma, carrying less T4 than thyroxine-binding globulin (TBG) and albumin. In its native state TTR is a tetramer (four single chain TTR monomers form a tetrameric complex).

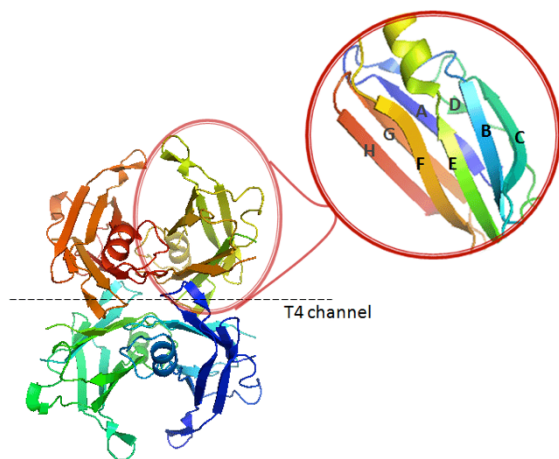


Figure 1: X-ray structure of Transthyretin. Structurally, in its native state, TTR contains eight strands (A-H) and a small α -helix. The contacts between the dimers form two hydrophobic pockets where T4 binds (T4 channel). As shown in red, each monomer contains one small α -helix and eight β -strands (CBEF and DAGH). Adapted from a model; PDB code 1DVQ

Systemic senile amyloidosis (SSA) or Wild-type transthyretin amyloidosis (ATTRwt) is linked to deposits of transthyretin (TTR). With age, this protein can be degraded into monomers and form amyloid fibrils in several organs: intestines, lungs, subcutaneous fat and the heart. The prevalence of these interstitial deposits increases gradually in the left ventricle with age and can reach up to 25% in people above 80 years old. This disease mainly affects men (95% of cases) and cardiac involvement is always present.

Hereditary transthyretin amyloidosis (h-TTR) is a hereditary form of ATTR caused by autosomal dominant mutations in the TTR gene. This form is rare⁷. The mutation of the

transthyretin (ATTR) gene makes TTR tetramers unstable: they dissociate and ultimately self-assemble to amyloid fibrils. Cardiac involvement is inconstant and depends on the mutation.

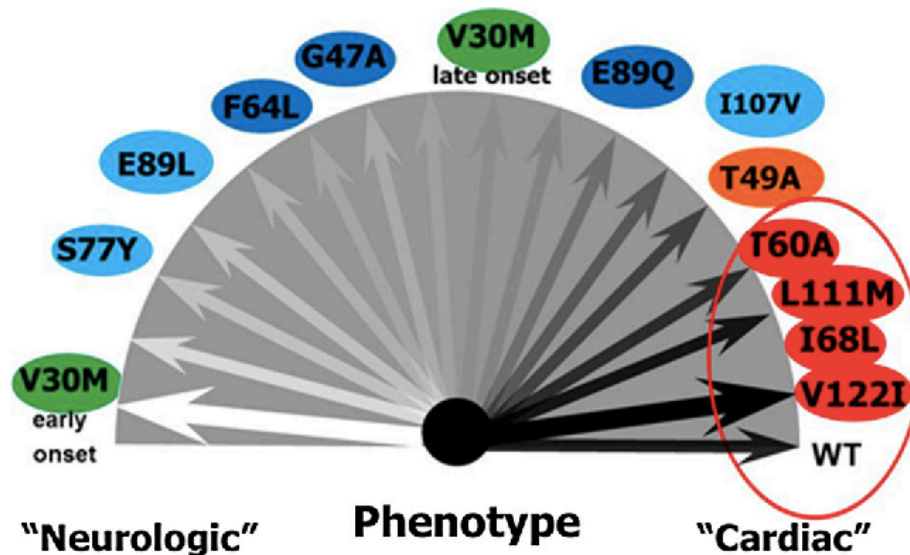


Figure 2: Genotype–phenotype correlation in ATTR. Modified from Rapezzi et al., Eur Heart J 2013.

In fact,, some are responsible for neurological form (early Val30Met) or cardiac form only (Val122Ile), others lead to mixed affection. The most common mutation responsible for cardiac affection is Val122Ile and occurs in heterozygous subjects in almost 4% of patients of African descent⁸. There are more than 120 reported TTR single point mutations that have been associated with hereditary ATTR. Penetrance is incomplete and symptoms often appear late in the history of the disease (often in patients older than 50 years, but variable depending on the mutation)⁹.

Various other forms of hereditary amyloidosis have been described: amyloidosis with apolipoproteins (AI or AII), with gelsolin (also called “Finnish amyloidosis”, with an often limited cardiac affection based on conductive disorders), with cystatin C (predominant cerebrovascular impairment), β 2-microglobulin, lysozyme or fibrinogen (predominant renal impairment).

Other Forms of Amyloidosis

AA-amyloidosis is mostly secondary to chronic inflammatory reaction such as autoimmune diseases or chronic infections, and cardiac involvement is rare.

Isolated Atrial Amyloid is a common finding in autopsy of elderly patients. It has been reported in 80% of patients older than 80 years.

Dialysis-related amyloidosis due to deposition of fibrils derived from beta-2 microglobulin, which accumulate in patients with end-stage kidney disease who are being maintained for prolonged periods of time by dialysis.

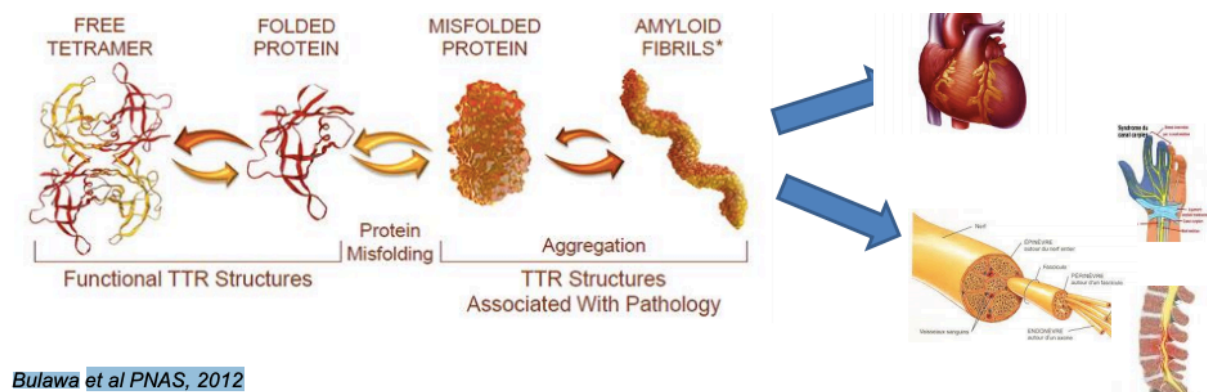


Figure 3: Bulawa and *al*, PNAS, 2012

2-2 Cardiac Amyloidosis

There are 3 main forms of cardiac amyloidosis LA, SSA and TTR-related.

Among the many types of amyloidosis, nearly all cases of clinical cardiac amyloidosis (>95%) are caused by transthyretin amyloidosis (ATTR-CM) or light chain amyloidosis (AL).

Cardiac amyloidosis (CA) is the most frequent cause of restrictive cardiomyopathy in Western countries. Unfortunately, this disease is generally misdiagnosed, or the diagnosis is often delayed, and its natural history and outcomes differ from other causes of heart failure. Early diagnosis of cardiac amyloidosis and its type is critical to initiating appropriate treatment, but because of the variation and non-specificity of clinical manifestations, the diagnosis is often

delayed. Cardiac amyloidosis portends a poor prognosis with a median survival of less than 6 months without treatment. However, if diagnosed early there are specific treatments available. This is the reason why an early diagnosis and treatment of patients with cardiac compromise is crucial.

Cardiac amyloidosis (CA) can be classified according to current recommendations among hypertrophic, infiltrative and restrictive cardiomyopathies¹⁰.

2-3 Diagnosis of TTR-Related Cardiac Amyloidosis

2-3-1 Diagnosis of ATTR-CM

Transthyretin Amyloid Cardiomyopathy (ATTR-CM) has been considered rare, but the true prevalence is difficult to estimate because it is frequently underrecognized. In the oldest part of our European population, transthyretin amyloidosis (ATTRwt) is common and has to be differentiated from other amyloid types. As a matter of fact, it is reported that 13% of HFpEF cases were diagnosed as ATTR-CM¹¹, several post-mortem studies found cardiac amyloid deposition in up to 25% of individuals >80 years of age¹².

Presenting signs and symptoms were often attributed to aging, hypertension, hypertrophic cardiomyopathy, and heart failure with preserved ejection fraction (HFpEF), and, until recently, the lack of effective treatments, made a precise diagnosis less relevant. Observational studies in patients with ATTR-CM suggest that median survival, in the absence of any disease-modifying treatment, varies between 3 and 5 years¹³.

Given the nonspecific presenting findings, the key to diagnosis is a high index of suspicion.

ATTR-CM should be suspected in patients with heart failure with preserved ejection fraction, non-diabetic neuropathy, or unexplained gastrointestinal symptoms/hepatomegaly^{14,15}, nondiabetic nephrotic proteinuria.

ATTR-CM can be prevalent in certain clinical contexts, as patients with degenerative aortic stenosis (16%)¹⁶, and 13% to 17% of patients with HFpEF^{17, 18}.

Clinical Presentation

Usually, clinical signs of cardiac amyloidosis are not specific, which is one of the main reasons the delayed diagnosis of patients.

General symptoms may include asthenia, progressive dyspnea (60% of patients), loss of weight which may represent the effects of cardiac cachexia or gastrointestinal manifestation (68%), chest pain.

Cardiac symptoms are dominated by congestive heart failure signs (right and/or left), palpitations related to supraventricular trouble disorder that can occur. Hypotension is found in 14% of cases, and postural hypotension usually observed (40%) as a manifestation of decreased cardiac output and/or autonomic dysfunction. Amyloid infiltration can also affect the coronary network leading to the phenomena of myocardial ischemia and trigger chest pain^{19,20}.

Other symptoms can appear due to extracellular deposition as neuropathy (carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, and autonomic or sensory polyneuropathy), macroglossia, muscle enlargement (pseudohypertrophy), ungual dystrophy, petechiae and skin ecchymosis, especially periorbital. Arthropathy may be caused by amyloid deposition in joints and surrounding structures. The "shoulder pad" sign is visible enlargement of the anterior shoulder caused by fluid in the glenohumeral joint and/or amyloid infiltration of the synovial membrane and surrounding structures.

A family history of heart disease, kidney failure, or neurological disease as well as ethnic origin (Portugal, Sweden, Japan, Finland, Africa, etc.) can be a reason for a hereditary amyloidosis.

Electrocardiogram

ECG is often abnormal, with the presence of a micro voltage, pathological Q waves (especially in the antero-septal derivations), conduction disorders at all levels (sino atrial block, atrioventricular block, bundle branch block) and rhythmic disorders (supra-ventricular and ventricular)²¹. The absence of low QRS voltage does not exclude cardiac amyloidosis, particularly in patients with ATTRwt.

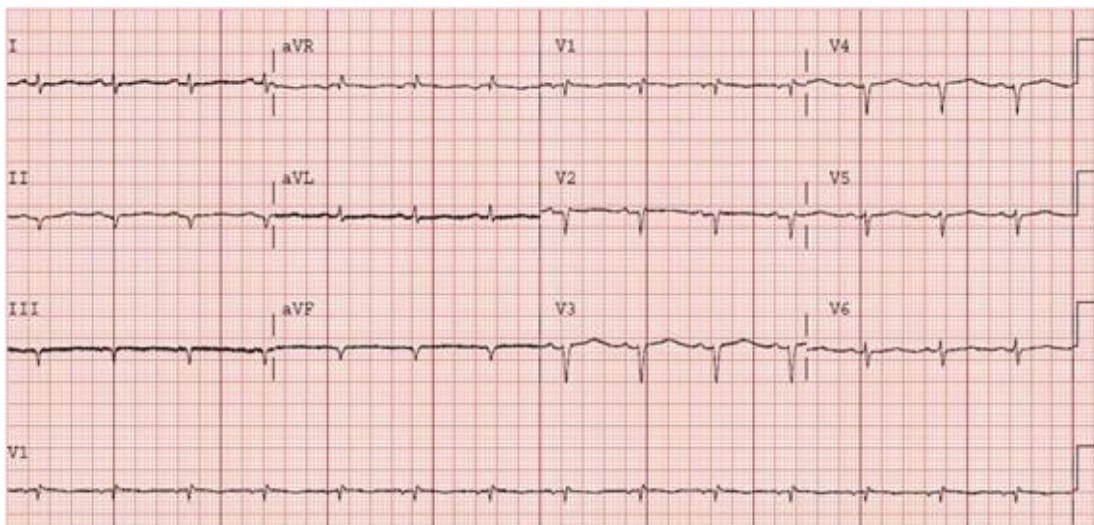


Figure 4: ECG from a patient with CA, sinus, low voltage, q-waves

Echocardiography (TTE)

Echocardiography is often the initial imaging test for patients who have a high suspicion of ATTR-CM. ATTR-CM is characterized in transthoracic echocardiography (TTE) by an increase in the wall thicknesses of the two ventricles due to the deposition in the extracellular matrix (inter-ventricular septum and posterior wall > 12 mm, increased of left ventricular mass (LVM)), thickness of the right ventricle > 5 mm). This thickening is mostly asymmetric (septal thickening) associated with a sigmoid septum (in 70% of cases) or reverse septal curvature (in 30%). LV outflow obstruction is rare²².

Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking

echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. In fact, this alteration of longitudinal strain alteration has very sensitivity (93%) and specificity (82%) for cardiac amyloidosis, which is useful for differentiating cardiac amyloidosis from other hypertrophic phenocopies²³.

Historically, a granular “sparkling” or “speckling” of the myocardium have been described but the description is inconstant. Infiltration of ventricular walls produces an appearance of hypertrophy with non-dilated or small ventricles, while the dilated aspect of the LV is rare.

Diastolic dysfunction is almost invariably affected with an impaired relaxation, which then progresses inevitably to restrictive physiology²⁴, (mitral E wave deceleration time <150 msec, E / A > 2) and increased filling pressures of the left ventricle (E / E' > 15), although the LV ejection fraction is typically normal until end-stage, in which it is typically only mildly reduced²⁴.

There is often a moderate pulmonary hypertension pulmonary estimated from the peak velocity of the tricuspid valve regurgitant jet (40 to 50 mmHg). These systolic and diastolic changes are present in both sides of the heart.

Echocardiogram assessment is helpful for many reasons. It is one of the most accessible paraclinical examination, and one of the least expensive imaging examinations that can be performed. What is more, the interpretation doesn't require a specific expertise when there is a finding such as myocardial wall thickness (moderate or severe thickening ≥ 14 mm). It is possible to identify a non-amyloid reason of LV thickening (valvular disease, Fabry disease). Even if some findings are often nonspecific for ATTR-CM, finding of myocardial wall thickness should trigger consideration of ATTR-CM especially if there is discordance between wall thickness on echocardiogram and QRS voltage on ECG.

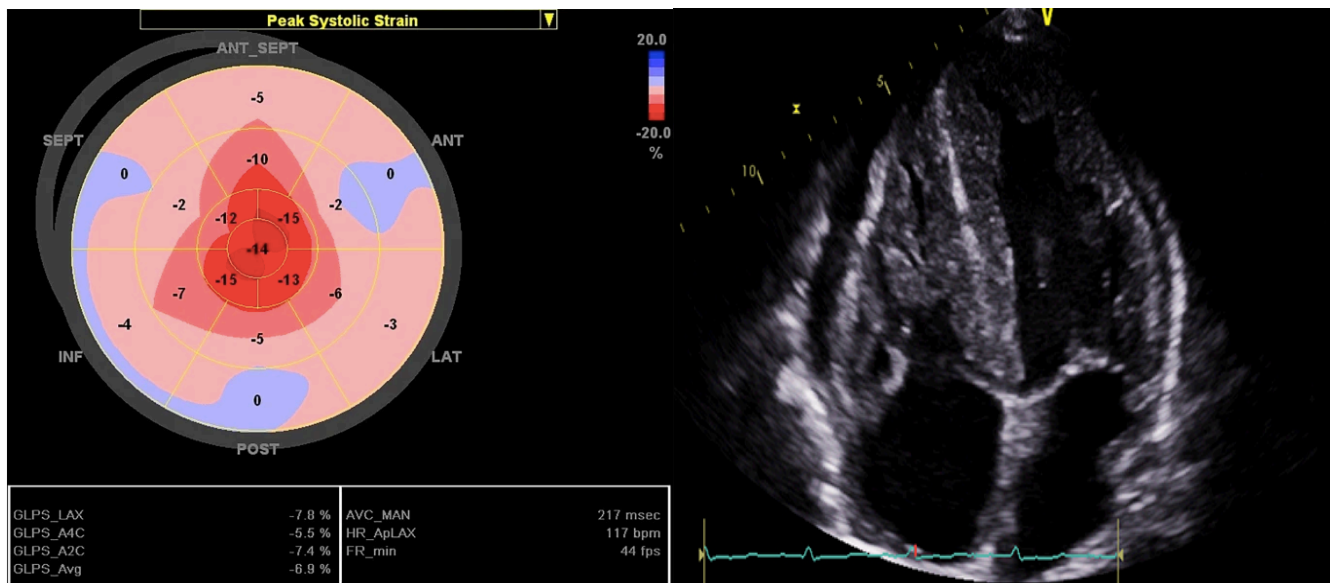


Figure 5: 2D TTE from a patient with CA, showing apical sparing pattern of the LV longitudinal strain, a marked thickening of both ventricles' walls, bi atrial dilatation, pericardial effusion

Cardiac Magnetic Resonance Imaging (CMR)

CMR can be used in the diagnosis of cardiac amyloidosis in general. It is generally performed with a combination of native and contrast imaging in this setting²⁵.

CMR provides detailed assessment of cardiac structure (including identification and quantification of LVH), function, and tissue characteristics. In fact, T1-sequences have the same morphological information as in echocardiography. CMR can detect early cardiac amyloidosis before the development of LVH. However, CMR cannot distinguish cardiac AL from ATTR-CM²⁶. CMR has a great diagnostic value in cardiac amyloidosis, but false-positive and false-negative CMRs are not infrequent. Typical findings include restrictive morphology, abnormal gadolinium kinetics, and extracellular volume expansion on T1 mapping²⁷. Nevertheless, CMR is expensive, available only in specialized centers, and it can be contraindicated in a substantial proportion of patients.

Bone Tracer Cardiac Scintigraphy

^{99m}Tc-labeled phosphate agents have been used as skeletal imaging agent or cardiac imaging agent in the diagnosis of acute myocardial infarction from their introduction in 1974.

Since the end of the 1970s, radionuclide bone scintigraphy with technetium-labeled bisphosphonates has been reported to localize to cardiac amyloid deposits^{28,29}.

In the early 1980s, studies demonstrated that the intense diffuse myocardial uptake of bone tracer on scintigraphy strongly suggest the existence of CA on the basis of echocardiography in patients with extracardiac biopsy-proven amyloidosis, even if the molecular basis for this remains unknown³⁰.

Nowadays, bone tracer cardiac scintigraphy (^{99m} technetium [Tc]-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], ^{99m}Tc-labeled pyrophosphate [PYP], or ^{99m}Tc-labeled hydroxymethylene diphosphonate [HMDP]) is pivotal test to identify ATTR-CM.

In order to assess the heart's radiolabelling, the Perugini staging system is used. It is a simple visual scoring of the three-hour planar image. Systematic review showed that the presence of grade 1, 2, or 3 scintigraphy had high sensitivity (pooled value of 82%) and specificity (98.8%) for cardiac amyloidosis as compared with tissue biopsy in studies evaluating the diagnostic performance of scintigraphy for CA³¹. Bone tracer scintigraphy can also distinguish ATTR-CM with cardiac AL.

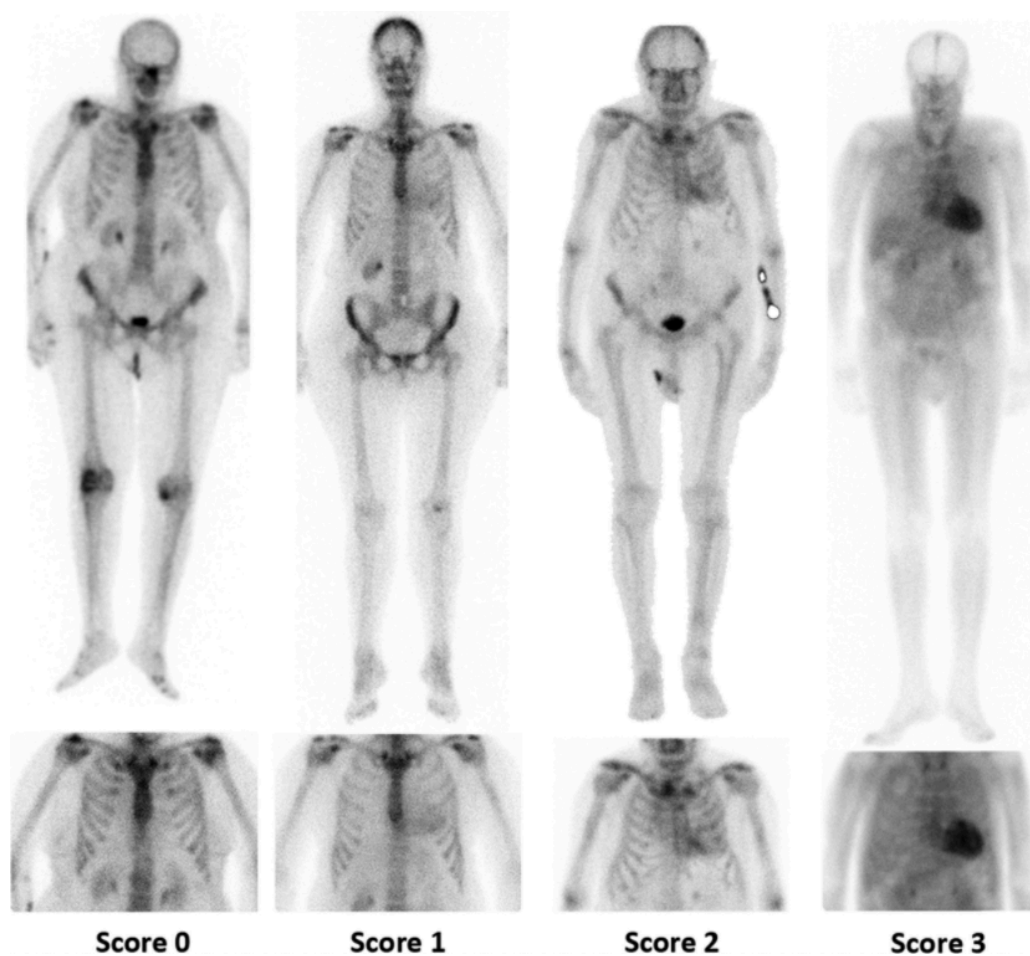


Figure 6 from O. Lairez et al. / Médecine Nucléaire 41 (2017) 108–114: Bone Scintigraphy from a patient with ATTR-CM, and Perugini Score from 0 to 3

grade 0: no cardiac uptake and normal bone uptake

grade 1: cardiac uptake which is less than bone uptake

grade 2: cardiac uptake with intensity similar to or greater than bone uptake

Biology

Natriuretic proteins (NtproBNP) and Troponin (T and I) are usually elevated in cardiac amyloidosis in general. The troponin elevation is a sign of a subclinical myocardial damage due to the deposition of TTR in the extra cellular matrix. This could be used as a potential early disease marker.

Biological signs of right heart failure signs as elevated creatinin, elevated liver enzymes and bilirubin because of a congestive hepatopathy, can be present.

Searching for monoclonal gammopathy in order to exclude an AL amyloidosis diagnosis is systematically performed. This is done using serum protein electrophoresis, testing for urinary proteinuria (Bences-Jones protein) and completed by urinal and serum immunofixation electrophoresis. The sensitivity of serum plasma electrophoresis for AL amyloidosis is $\approx 70\%$, whereas the sensitivity of serum IFE is $>90\%$.² Together, measurement of serum IFE, urine IFE, and serum free light chain is $>99\%$ sensitive for AL amyloidosis³².

Tissue Biopsy

Tissue biopsy is still the gold-standard technique to confirm amyloid deposition, in all types of cardiac amyloidosis. Amyloidosis deposition is a systemic disease, that allows a sample from a peripheral tissue. For many years, rectal biopsy was the one of the most performed procedures when systemic amyloidosis was suspected. Sensitivity of detecting TTR in peripheral tissue varies by sites²:

- Labial salivary gland biopsy: 91%,
- Sural nerve biopsy: 80%,
- Abdominal fat pad biopsy: 14-83%

Amyloid deposits (regardless of the nature of the amyloidogenic protein) are stained with alkaline Congo red and thioflavin: they are extracellular deposits with a yellow-green dichroism in polarized light. Optical microscopy, if performed, shows amyloid fibrils.

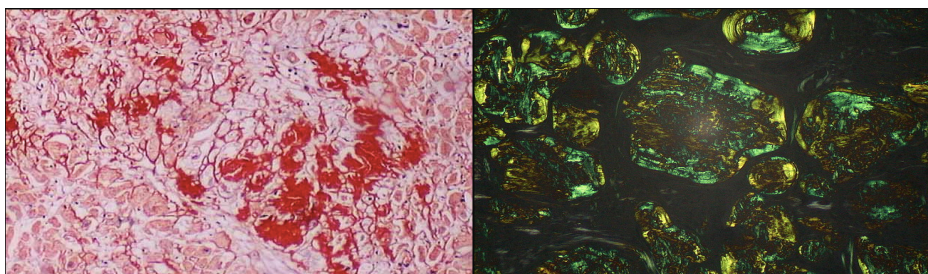


Figure 7 and 8: Amyloid deposition colored in red with alkaline congo red (nucleus in blue) and seen with a polarized microscope: yellow-Green birefringence

Performing a cardiac tissue biopsy in the context of high suspicion of ATTR-CM, has the advantage of establishing a cause-and-effect relationship between organ dysfunction and amyloid deposition. EMB is associated with a risk of complications, including myocardial perforation and tamponade, that may be fatal and requires expertise that can introduce diagnostic delay³⁴.

After Congo red staining establishes a diagnosis of amyloidosis, the specific type of amyloidosis must be determined with immunostaining of a biopsy specimen using antiserum against TTR. However, in 25% of cases, these markings do not identify the responsible protein³⁵.

In addition to that, false positives results are not uncommon, especially for TTR labelling (specificity of 42.8%)³⁶. Mass spectroscopy is then useful to determine the protein subunit and classify the disease as immunoglobulin light-chain amyloidosis or ATTR³⁷, with a high specificity and sensibility (near 100% for both)³⁸.

2-3-2 New Approach to Testing in Cardiac Amyloidosis

Diagnosis of ATTR-CM used to be difficult because of its clinical presentation with nonspecific signs, and the need of tissue biopsy as endomyocardial biopsy that can delay the diagnosis and the introduction of an effective specific treatment.

The option of a fast and effective diagnosis with noninvasive methods was made possible by the use of bone scintigraphy³⁹, which became the cornerstone of management of TTR-CM, in combination with high index of suspicion of ATTR-CM, screen for presence of monoclonal light chain to exclude definitively a diagnosis of AL.

Genetic testing is performed, only after a confirmation of ATTR-CM. The recognition of hereditary ATTR amyloidosis is important, even if there is not a clear family history, for

estimating prognosis, proper familial counselling and guiding use of therapies, such as liver transplantation.

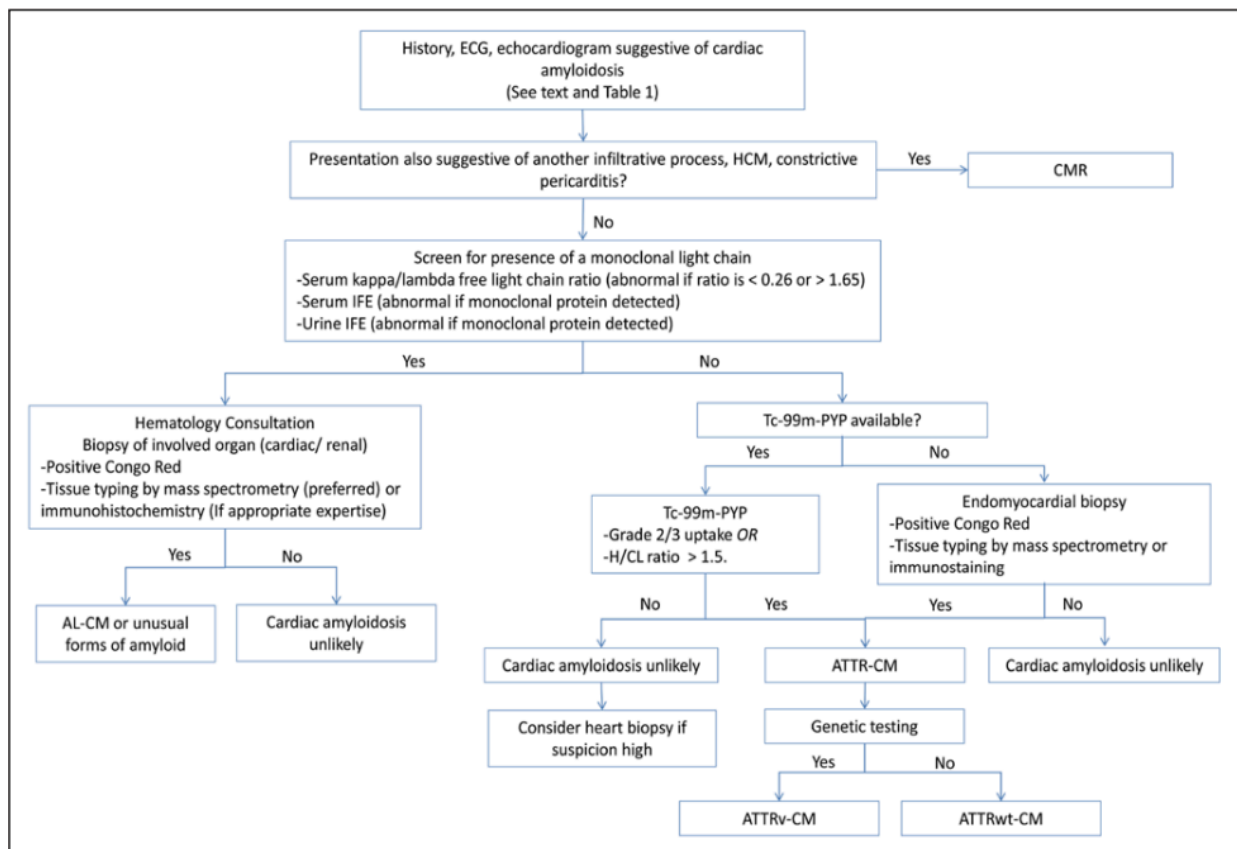


Figure 9: Testing algorithm for transthyretin amyloidosis (ATTR). From Michelle M. Kittleson. Circulation. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement from the American Heart Association, Volume: 142

2-4 Overview of therapies in ATTR-CM

Therapeutic management of ATTR-CM is based around 3 priorities:

- management of heart failure
- management of arrhythmias and conduction system disease
- initiation of disease-modifying agent

Management of Heart Failure

Because of the restrictive LV filling, the decrease of the stroke volume, and the cardiac output, signs of cardiac congestion appear gradually. Thus, fighting against water retention is

fundamental. Loop diuretic are helpful in this case, associated or not with aldosterone antagonist. We have to point out that the classic treatment for heart failure (with reduced EF or HFpEF) combining betablocker, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or angiotensin receptors blockers–neprilysin inhibitors is not indicated in this situation because of the risk of aggravation of a low cardiac output, orthostatic hypotension and an existing conduction system disease.

Management of Arrhythmias and Conduction System Disease

Amyloid cardiomyopathy is associated with atrial dysfunction and both atrial and ventricular arrhythmias.

In case of supraventricular tachycardia, anticoagulation is indicated for atrial fibrillation/flutter regardless of CHA₂DS₂-VASc score. There is no effective data comparing warfarin and direct oral anticoagulants in this setting, so both are empirically used.

Because of the high risk of conduction system disease, the indications for pacemaker implantation should be broad as soon as abnormalities appear on the surface ECG or after (AV block, Bundle branch block, etc.), according to Heart Rhythm Society consensus guidelines. There is no specific recommendation for amyloidosis.

The use of ICDs for primary prevention of sudden cardiac death in patients with ATTR-CM is not well established⁴⁰. As betablocker are poorly tolerated, amiodarone is an excellent option for rhythm and rate control. Digoxin should be used with caution for rate control, due to a potential accumulation of digoxin within cardiac amyloid fibrils demonstrated in vitro.

Initiation of Disease-Modifying Agent

Historically, the treatment of hereditary transthyretin amyloidosis consists of performing a liver transplant combined with a heart transplant in case of severe cardiac involvement.

Specific therapies are now available. They include TTR silencer, TTR stabilizer, and TTR disruptor.

TTR silencers target the hepatic synthesis of TTR. In this group, two molecules are available, patisiran, which is an intravenously administered siRNA that degrades TTR mRNA, and inotersen, a subcutaneously administered single-stranded antisense oligonucleotide, that binds TTR mRNA, leading to degradation. Both therapies result in >85% reduction in circulating TTR protein concentration^{41,42}.

Stabilization of the TTR homotetramer are targets for new therapies to prevent progression of TTR amyloidosis^{43,44}.

Diflunisal, a non-steroidal anti-inflammatory drug (NSAID), and tafamidis, an analog of diflunisal without NSAID properties, are the two molecule stabilizers of the TTR tetramer currently used. Tafamidis binds the thyroxine-binding site of TTR.

In the ATTR-ACT randomized trial (Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy) of patients with ATTRwt-CM or ATTRv-CM, tafamidis was associated with a significantly lower all-cause mortality (29.5% versus 42.9%) and lower cardiovascular-related hospitalization (0.48 versus 0.70 per year) after 30 months of treatment. Tafamidis was also associated with a lower rate of decline in 6-minute walk distance ($P<0.001$) and a lower rate of decline in Kansas City Cardiomyopathy Questionnaire-Overall Summary score ($P<0.001$). In the same study, there was a higher rate of cardiovascular-related hospitalizations in the prespecified subgroup of patients with NYHA class III heart failure, which have been attributable to longer survival during a more severe period of disease, insisting on the importance of early diagnosis and treatment⁴⁵.

TTR disrupter target the clearance of amyloidosis fibrils from tissues. Preclinical studies demonstrated that doxycycline plus TUDCA (tauroursodeoxycholic acid) removed amyloid deposits, although they don't inhibit their formation until a certain stage⁴⁶. However, some small open-label studies demonstrated a high incidence of side effects with conflicting results on efficacy^{47,48}.

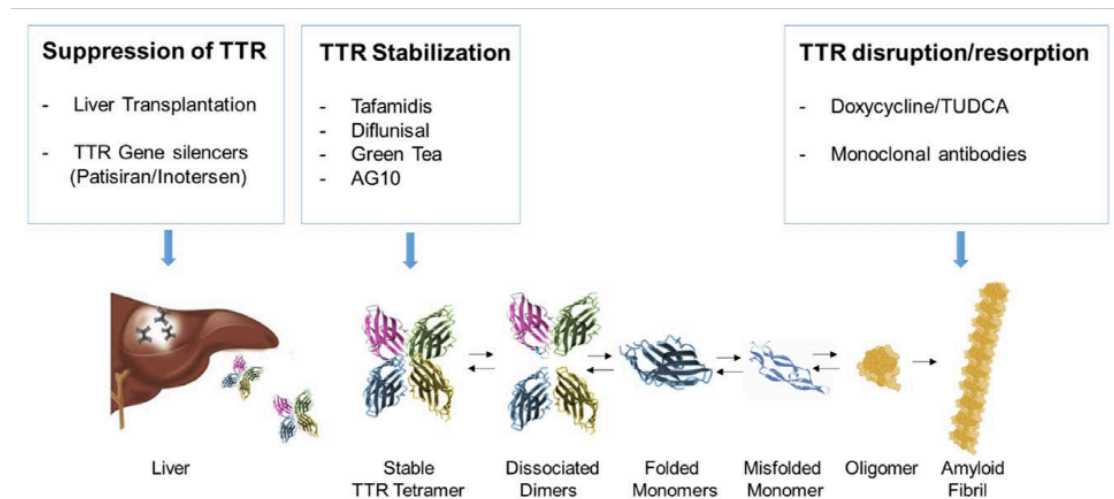


Figure 10: TTR (transthyretin) production and targets of therapy from Michelle M. Kittleson. Circulation. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement from the American Heart Association, Volume: 142

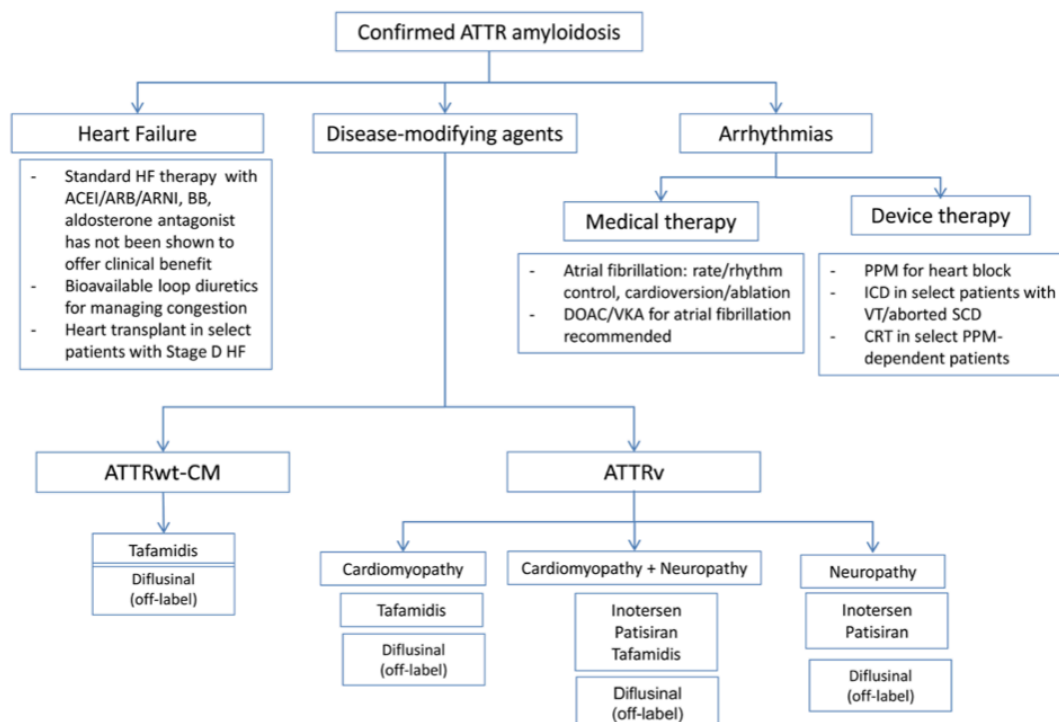


Figure 11: Treatment algorithm for ATTR-CM from Michelle M. Kittleson. Circulation. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement from the American Heart Association, Volume: 142

3-STUDY OBJECTIVES

We sought to describe the characteristics of the patients diagnosed in the Rennes University Hospital for a better understanding of the strengths and weaknesses of our management.

We looked at TTE and biological parameters after 12 months of treatment by Tafamidis or not.

We looked at the occurrence of events as readmission, readmission for heart failure, death of all causes and death for cardiovascular reasons.

4-MATERIALS AND METHODS

4-1 Study Design

Using the local database of the patients diagnosed in the Rennes University Hospital Competence Center in Cardiomyopathies, we retrospectively collected out of 500 patients, all consecutive and suspected patients for a diagnosis of ATTR-CM from September 2015 to September 2019. Confirmed ATTR-CM cases were defined as cardiac hypertrophy with a mean end-diastolic interventricular septal wall thickness exceeding 12 mm in TTE, apical sparing of the GLS, and characteristics of diastolic dysfunction (mitral E wave deceleration time <150 msec, E / A > 2) history of heart failure, among suspected cases of ATTR-CM with or without hospitalization, positive bone scintigraphy (Perrugini score >1), available genetic test results, and exclusion of AL-amyloidosis. We excluded all patients who didn't have bone scintigraphy, or genetic test from our study population. Patients were divided into 2 groups, one group with a modifying treatment of ATTR-CM by Tafamidis (20, 61 or 80 mg according to the ATTR-ACT trial) and the other group without modifying treatment. Information as clinical presentation, laboratory results, echocardiography, immediate and 12-month outcomes were retrospectively collected.

4-2 Patients' Characteristics

Information regarding clinical presentation, past medical history and laboratory results were retrospectively collected from patients' charts. Glomerular filtration rate was calculated using the Cockcroft–Gault formula according to sex⁴⁹. Nt-ProBNP was measured the same day as the first TTE was performed and at 6-12 months of follow up. All echocardiographic reports were reviewed and when needed measurements were retrospectively performed on digitally stored images. ATTR-CM etiology were classified as hereditary (ATTRm) or senile/wild type (ATTRwt) depending on genetics results. TTE was performed at the first consultation and at 1 year. Left-ventricular (LVEF) ejection fraction was measured by using the biplane method of disks (modified Simpson's rule). Global longitudinal strain was performed as recommended to assess the systolic function of LV, RV free wall, but also RA and LA. Doppler and Tissue Doppler imaging, was used to evaluate global and regional myocardial systolic and diastolic function, to estimate LV filling, cardiac output and stroke volume⁵⁰. The LA and RA diameters were measured in the apical four-chambers, and the PSGLA only for the LA.

Outcome

The primary endpoint was a composite endpoint including death for all causes, death for CV reasons, readmission for all causes, and readmission for heart failure during the 12 months of follow-up. We assessed the evolution of biological (Nt-proBNP) and TTE's parameters (LVEF, GLS, E/e', e', SPAP) to all patients.

Statistical Analysis

In order to describe the continuous and categorical variables, we calculated the means, standard deviations, standard error and the percentages, respectively. Normality tests (Shapiro-Wilk)

was performed to verify the distribution of the continuous data.

The group comparisons were carried out using Student's T test and Welch's T test (to compare two means for a continuous variable with a normal distribution), and the Mann-Whitney-Wilcoxon test (to compare more than two means for a continuous variable not having a normal distribution).

Chi-2 test was used to evaluate the correlation between the treatment by TAFAMIDIS and readmission for all causes, readmission for heart failure, and death. Trends in LVEF, GLS, cardiac output (CO), E/e' and pulmonary arterial systolic pressure (sPAP), between the baseline and the follow-up were assessed by the ANOVA, and the Mann-Whitney-Wilcoxon test.

Finally, we assessed the risks of death, death for cardiovascular reasons, readmission for all causes, readmission due to heart failure, in both groups treated and not treated by Tafamidis, using the Kaplan-Meier method. Statistical analyses were performed using SAS version 9.4 statistical software (SAS Institute Inc, Cary, NC, USA). All p-values less than 0.05 were considered statistically significant.

RESULTS

Clinical Presentation and Etiologies of ATTR-CM

Out of 500 patients diagnoses in the Rennes University Hospital Competence Center for Cardiomyopathies, a total of 91 adult patients were suspected of ATTR-CM between September 2015 and September 2019. Among them, 70 patients had confirmed ATTR-CM (Figure 12). ATTR-CM represents almost 10% of all HCM in the Rennes University Hospital.

Characteristics of the 70 patients with confirmed ATTR-CM are presented in Table 1 and 2. Overall mean age was 81.5 ± 7.54 years and 63 patients (90%) were male. 7 (10.1%) had a confirmed TTR mutation. The large majority of the population were moderate to severely symptomatic (51% NYHA II, 32.9% NYHA III), and 47 (67.1%) presented congestive heart

failure signs (right and/or left sided signs). 58.9% of the population have already been admitted for heart failure, 49% of the population had sign of asthenia.

Atrial fibrillation (66.7%) is frequent. Atrio-ventricular block are more frequent especially the first-degree AV block (77.1%). 19 carriers had an indication for a pacemaker (27.5%) (DDD). The medical background was dominated respectively by hypertension (66.7%), aortic stenosis severe or not (37,7%), coronary artery disease (33.3%) and cancer (32.4%). Some patients had extra cardiac signs, as carpal syndrome tunnel in 26 patients (38.2%), narrow lumbar spinal canal syndrome in 11 patients (16.2%).

In this population, 74.3% of the patients were treated by Furosemide with a mean dose of 169 mg per day, 42.6% by aldosterone antagonist, 68.1% patients had oral anticoagulant (50.2% of DOAC, 17.4% VKA), and 72.1% had a treatment by TAFAMIDIS with an average dose of 27,5 mg per day. Betablocker's treatment had been stopped for all patients (0%).

Chronic kidney disease was present in 38 patients (54.3%). Troponin and NtproBNP were elevated, respectively 62.5 ± 54.7 pg/mL, and 5172 ± 5694 pg/mL. Urinal Ig light chain and blood Ig light chain were positive in 9.4% and 21.5% of patients respectively.

There was a significant thickening of the inter ventricular septum in diastole ($16.2\text{mm} \pm 4.29$). Systolic function according to LVEF measurement was preserved ($53.4\% \pm 14.6$). While LV global longitudinal strain ($-10.6\% \pm 6$) was severely impaired, reflecting a myocardial dysfunction with the characteristic pattern of apical sparing (normal range GLS $> -18.6\%$). On the right side, right ventricular free wall global longitudinal strain (RVFW-GLS) was affected as well (mean -16.6 ± 6.19), confirming a bi-ventricular affection. TAPSE remained preserved (16.2 ± 5.74 mm). We showed an important impairment of the LA reservoir function from the basis. There was a strong diastolic impairment with a restrictive pattern with elevated LV filling pressure ($E/e' 19.9 \pm 9.4$), enlarged left atrium, and moderate elevation sPAP at 43.5 ± 12.5 mmHg. Cardiac output (CO) was preserved ($4.82\text{l/min} \pm 1.89$).

ATTR-CM etiology was mostly wild-type in 60 patients (90%) and genetic for 7 patients (10%). Among all patients, 100% had a bone scintigraphy with an average Perrugini score of 2.36 ± 0.59 , and only 18.8% of patients had a biopsy (fat pad, salivary gland biopsy, etc.).

Follow-up Outcomes

Follow-up was 94% complete. There were no echocardiographic differences between the two groups from the baseline and after 1-year follow-up (table 3). Average age was $81.9 (\pm 7.6)$. TTE parameters remained steady from the beginning and after 1 year between both groups, including GLS, E/e' , mean e' according to the Mann-Whitney-Wilcoxon. The Mann-Whitney-Wilcoxon test showed a significant difference in NtproBNP between the Tafamidis group and the non-treated group at the baseline ($p = 0.018$), with a higher NtproBNP in the non-treated group. After 1-year follow-up, the level of NtproBNP was, with borderline statistical significance ($p = 0.064$), different. NtproBNP between the baseline and after 1 year in the two groups decreased after 1-year follow-up with a statistical significance ($p = 0.049$) (table 4, figure 13).

There were 13 deaths and 25 patients were readmitted including 18 patients for HF (table 5). There was no correlation between a readmission for all causes and the treatment by Tafamidis ($p = 0.397$), and there was no correlation between a readmission for heart failure and the treatment by Tafamidis ($P = 0.443$) (table 6). Nevertheless, we can point out that 64,58% of patients who were treated by Tafamidis weren't hospitalized. Finally, there was a significant correlation between death for all causes and the treatment by Tafamidis with a lower number of deaths in the Tafamidis group ($p = 0.032$) (table 6).

Survival free of readmission for all causes, survival free of death for all causes, and survival free of death for CV reasons are presented in figure 4. It showed that the survival free of readmission for all causes wasn't different between the two groups ($p\text{-value log rank} = 0.95$),

survival free of death for all causes was better in the Tafamidis group but without no statistical significance (p-value log rank = 0,57), and survival free of death for CV reason was better in the Tafamidis group but with a border line statistical significance (p-value log rank = 0,06).

DISCUSSION

In this retrospective series, we collected all confirmed cases of ATTR-CM, diagnosed in Competence Center for Cardiomyopathies in the Rennes University Hospital between September 2015 and September 2019 and assessed the clinical presentation, biological and TTE parameters from the baseline and after 1-year follow-up. Patients were mostly men (90%), with a medical background and symptoms of heart failure, atrial fibrillation and heart block, signs of diastolic restrictive cardiomyopathy in TTE, and some extra cardiac signs as carpal syndrome tunnel (38,2%) or narrow lumbar spinal canal syndrome (16,2%). The majority of their symptoms weren't specific, but the association of those signs should be taken into account as high index of suspicion and push to consider ATTR-CM as a potential diagnosis.

ATTR-CM has been considered as a rare disease ⁵¹, however, more and more studies have proved its non-negligible prevalence in degenerative aortic stenosis (16%)¹⁶, and 13% to 17% of patients with HFpEF^{17, 18}. The true prevalence is challenging to estimate. It is more likely to affect the elderly (men mainly). Due to the complexity of the diagnostic strategy (the initial necessity to perform an endomyocardial biopsy), the lack of specific treatments, a high number of patients have not been diagnosed. For a few years now, the work-up for the diagnosis and the management have changed considerably (bone scintigraphy, tafamidis, need to stop beta-blockers and to prevent hypotension)^{66,67}. The new diagnostic approach gathers a combination of patients' medical background, clinical presentation, TTE, biology test to exclude a potential plasma cell process (serum free light chain and IFE) and bone scintigraphy without any need for extra cardiac biopsy for most patients. Serum free light chain concentration and serum and

urine immunofixation electrophoresis (IFE) are assessed to rule out AL-CM, because of the elevated proportion of MGUS in the general population above 70 years old ($> 5,3\%$)⁶⁰. The presence of serum free light chain and positive IFE has a high sensitivity $>99\%$ for AL amyloidosis^{58,59}. Bone scintigraphy is the key for this simplified and non-invasive strategy. A multicenter study of over 1200 patients has shown that bone scintigraphy has $> 99\%$ of sensitivity and 86% of specificity for ATTR-CM, with false positives almost exclusively in patients with AL-CM. The combination of Perrugini visual score 2 or 3 and the absence of a monoclonal protein in serum or urine has a specificity and positive predictive value for ATTR-CM of 100%⁵⁸.

In the population of our study, we had 7 cases of hereditary ATTR-CM (10%), which is a non-negligible number of patients with a TTR mutation. A French study already estimated that 5.7% of patients with diagnosis of hypertrophic cardiomyopathy carried a potential amyloidogenic TTR mutations, particularly, those of African descent with neuropathy, carpal tunnel syndrome, ECG low voltage⁵⁴. Median survival after diagnosis of ATTR-CM in untreated patients is poor: 2.5 years for ATTRm caused by the TTR Val122Ile (or pV142I) mutation and 3.6 years for ATTRwt.^{52,53}. This suggests that molecular screening for TTRm should be included in genetic screens of possible HCM subjects.

In our study, we followed patients with ATTR-CM including some involved in the ATRA-ACT- Extension study. It means that patients could get Tafamidis 20 or 61 mg (equivalent to 80 mg). So far, there is not a clear definition of progression or response to therapy of ATTR-CM, but several measures have been proposed such as NHYA level, survival, readmission and readmission for CV reason, cardiac imaging and cardiac biomarkers.

First of all, in this study, we showed that with a specific optimized treatment in patients with ATTR-CM, we can have an impact on the heart failure level, by decreasing NtproBNP in the whole population, with or without Tafamidis ($p = 0,049$). When it comes to the general

approach regarding HFrEF, guidelines usually recommend therapy including betablocker and neurohormonal blockers as ACE, ARB, aldosterone antagonist and loop diuretics to maintain euvolemia⁵⁵. In case of HFpEF, medical treatment is based on controlling risk factors as hypertension, diabetes mellitus, rate control in patients with AF, revascularization if needed. Regarding medical therapy in ATTR-CM, the corner stone is to maintain a stable fluid level, with sodium control, weight control with loop diuretic, keeping an effective cardiac output. It is not possible to apply the same algorithm as in HFrEF. The unique way to keep an effective cardiac output in restrictive cardiomyopathy, is to rise the heart rate. Therefore, HF therapy in ATTR-CM should include only loop diuretics and aldosterone antagonist^{56, 57}. As demonstrated in our cohort, we avoid beta-blockers and a high proportion of patients require a pace maker that has to be programmed with a minimum tolerated heart rate about 80/min (very different from the usual practice).

Secondly, we showed that the control of natriuretic peptide level was greater in the Tafamidis group ($p=0,049$). This finding is aligned with ATTR-ACT study which proved that treating patients with ATTR-CM (ATTRm or ATTRwt) with Tafamidis vs placebo for 30 months reduced all-cause mortality, the risk of cardiovascular-associated hospitalizations. Tafamidis might improve the quality of life⁶³.

We also showed in our population a better survival free of death related to cardiovascular reasons ($p=0,06$), in the treated group, and lower rate of death in the Tafamidis group ($p=0,032$). However, one of our objectives concern the change in TTE markers over 1-year follow-up in our patients. TTE parameters remained similar in both group despite the use of Tafamidis for 1 year (table 3 and 4). The average e' value at the baseline was 5.06 for the Tafamidis group and 5.2 for the non-treated group, and 5.07 for the Tafamidis group and 5.4 for the non-treated group after 1 year follow-up ($p=0.6$). For GLS at the baseline was -10.9% for the Tafamidis

group and -11.2% for the non-treated group, and -9.53% for the Tafamidis group and -9.2% for the non-treated group ($p=0.84$) after 1-year follow-up.

We know that Tafamidis is completely effective only after 30 months of treatment, also its impact is on the new fibrils and not so much on the existing ones that are already included in the myocytes. One hypothesis for this weak improvement that we observed is that patients we saw and diagnosed had been diagnosed late with already a severe LVH in most of them. 67.3% were in AFib, and the strain was severely impaired.

Based on these findings, we think that all cardiologists should be aware of the existence of ATTR-CM, and to consider it as a potential etiology of heart failure when there is concentric hypertrophy and restrictive pattern in TTE, associated to heart failure signs, asthenia, carpal tunnel syndrome, and to follow the indicate testing strategy including biology testing, bone scintigraphy, and potentially introduce a specific therapy when needed. Early diagnosis is key for the use of treatment like Tafamidis as the goal with such treatment is to stop the deposit and not to reverse it⁶⁴.

Several therapies in ATTR-CM as TTR- silencers, are currently developed and have promising results. Two randomized trials of TTR silencers in patients with ATTRm amyloidosis and polyneuropathy have been reported: the APOLLO trial (a phase 3 study evaluating the safety of Patisiran in Patients with TTR mediated amyloidosis) and NEURO-TTR (phase 3 trial evaluating the safety of Inotersen in familial amyloid polyneuropathy). Patisiran is an intravenously administered siRNA that degrades TTR mRNA, and Inotersen is a subcutaneously administered single-stranded antisense oligonucleotide that binds TTR mRNA, leading to degradation. Both therapies result in >85% reduction in circulating TTR protein concentration and demonstrated slower progression of amyloidosis-related polyneuropathy.

There is also evidence that TTR silencers may have beneficial cardiac effects, even if these therapies were not tested for that purpose.

Hence, trials to assess the efficacy of TTR silencers in ATTR-CM are ongoing: APOLLO-B (A Study to Evaluate Patisiran in Participants with Transthyretin Amyloidosis With Cardiomyopathy), HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy), and CARDIO-TTRansform (A Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx in Participants With Transthyretin Mediated Amyloid Cardiomyopathy). Other agents, including monoclonal antibodies targeting Serum Amyloid Protein (SAP), are leading fibrils toward degradation are under investigation (phase 2 study in progress).

Strengths and limitations of the present study need to be discussed.

First, we retrospectively collected all initial cases of ATTR-CM in our single center.

Second, we sought to be descriptive and to analyse our patients, the results of our management with no specific objective in terms of comparison of strategies. Our work should not be over-interpreted and it is just a report about one cohort.

We observed interesting results with natriuretic peptide but again, it is descriptive, and it shouldn't be overinterpreted. The main message is probably based on the initial characteristics of our patients: they have a decrease (severe) in GLS, a severe LVH and a high proportion of AFib so the diagnostic might have been to delayed. We can consider our work as a warning for increasing the degree of awareness in our community and then for an earlier referral for treatment. The same observation is made for the AL-amyloidosis⁶⁵.

Third, as a retrospective study, not all laboratory and echocardiographic parameters could be collected for all patients. We did not collect and quantify some physical findings in ATTR-CM patients as pain, itching, chest pain, that can be disabling for patients.

Finally, we could only show a rate of death, mostly from heart failure in the not treated group.

Further studies will have to take advantage of our observations.

Tafamidis is still considered as an orphan medication for a rare disease, and this justifies its extremely high price, for a disease that might not be so rare. Due to its price, and the result of some findings that show a prevalence of 13% among patients hospitalized with heart failure with preserved ejection fraction and an increased wall thickness. The burden of this pricey therapy could be considerable, unless we reconsider the orphan drug designation, that could be used only for genetical ATTR-CM. The medication is available for the competency centers according to a RTU. There is no medico-economical study that applies to the French healthcare system, but the medicine has been validated and re-imbursed for its relevance in all the industrialized countries. Post-marker evaluation of the medico-economical value of the treatment are on-going in Canada.

CONCLUSION

In this monocentric study, we collected all cases of confirmed ATTR-CM in the Rennes University-Hospital between September 2015 and September 2019 and assessed the clinical presentation, biological and TTE parameters from the introduction of Tafamidis and after 1-year follow-up. Nowadays, there is a clear and non-invasive diagnosis approach which should ease the management of these patients. Our results tend to support a more aggressive diagnostic approach. It will lead to the adaptation of the medical management of the heart failure and in the youngest and less advanced patients too, an as early as possible introduction of Tafamidis (costly but effective therapy for stopping the disease progression).

Table 1 and 2: Baseline characteristics of the population

Variable	Total (N)	Mean	SD	Min	Max
Age	70	81.4	7.54	53	92
Weight (Kg)	69	71	10.5	50	110
Height (cm)	69	167	7,69	144	188
Body surface area (m2)	69	1.79	0.158	1.45	2.35
Heart beat (BPM)	70	74.7	13.5	46	100
Aortic diameter (mm)	68	35.2	12.6	23.7	42
Annulus diameter (mm)	68	23	7,73	19	25.5
IVSd (mm)	69	16.2	4.29	1.08	27.4
IVSs (mm)	69	19.2	4.07	10.0	32.0
LV end diastolic diameter (mm)	69	45.3	6.50	24.0	62.0
LV end systolic diameter (mm)	69	34.4	8.38	4.00	50.5
LV mass (gr/m2 ASE)	65	168	70.9	66.0	430
End systolic volume of left ventricle	69	52.9	29.2	15.0	155
End diastolic volume of left ventricle	69	107	39.2	20.0	227
LVEF (simpson biplan%)	69	53.4	14.6	17.0	81.0
Left ventricle sphericity index	69	0.514	0.0796	0.372	0.757
DPS (Dispersion Peak Standard msec)	60	71.1	29.2	23.0	170
LV mean GLS	66	-10.6	6.00	-3.2	-25.3
Mitral filling time/RR	67	0.45	0.12	0.15	0.77
Deceleration time of mitral valve(msec)	69	175	65.0	84.0	439
E/A	32	1.67	1.12	0.680	5.07
E/e' mean	66	19.9	9.40	9.30	62.5
e' mean (cm/s)	68	5.19	1.41	1.70	9.30
Aa mean (cm/s)	38	5.31	3.04	0.00	9.70
Sa mean (cm/s)	66	4.98	1.36	2.00	8.60
S' wave tricuspid valve TDI (cm/s)	68	9.75	2.80	3.00	17.0
TAPSE (mm)	64	16.2	5.74	8.00	34.0
Left atrium diameter PSLA (mm)	68	48.2	8.22	29.7	70.8
Left atrium transversal diameter A4C (mm)	69	49.7	6.65	37.5	68.0
Left atrium long diameter A4C	69	66.4	9.93	30.6	86.0
Left Atrium volume BIPLANE (ml)	69	102	33.8	29.0	202

Left atrium Volume index (mL/m2)	69	57.4	17.2	20.9	119
Diameter transversal right atrium A4C(mm)	69	45.3	9.10	26.0	68.0
Right atrium long axis diameter (mm)	68	60.2	9.22	28.7	79.5
Right atrial volume index (ml/m2)	68	38.7	16.9	10.0	78.0
Left atrium strain reservoir (%)	58	-9.57	6.45	-1.00	-34.1
RV_Long axis mm PSLA (mm)	67	34.4	7.06	23.5	70.6
RV fractional shortening surface	67	0.38	0.14	0.08	0.80
TV Annulus (mm)	67	35.7	5.95	25.0	52.5
RV wall strain mean (%)	54	-16.6	6.19	-6.60	-31
Variable cardiac output (L/min)	69	4.82	1.89	1.99	13.2
Cardiac index (ml/min/m2)	69	2.72	1.14	1.20	7.63
AVA (cm2)	61	2.07	0.881	0.560	4.30
Mitral regurgitation (/4)	68	1.10	0.650	0	2
Tricuspid regurgitation (/5)	69	1.42	0.902	0.00	5.00
Variable tricuspid regurgitation vmax (m/s)	65	2.74	0.686	0.00	3.90
Pulmonary artery systolic pressure PASP (mmhg)	66	43.5	12.5	20	75
Hemoglobin g/dl	67	13.6	1.51	9.40	16.4
Platelet (G/L)	67	204	78.3	3.70	563
natremia (mmo/L)	66	140	10.5	128	220
Creatinin (μmol/L)	67	114	40.1	40.0	208
Clearance (Cockcroft ml/min)	66	57.0	19.5	23.0	103
AST (ui/L)	65	68.2	301	0	2453
ALT (ui/L)	65	50.8	183	10	1493
GGT (ui/L)	65	104	123	12	758
ALP (ui/L)	65	89.2	49.8	23	292
total_bilirubin (mmol/l)	63	12.6	7.67	4.00	44.0
Troponine (pg/ml)	56	62.5	54.7	11.0	258
Ntprobnp_(pg/ml)	66	5172	5694	358	30267
Transferrin sat%	45	23.9	9.01	4.00	42.0
PT (%)	65	66.6	27.7	1.23	110
Loop diuretic	65	105	222.8	0	500

Table 2

Variable	Total (N)	% of Total
Urinal Ig light chain negatif	58	90.6
Blood Ig light chain	51	78.5
Genetic test	67	95.7
ATTRwt	60	87.0
ATTRm	7	10.1
Biopsy	56	81.2
Sinusal rythm	31	44.3
Heart block	54	77.1
Bone scintigraphy	70	100
VO2 max testing	24	34.3
Dyspnea	64	91.4
NYHA 0-1	10	14.2
NYHA 2	36	51.4
NYHA 3	23	32.9
Asthenia	34	49.3
Heart failure signs	47	67.1
HTA	46	66.7
Coronary artery disease	23	33.3
Hospitalization for heart failure	33	58.9
Atrial fibrillation	46	66.7
Pacemaker	19	27.5
Aortic stenosis	26	37.7
Chronic renal failure	38	54.3
Diabetes mellitus	9	13.2
Cancer	22	32.4
Carpal tunel syndrom	26	38.2
Lumbar spinal stenosis	11	16.2
Peripheral neuropathy/stroke	20	29.4
Cancer	22	32.4
Aortic stenosis	26	37.7
Loop Diuretic	52	74.3
ACE	19	27.5
ARB	9	13

Spirolacton or Eplerenon	29	42.6
Betablocker	0	0
VKA or DOA	47	67
Aspirin or P2Y12 inhibitors	16	23.1
Tafamidis	49	72.1

Figure 12: Flowchart

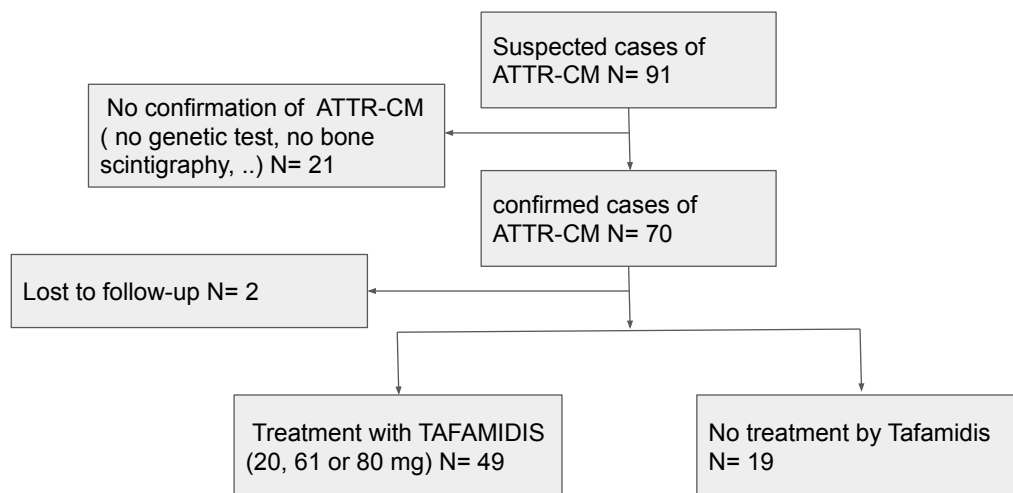


Table 3:

Independent Samples T-Test				
		statistic	df	p
LVEF simpson biplan	Welch's t	-1.63	24.0	0.117
Ea mean cm/s	Student's t	0.731	64.0	0.468
Follow up GLS	Student's t	0.194	42.0	0.847
Follow up_tricuspid_vmax m/s	Student's t	-0.576	41.0	0.568
Follow up LVEF	Student's t	-1.057	45.0	0.296
LVEF_evolution	Student's t	0.638	45.0	0.526

Table 4: Follow-up characteristics

Mann-Whitney-Wilcoxon test			
	χ^2	df	p
Ea cm/s	0.847	1	0.357
e' mean T0	1.165	1	0.280
E/e' mean T0	0.339	1	0.560
Cardiac output_L/min T0	1.157	1	0.282
Tricuspid regurg vmax T0	1.976	1	0.160
Ntprobnp pg/ml T0	5.562	1	0.018
Cardiac output L/min T1	0.585	1	0.445
e' mean cm/s T1	0.240	1	0.624
E/e' mean T1	0.121	1	0.728
NtproBNP pg/ml T1	3.429	1	0.064
E/Ea mean_evolution	0.270	1	0.603
e' mean evolution	0.742	1	0.389
Cardiac output evolution	2.251	1	0.134
Tricu reg evolution	2.241	1	0.134
NTproBNP evolution	3.866	1	0.049

Table 5: Follow-up characteristics

Variable	Total (N)	% of Total
readmission	25	37.9
Readmission for heart failure	18	27.7
NYHA 0-1	12	21.4
NYHA 2	26	46.4
NYHA 3	15	26.8
NYHA 4	3	5.4
DEATH	13	20

Figure 13: global evolution of follow-up parameters in the overall population

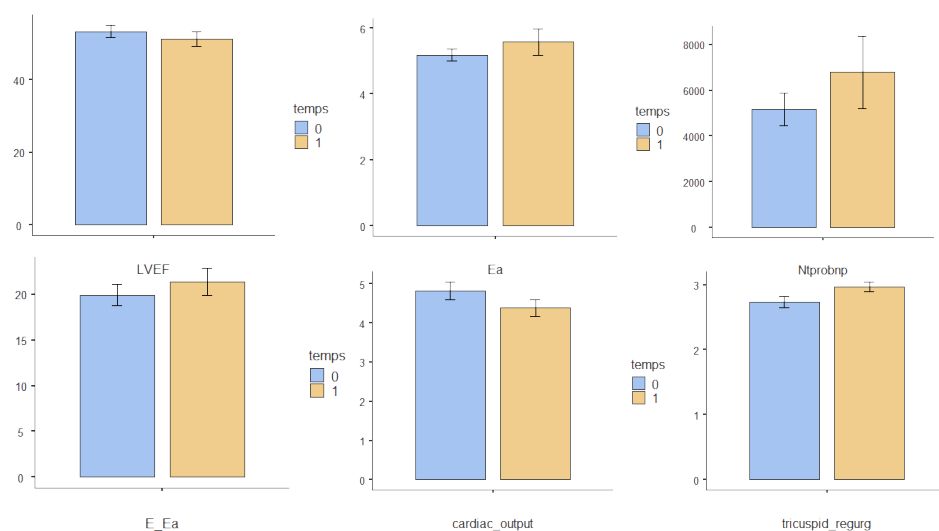


Figure 14: Evolution of follow-up parameters according the treatment with Tafamidis or without Tafamidis

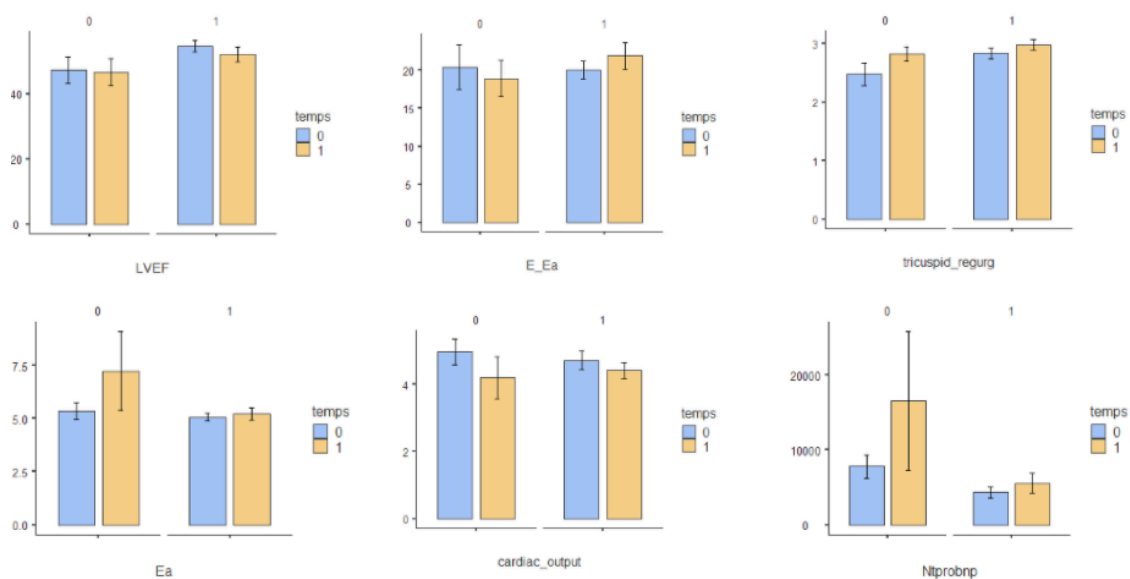


Table 6: Chi-2 test exploring a potential link between Tafamidis and readmission, and death (There is less death in the Tafamidis group p=0,032)

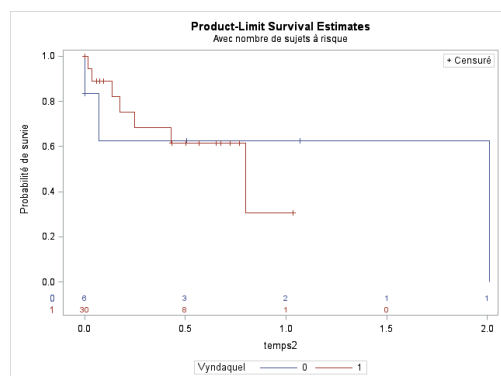
Variable	N	χ^2	df	p
readmission	65	0.719	1	0.397
Readmission for heart failure	64	0.589	1	0.443
Death	64	4.59	1	0.032

Table 7: Repeated Measures ANOVA (Non-parametric) of follow-up parameters between T0 and T1

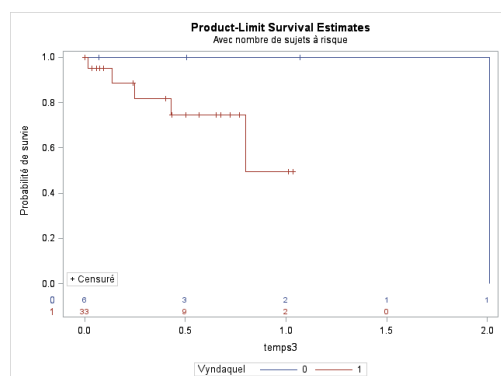
Variable	χ^2	df	p
LVEF	0.0870	1	0.768
E/e'	0.364	1	0.546
e'	0.857	1	0.355
Cardiac output	1.39	1	0.238
Tricuspid regurgitation Vmax	2.95	1	0.086
NtproBNP	1.96	1	0.162

Figure 15, 16, 17, 18: Events rate according to the presence of treatment by Tafamidis or not
The figure displays Kaplan–Meier curves of readmission for ALL CAUSES, readmission for HF, death for all causes, death for cardiovascular reason.

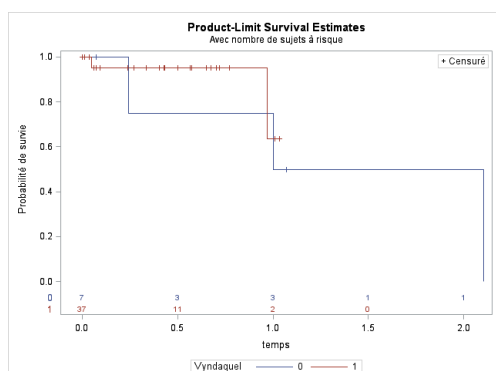
Survival free of readmission for all causes (p-Value log rank:0,95):



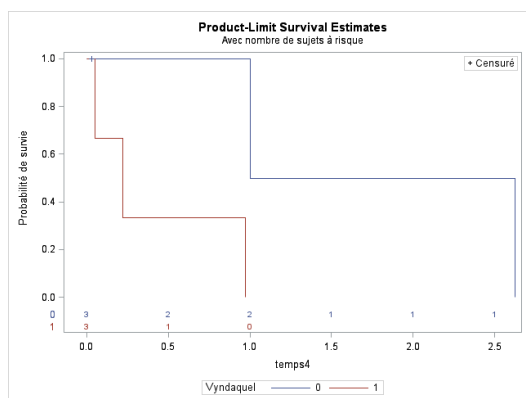
Survival free of readmission for HF (p-Value log rank:0,



Survival free of death for all reasons (p-Value log Rank = 0,57)

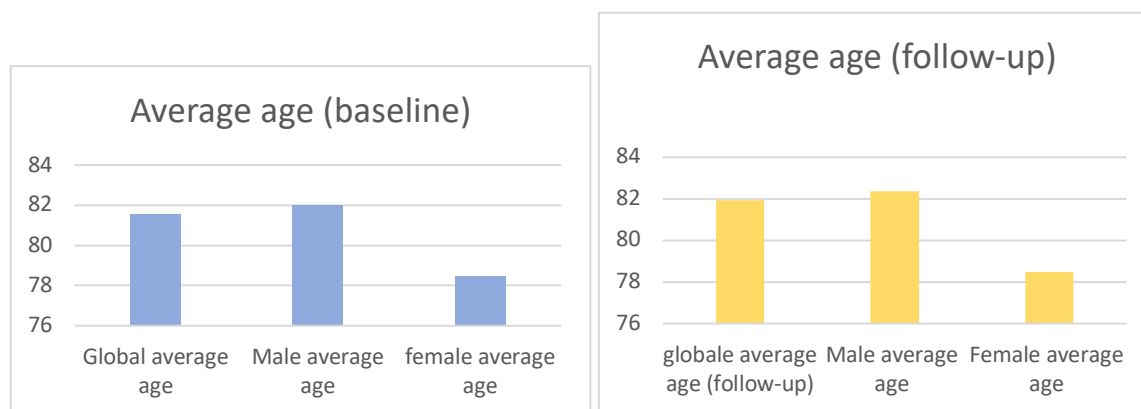


Survival free of death for CV reasons (p-Value log Rank = 0,06):



Fréquence Pctage en ligne Pctage en col.	Table de FU_rehospit par Vyndaquel		
	FU_rehospit(FU_rehospit)	Vyndaquel(Vyndaquel)	
		0	1 Total
	0	9	31 40
		22.50	77.50
	1	8	17 25
		32.00	68.00
		47.06	35.42
Total		17	48 65

Figure 19: Average ages of the population (baseline and follow-up)



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Résumé français

La cardiopathie amyloïde à transthyréine n'est plus considérée comme une pathologie rare dans sa forme sénile. Le traitement par Tafamidis a démontré une amélioration clinique et fonctionnelle des patients. Nous avons recueilli de manière rétrospective, les données cliniques, biologiques et échocardiographiques des patients sous TAFAMIDIS inclus dans le protocole ATRACT-Extension, et comparé aux patients non traités. Nous avons démontré une plus faible mortalité à 1 an, un taux de NtproBNP plus faible, mais sans modification des paramètres échocardiographiques. L'absence de modification des paramètres échocardiographiques, malgré le traitement spécifique sont probablement en lien avec une prise en charge tardive de la maladie.

La cardiopathie amyloïde à transthyréine devrait être prise en charge de manière précoce.

Résumé anglais [facultatif]

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