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Review Article

Breakthrough advances enhancing care in ATTR amyloid cardiomyopathy☆

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A B S T R A C T

Transthyretin amyloid cardiomyopathy (ATTR-CM) has been traditionally considered a rare and inexorably fatal condition. ATTR-CM now is an increasingly recognized cause of heart failure (HF) and mortality worldwide with effective pharmacological treatments. Advances in non-invasive diagnosis, coupled with the development of effective treatments, have transformed the diagnosis of ATTR-CM, which is now possible without recourse to endomyocardial biopsy in ≈70 % of cases. Many patients are now diagnosed at an earlier stage. Echocardiography and cardiac magnetic resonance have enabled identification of patients with possible ATTR-CM and more accurate prognostic stratification. Although radionuclide scintigraphy with 'bone' tracers has an established diagnostic value, the diagnostic performance of the bone tracers validated for non-invasive confirmation of ATTR-CM may not be equal. Characterising the wider clinical phenotype of patients with ATTR-CM has enabled identification of features with potential for earlier diagnosis such as carpal tunnel syndrome. Therapies able to slow or halt ATTR-CM progression and increase survival are now available and there is also evidence that patients may benefit from specific conventional HF medications. Cutting-edge research in the field of antibody-mediated removal of ATTR deposits compellingly suggest that ATTR-CM is a truly reversible disorder, bringing hope for patients even with advanced disease. A wide horizon of possibilities is unfolding and awaits discovery.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is the paradigm of infiltrative cardiomyopathy [1] and is caused by progressive accumulation of misfolded, cleaved and aggregated transthyretin (TTR) protein in the myocardial extracellular space [2]. The more prevalent non-hereditary form of ATTR (wild-type ATTR [ATTRwt]) amyloidosis is associated with aging whilst destabilizing mutations in the TTR gene hereditary underlie familial ATTR (variant ATTR [ATTRv]) amyloidosis, which can occur in younger adults [2,3]. The number of patients diagnosed with ATTR-CM has increased exponentially following adoption of cardiac magnetic resonance (CMR) imaging for suspected cases [4], and validation of an imaging based algorithm enabling diagnosis of ATTR-CM without recourse to tissue biopsy in ≈70 % of cases [5,6]. As a result, many patients are now diagnosed at an earlier stage, a shorter duration of symptoms being associated with better preserved cardiac structure and function. A 20 year nationwide UK study [7] reported a substantial increase in diagnosis of ATTR-CM, especially the wild-type, and with ≈60 % of patients diagnosed most recently during 2017–2021 having early National Amyloidosis Centre (NAC) ATTR stage I disease. This has provided the opportunity to broaden our understanding of disease progression and factors associated with its variable clinical course.

ATTR-CM has thus evolved from a rare, progressive and ultimately fatal cardiomyopathy to a relatively prevalent disorder with available and upcoming treatments that can slow or potentially halt disease progression. However, many aspects of ATTR-CM remain mysterious and numerous grey areas need to be addressed [8]. This review article will discuss advances and ongoing challenges in the field from a clinical expert perspective.

1. The contemporary paradigm for diagnosing ATTR-CM

1.1. Non-invasive confirmation of ATTR-CM using repurposed bone scintigraphy

The remarkable but unexplained myocardial uptake of various technetium labelled bone tracers into cardiac amyloid deposits does not

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in isolation confirm the diagnosis of ATTR-CM [9] since localisation also occurs in 40 % of patients with cardiac light chain (AL) amyloidosis, including Perugini grade 2 or 3 positivity in ≈10 % [2]. It is imperative both that the diagnosis AL amyloidosis is not missed, since such patients require urgent chemotherapy, and that it is excluded as an essential step in the non-invasive diagnostic algorithm for ATTR-CM through a comprehensive and sensitive search of monoclonal proteins in serum and urine. Demonstration of a clonal immunoglobulin or an abnormal kappa/lambda (κ/λ) serum free light chain (FLC) ratio supporting the presence of a clonal plasma cell dyscrasia denotes that a nonbiopsy diagnosis of ATTR-CM cannot be achieved. Of note, an abnormal κ/λ ratio may also occur in chronic kidney disease due to preferentially reduced clearance of κ versus λ FLCs. A recent refinement of the original nonbiopsy diagnostic algorithm taking the latter into account has increased the proportion of cases in which a non-invasive diagnosis of ATTR-CM can be established [10]; in a large, real-world, multicenter cohort of >3000 patients referred with suspected amyloid cardiomyopathy, Rauf et al. [10] redefined normal ranges for κ/λ ratio adjusted for estimated glomerular filtration rate (eGFR) to determine when an imbalance in FLCs is consistent with the degree of renal impairment and thus that a clonal immunoglobulin disorder can safely be ruled out (Table 1). For example, a patient with a Perugini grade 2 or 3 myocardial uptake and a modestly elevated κ/λ FLC ratio of 2.3 would not satisfy the original nonbiopsy criteria for ATTR-CM. However, if such a patient's eGFR was in the range of 30–60 ml/min, this κ/λ ratio can be considered normal, and a diagnosis of ATTR-CM is possible without recourse to biopsy.

1.2. Nuclear medicine imaging

The mechanisms underlying myocardial uptake of bone tracers and the differences in degree of myocardial uptake among different forms of amyloidosis is an area of active investigation [11]. Beyond the properties of specific amyloid fibril types, there is a growing suggestion that the diagnostic performance of different bone tracers may not be equal, which might lead to incorrect diagnosis in some cases. Worryingly, in an observational study of patients with suspected ATTR-CM who firstly underwent a ^{99m}Tc-HMDP scan followed within a median of 5 months by a second ^{99m}Tc-DPD scan, the Perugini uptake score differed in 33 % patients, all with ATTRwt-CM and all having greater uptake of ^{99m}Tc-DPD [11]. Given also that the basis for localisation of bone tracers to cardiac amyloid remains unknown, carefully conducted prospective clinical research studies in this area are required to ensure refinement and unified best practice in the diagnosis of ATTR-CM throughout the world [12].

Positron-emission tomography with computed tomography (PET-CT) has also been explored as a diagnostic tool for cardiac amyloidosis. A preliminary study using [18F]-florbetaben, a tracer developed to image brain Abeta amyloid in Alzheimer disease, potentially different and clinically informative patterns of cardiac localisation were reported among a cohort of 40 patients with AL-CM or ATTR-CM and 20 control subjects [13]. However, at present it must be emphasized that no type of nuclear medicine study nor any other form of cardiac imaging has been validated to confirm amyloid type.

Table 1
κ/λ free light chain reference ranges according to eGFR.

eGFR (mL/min/1.73 m^2)	"Normal" κ/λ ratio
> 90	0.26–1.65
60–90	0.26–2.00
30–60	0.26–2.50
< 30	0.26–3.10

Legend: eGFR, estimated Glomerular Filtration Rate; κ/λ, kappa and lambda. Values of free light chains outside these cut-offs (when measured with FreeLite assay) are suggestive of clonality.

1.3. Cardiac magnetic resonance (CMR) imaging

CMR imaging provides essential information on myocardial tissue composition and is a cornerstone of the diagnostic work-up of suspected amyloidosis and other cardiac conditions presenting with increased wall thickness [14,15]. CMR with extracellular volume (ECV) mapping can measure the extracellular space between cardiomyocytes where amyloid accumulates. In non-amyloid hearts, cardiomyocytes are densely packed and the ECV represents ~22–28 % of the total myocardial volume, a generally accepted normal ECV being regarded as ≤30 % [16]. Since expansion of the extracellular matrix occurs at the very initial stages of infiltration, elevated ECV is also an early marker of disease becoming abnormal before structural changes or subendocardial late gadolinium enhancement (LGE) are evident; the latter typically manifests when the ECV value exceeds ≈40 % [17]. ECV is an unconditional measures of amyloid burden in the heart as compared to serum biomarkers (i.e., troponin and natriuretic peptides) which reflect function [15,18].

2. Natural history of ATTR-CM and early clinical markers

2.1. Cardiac structural and functional consequences of amyloid deposition

The natural history of ATTR-CM is characterised by progressive amyloid deposition leading to increased wall thickness, with diastolic and systolic dysfunction and development of heart failure (HF). Amyloid deposition results in reduced ventricular dimensions and increased ventricular stiffness with a fixed stroke volume and causes an upward and leftward shift in the end-diastolic pressure–volume relationship. Under these circumstances, maintaining an adequate cardiac output is dependent on the ability to increase the heart rate, which explains poor tolerability to beta blockers therapy in advanced ATTR-CM [19]. The likelihood of abnormal echocardiographic findings increases in parallel with the severity of cardiac amyloid infiltration. Global longitudinal strain (GLS), mitral annular plane systolic excursion (MAPSE), left ventricle (LV) mass index and E/e' are the parameters most likely to be abnormal in early stages of cardiac amyloid infiltration [20]. Tricuspid annular plane systolic excursion (TAPSE) and stroke volume index are abnormal in intermediate stages of cardiac infiltration, while LV and RV ejection fraction and RA and left atria area index become abnormal in the advanced stages of ATTR-CM [20]. Amyloid deposition also affects the conduction system with development of atrio-ventricular (AV) delays, most commonly presenting with prolongation of the PQ interval (i.e., first degree AV block) and intraventricular delays with bundle branch blocks, leading to a significant proportion of patients requiring permanent pacemaker implantation (PPM) due to brady-arrhythmias [21]. The presence of a wide QRS interval (>120 ms) is the only ECG parameters being independently associated with the development of high-grade AV block [22]. A recent multicentre study has investigated baseline ECG predictors of PPM in AL-CM and ATTR-CM and identified an increased risk among patients with history of atrial fibrillation (any type), a PQ interval >200 ms and a QRS interval >120 ms [23]. The absence of all three risk factors identified patients without need for PPM in the following 6 months with an accuracy of 91.8 % and a negative predictive value of 92 %. Advanced stages of disease may also be associated with an increased risk of tachyarrhythmias, but the prognostic value of non-sustained ventricular tachycardia has been investigated with conflicting results [24–26]. Although some algorithms have been developed to identify patients at higher risk of arrhythmic death, conclusive evidence is lacking as to which parameters should be used to stratify this risk and hence guide implantation of cardioverter defibrillator for primary prevention of arrhythmic death.

2.2. Early clinical and echocardiographic markers

Characterising the wider clinical phenotype of patients with ATTR-

CM has enabled identification of features with potential for earlier diagnosis. Soft tissues have been identified as a common extracardiac site for ATTR amyloid deposition. In particular, carpal tunnel syndrome (CTS) has been identified as a red flag to rise suspicion of ATTR-CM among patients with increased ventricular wall thickness, and as early clinical marker which can precede by 5 to 10 years the future development of ATTR-CM [27,28]. Although patients with AL amyloidosis can present with CTS, the frequency of this finding in AL amyloidosis is comparable to that of the general population, with a lifetime prevalence of 3.1 % of developing this condition [27]. By contrast, CTS is strongly associated with ATTR amyloidosis, both wild-type and variant [27]. In a retrospective study of patients who had an echocardiogram at the time of carpal tunnel surgery, the presence of increased wall thickness in the absence of abnormal loading conditions (i.e., unexplained cardiac hypertrophy) was associated with a higher likelihood of being diagnosed with ATTR-CM during the follow up [29]. In a recent, prospective analysis of 98 adults undergoing carpal tunnel surgery, TTR amyloid deposits in the tenosynovial tissues were found in 10 % of cases and a diagnosis of ATTR-CM was established in 2 of them at the time of surgical intervention [30]. In a consecutive cohort of 185 patients >50 years of age undergoing carpal tunnel release, amyloid deposition was identified in the tenosynovium in 54 (29 %) cases, the vast majority of wild- type ATTR type [31]. A recent study reported on the prevalence of undiagnosed amyloid cardiomyopathy among 250 patients who had bilateral carpal tunnel release between 5 and 15 years before enrolment [32]. All patients underwent comprehensive diagnostic work-up for amyloidosis and amyloid cardiomyopathy was established in 5 % of them (ATTRwt-CM in all cases). The prevalence of ATTR-CM achieved 8.8 % among men and 21.2 % among men aged 70 years or older with a BMI <30 kg/m2, suggesting a potentially meaningful clinical impact for early diagnosis if systematic screening for amyloidosis is undertaken in this population. Altogether, these data strongly support the use of CTS as the earliest clinical marker of disease to raise suspicion of ATTR-CM and to identify subjects at risk of developing the disease in the future who need to be monitored over time.

A remarkable male predominance has been reported in ATTR-CM approaching >80–90 % of cases, and exceeding this in ATTRwt-CM, but the reason is not known [33]. Increased wall thickness is the hallmark of ATTR-CM and, according to recent international guidelines on diagnosis and management of cardiac amyloidosis, a LV wall thickness ≥12 mm in presence of at least one red flag should raise the suspicion of ATTR-CM [4]; however, the proposed cut-off value is not sex-specific. Normal reference values for LV wall thickness in women are lower than in men. Therefore, adoption of the same threshold might lead to women being underdiagnosed (i.e., lower number of female patients fulfilling thickness criteria) and diagnosed at a later disease stage compared to men, providing the rationale for the perception of male predominance in ATTR-CM worldwide. This hypothesis was elegantly suggested in a recent analysis of deep phenotyping of >1700 ATTR-CM patients at presentation, in which female patients had a thinner interventricular septum (IVS) thickness compared to male patients when using absolute values [33]. However, when values were indexed for body surface area (BSA), female patients had a significantly greater IVS thickness in keeping with a worse cardiac phenotype compared to male patients. There was no sex difference in survival rates, but women were on average 3 years older than men at clinical presentation. These findings suggest that using non-indexed IVS thickness values may lead to inaccurate perception of a milder clinical phenotype in women compared to men, and highlight the need for developing sex-specific indexed thresholds for wall thickness (by BSA or by height) to refine criteria of cardiac involvement in males and females [33,34]. Large prospective studies are required to assess the clinical impact of sex-specific cut off values in patients referred for suspected amyloidosis.

3. Disease staging

Several staging systems based on serum biomarkers have been developed and clinically validated in ATTR-CM, and include natriuretic peptides (either BNP or NT-proBNP), cardiac troponin (type T or I), and estimated glomerular filtration rate. NT-proBNP has an established independent prognostic role in ATTR-CM and changes over time have been demonstrated useful for monitoring disease progression. The prediction model developed by Grogan et al. [35] and the NAC ATTR staging system proposed by Gillmore et al. [36] are the most commonly used in clinical practice. The latter score has some specific advantages including a) the absence of troponin, which has great heterogeneity in assay accuracy and methods of quantification; b) the adjustment of the model for the effect of TTR variant on survival, with p.(Val142Ile) TTR associated with the poorest prognosis compared to ATTRwt-CM [36]; and c) the initial evidence that changes in the NAC staging system might predict survival throughout the clinical course of disease [37]. Recently, the NAC ATTR stage I (defined as a NT-proBNP <3000 ng/L and an eGFR ≥45 ml/min) has been further sub-stratified according to NT-proBNP concentration and loop diuretic dose at diagnosis, patients diagnosed with stage Ia and Ib having median survivals of >100 months and 75 months respectively [38]. Of note, although patients with early (i.e., NAC stage Ia) ATTR-CM had excellent long-term survival, they did experience substantial cardiovascular morbidity during follow up. Similar findings have been recently reported in a study on patients with likely ATTR-CM and no HF signs and symptoms (i.e., NYHA class I), no diuretic therapy at diagnosis and a NT-proBNP <600 ng/L [39]; within four years of follow-up, 1 in 3 of these patients did developed HF symptoms and a similar proportion died or required cardiac transplant. Therefore, it is clear many individuals with early ATTR-CM do go on to develop substantial cardiac morbidity and mortality, suggesting a potential role for disease-modifying therapy even in the absence of HF symptoms.

An increasing number of parameters beyond biomarker-based staging systems have an established association with outcome. In a study of >800 untreated patients with ATTR-CM who had echocardiography at diagnosis, an independent association with all-cause mortality was demonstrated for severe aortic stenosis (AS), stroke volume index, RA area index and GLS, also after adjustment for NYHA class and the NAC ATTR stage [40]. Among ATTR-CM patients without severe AS, E/e' was also independently associated with outcome, with no changes in the other predictors. Studies using serial echocardiographic evaluation have recently demonstrated that TTR genotype influences cardiac structural and functional changes during follow up. In particular, V122I-associated ATTRv-CM seems to be associated with the most rapid rate of disease progression, followed by ATTRwt-CM (intermediate rate) and T60A-associated ATTRv-CM, which shows the slowest rate of progression. Of note, valves and sub-valvular apparatus are commonly involved in ATTR-CM as this condition is either a myocardial or a valvular disease model. ATTR-CM and AS coexist in a significant proportion of cases [28], described as dual pathology. The prognostic burden associated with the presence of severe AS is independent from that of ATTR-CM. In multicentre studies, patients with dual pathology had similar outcomes following transcatheter aortic valve replacement (TAVR) compared to patients with isolated severe AS. Of note, mortality rates were not significantly different among patients with dual pathology and those with isolated AS when they were managed conservatively [41]. In the past, AS replacement was considered futile in presence of an untreatable and fatal condition such as amyloid cardiomyopathy. Although patients with dual pathology have a more decompensated clinical phenotype at presentation, available data strongly suggest that the presence of ATTR-CM should not preclude *per se* suitability for TAVR in patients with severe AS. The possibility of isolated amyloid deposition in the aortic valve as an independent entity from the presence of ATTR-CM has been recently suggested by a group of Indian researchers [42] using EMB coupled with bone tracer scintigraphy to investigate the presence of

amyloid cardiomyopathy among patients with severe AS who underwent surgical aortic valve replacement. Whether isolated valvular amyloidosis exists and should be considered an entity of clinical relevance is unclear and requires further large studies.

Atrio-ventricular valves are commonly abnormal as a result of cardiac amyloid deposition inducing a slow, but progressive process of cardiac remodelling affecting the fibrous annulus, tendon cords and papillary muscles. In heavily infiltrated hearts, this process may lead to a dislocation of the valve annulus, a distortion of the sub-valvular apparatus and may also extend to valve leaflets which can be directly infiltrated by amyloid deposition or restricted in their movements when an abnormal balance between closing and tethering forces during the cardiac cycles has established [43]. Mitral (MR) and tricuspid regurgitation (TR) are common findings, with 60–65 % of patients with ATTR-CM presenting with any degree of MR or TR. Of note, the development of new valve insufficiency or worsening in MR and TR is independently associated with a poorer survival [43]. Dynamic changes in the degree of valve regurgitation (even mild changes) cause a decrease in SV which, despite small in absolute terms, is hemodynamically significant for the amyloid infiltrated heart, resulting in a substantial reduction in forward flow and cardiac output (because of associated chronotropic incompetence) [43]. Atrial infiltration results in increased stiffness and reduced contraction, leading to atrial electro-mechanical dissociation in 20 % of patients with ATTR-CM at presentation [44]. This is defined as severely impaired atrial contraction accompanied by normal sinus rhythm on surface electrocardiogram and has been recently associated with poor survival [44].

Although CMR imaging cannot reliably distinguish the specific type of amyloid (i.e., ATTR vs AL), it can inform on disease stage. The presence and pattern of late gadolinium enhancement (LGE) is an independent predictor of outcome (even after adjusting for other know predictors), with transmural LGE being associated with the poorest survival compared to subendocardial LGE or none [17]. ECV value derives from isolation of signal from the extracellular space and is therefore a surrogate measure of cardiac amyloid burden. Unsurprisingly, ECV is a strong independent predictor of outcome in amyloid cardiomyopathy and, uniquely, it has recently proven useful for monitoring disease progression and tracking response to treatment in both AL and ATTR amyloidosis.

Beyond its diagnostic value, studies have failed to demonstrate any independent prognostic value of myocardial uptake in ATTR-CM [45–47]. Whilst Perugini grade is plainly influenced by cardiac amyloid burden, ranging from no cardiac amyloid infiltration in Perugini grade 0 to substantial cardiac amyloid infiltration in Perugini grade 2, there is a poor correlation with strong uptake and other cardiac findings and scoring of grade 3 is largely due to additional uptake in skeletal muscle amyloid obscuring the bones [14]. However, patients with ATTRwt amyloid associated with Perugini grade 1 scintigraphy do have excellent long-term survival [45]; of course, such patients by definition cannot be diagnosed to have ATTR-CM using the nonbiopsy algorithm, and are typically identified incidentally or as a result of having had ATTR amyloid identified histologically for some reason elsewhere in the body. An exception are patients with certain rare TTR variants that seem to bind bone tracers less avidly, and hence grade 1 or even grade 0 scans can occur in such patients despite overt or even advanced ATTRv-CM. A potential association of diffuse RV uptake assessed on single-photon emission tomography with worse outcomes has been reported in patients with ATTR-CM [48], but large studies are required.

4. Pharmacological treatment of ATTR-CM

4.1. Conventional HF medications

Old studies reporting poor tolerability and/or futility of HF medications in ATTR-CM were mostly conducted in patients with advanced disease. In recent years, earlier diagnosis on ATTR-CM has enabled assessment of the potential value of HF medications in a substantial number of patients. Of note, a recent analysis on conventional HF medication conducted at the National Amyloidosis Centre in a cohort of >2000 patients provided the first evidence of a potential benefit of these medications in ATTR-CM [19]. Patients with ATTR-PN or mixed phenotype were excluded as many have autonomic neuropathy limiting the use of conventional HF medication. Treatment with mineral-corticosteroid receptor antagonists (MRAs) was independently associated with a lower risk of mortality in the overall population and in the subgroup with a LVEF>40 %, but not in patients with a LVEF≤40 % [19]. Therefore, the benefit derived from MRAs may be greater in earlier stages of disease. Conversely, treatment with low-dose beta blockers (BBs) was associated with a lower risk of reduced mortality only in patients with a LVEF≤40 %, even after exclusion of patients with concomitant ischemic heart disease [19]. BBs have an established role in the treatment of HF with reduced ejection fraction in which have the ability to counteract the activation of adverse adrenergic and neurohormonal molecular pathways. The findings of this study, which is the largest analysis of conventional HF medications in ATTR-CM, strongly support the use of MRAs in all patients with ATTR-CM, especially in presence of a LVEF>40 %, and the use of low-dose BBs in patients with a LVEF≤40 %. Sodium-glucose cotransporter-2 inhibitors are a further class that holds promise for the treatment of ATTR-CM following demonstration of safety and efficacy across the full spectrum of ejection fraction in randomised clinical trials [49].

4.2. Understanding the target of treatment in amyloidosis

In all forms of amyloidosis studied which are amenable to treatment, achieving a greater reduction in the circulating concentration of the amyloid precursor protein is associated with better clinical outcomes. For example, in AL amyloidosis, patients achieving a complete hematological response (i.e., undetectable precursor protein) exhibit the best survival compared to patients with lower magnitude or no reduction in precursor protein following chemotherapy [50]. In ATTR amyloidosis, better understanding of the amyloidogenic cascade, though much is yet to be elucidated, has led to major advances in pharmacological treatment of ATTR-CM, which is now a treatable condition (Table 2). Whilst disruption and subsequent misfolding of the normal circulating TTR tetramer plainly must occur in ATTR amyloid fibril formation [2] (Fig. 1), the widely cited simple paradigm of the TTR tetramer dissociating into its sub-units as a critical first event, which can be modelled in vitro, has been challenged by Bellotti and colleagues who elucidated an alternative novel mechano-enzymatic cleavage mechanism for ATTR amyloidogenesis. Beginning with work on the particularly 'aggressive' p.(Ser72Pro) TTR variant, identified in a British family with very early onset and severe hereditary ATTR amyloidosis [51,52], these researchers concluded that variants of TTR confer increased intrinsic susceptibility to proteolytic cleavage of TTR, even in its tetrameric form, and that biomechanical forces provided by the shear stress of physiological fluid flow were additionally required for fibrillogenesis to occur. Enzymatic cleavage and dissociation could very well occur *in situ* within the interstitium of the heart muscle without dissociation of TTR in the plasma. The proposed mechano-enzymatic cleavage pathway not only seems to offer a highly plausible explanation for ATTR amyloid formation *in vivo,* but also provides a biological rationale for the 'tropism' of ATTR amyloidosis to anatomical sites in which notable mechanical forces occur - i.e., the heart and carpal tunnel.

4.3. TTR stabilizers

Tafamidis, which enhances the stability of TTR, is currently the only licensed therapy for ATTR-CM with a class I, level of evidence B [53] recommendation for treatment of patients with either ATTRwt-CM or ATTRv-CM and NYHA class I and II symptoms, regardless of coexisting ATTR-PN, in latest guidelines on diagnosis and treatment of HF by the

Table 2
Treatments for ATTR-CM.

Medication	Tafamidis	AG10	Patisiran	Vutrisiran	Eplontersen	NTLA-2001	NI006
Mechanism of action	Stabilizer	Stabilizer	siRNA	siRNA	ASO	CRISPR-Cas9	Recombinant human anti-ATTR Ab
Trial	ATTR-ACT	ATTRIBUTE-CM	APOLLO (substudy) and APOLLO-B	HELIOS-B	CARDIO-TTRansform	NCT04601051	NCT04360434
Dosage	80 mg orally once daily	800 mg orally twice daily	80-min intravenous infusion based on body weight every 3 weeks (< 100 kg = 0.3 mg/kg; > 100 kg = 30 mg)	25 mg subcutaneous injection every 3 months	45 mg subcutaneous injection monthly	0.1 mg/kg or 0.3 mg/kg single intravenous infusion	From 0.3 to 60 mg/kg intravenous infusion (dose finding study) At least 10 mg/kg for clinical benefits
Premedication*	Not needed	Not needed	√	√	Not needed	√	Not needed
Vitamin A supplementation	Not needed	Not needed	Needed	Needed	Needed	Needed	Not needed
Stage of approval	ESC and FDA approved for ATTRv-PN and ATTR-CM	–	FDA approved for ATTRv-PN	FDA approved for ATTRv-PN	Ongoing evaluation	Ongoing evaluation	Ongoing evaluation
Neurological Outcomes	Reduced the progression of neuropathy assessed by multiple scales	–	APOLLO: ↓ mNIS+7 ↓ Norfolk QOL-DN ↓ COMPASS-31 ↑ Gait speed	HELIOS-A: ↓ mNIS+7 ↓ Norfolk QOL-DN	NEURO-TTRansform ongoing	Awaiting trial	–
Cardiological Outcomes	↓ all-cause mortality and CV-related hospitalisation ↑ KCCQ-OS ↑6MWT	↓ hierarchical endpoint of all-cause mortality, CV-related hospitalization, NT-proBNP and 6MWT ↑ KCCQ-OS ↓ NT-proBNP ↑ TTR	APOLLO cardiac subgroup: ↓ NT-proBNP ↑ Gait speed ↓ LV wall thickness ↑ LVEDV APOLLO-B: ↑6MWT Trend towards ↓ all-cause mortality and hospitalization	HELIOS-B trial ongoing	CARDIO-TTRansform trial ongoing	Awaiting trial	↓ NT-proBNP ↓ Troponin T ↓ myocardial uptake of bone tracer ↓ ECV values on CMR Favorauble change in echocardiografic parameters
Potential adverse effect	–	–	Vitamin A deficiency Infusion related reactions Peripheral oedema	Vitamin A deficiency	Vitamin A deficiency Headache	Vitamin A deficiency Headache Nausea Chills Rhinorrhea	Arthralgia and musculoskeletal events Cytokine release syndrome Infusion related reactions Low platelet count

* Premedication may include corticosteroids, paracetamol, ranitidine and/or antihistamine

Legend: Ab, Antibodies; ASO, antisense oligonucleotide; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CV, cardiovascular; FDA, Food and Drugs Administration; ATTRv-PN, variant ATTR polyneuropathy; LV, left ventricular; LVEDV, left ventricular end diastolic volume; mNIS+7, Modified Neuropathy Impairment Score +7; NT-proBNP, N-terminal pro B-type natriuretic peptide; QOL-DN, Quality of Life Questionnaire-Diabetic Neuropathy; siRNA, small interfering RNA.

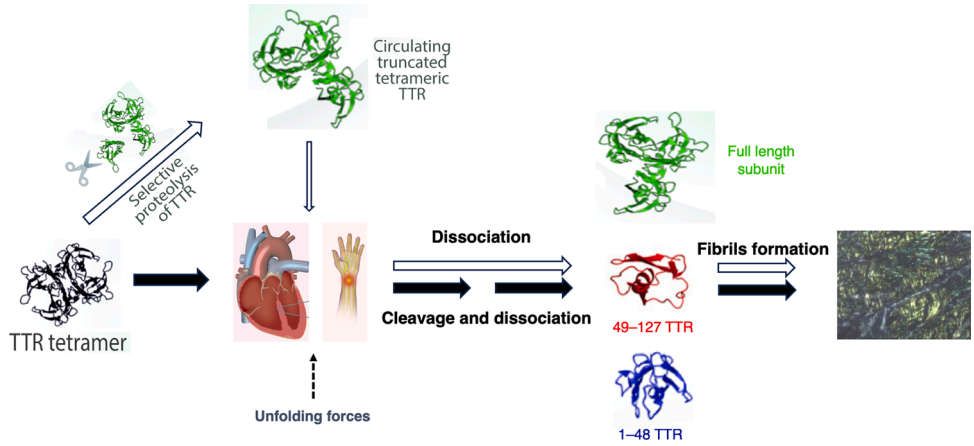

Fig. 1. Pathophysiology of transthyretin synthesis with main pathways of the amyloidogenic cascade and most common sites of amyloid deposition leading to clinical phenotypes. Legend: BNP, brain natriuretic peptide; HF, heart failure; NT-proBNP, N terminal brain natriuretic peptide; TTR, transthyretin. Modified from [2].

European Society of Cardiology (ESC). A recent analysis using data from the ATTR-ACT trial and its long-term extension phase [54] suggested an association between continuous treatment with tafamidis and better survival also in ATTR-CM patients with NYHA class III compared to the group on placebo-tafamidis, although further studies are required to clarify its role in advanced disease. The results from the ATTRibute-CM trial testing another stabilizer, acoramidis, have recently been presented and showed consistently positive results across all endpoints [55].

4.4. TTR gene silencers

Via very different mechanisms, antisense oligonucleotide (ASO) and small interfering RNAs (siRNAs) therapies [2] trigger degradation of TTR mRNA in hepatocytes resulting in knockdown of serum TTR concentration by around 75–90 % compared to pre-treatment values. Patisiran was the first siRNA therapy to be licenced, and has acquired an excellent safety record. The seminal APOLLO trial in patients with ATTR-PN confirmed high efficacy in reducing progression and even reversing aspects of neuropathy, whilst a sub-group analysis of participants defined to have co-existing cardiomyopathy suggested benefit in terms of myocardial structure and function assessed by echocardiography, reduced NT-proBNP serum levels and improved 10-m walk test gait speed compared to placebo [56]. More recently, the APOLLO-B study evaluated safety and efficacy of patisiran in patients with wild type and variant ATTR-CM. The primary endpoint of the study was met with reduction in rate of decline in the 6-minute walking test (6MWT) distance and Quality of Life Questionnaire (KCCQ) over a 12 months treatment period. In an open-label extension phase, at 18 months treatment with patisiran was associated with sustained benefit and a non-significant trend towards reduced rates in the composite outcome of all-cause death and hospitalizations. The value of second-generation ASOs and siRNAs is currently under investigation in randomised clinical trials of eplontersen and vutrisiran in patients with ATTR-CM.

4.5. TTR gene editing

In a quantum leap beyond gene silencing, profound and sustained suppression of TTR production has recently been achieved with just a single administration of NTLA-2001, the first CRISPR-Cas9-based gene-editing therapy to have ever been delivered *in vivo* [57]. In a phase 1, single-ascending dose study in patients with ATTR-CM, NTLA-2001 was well tolerated in each of the 12 participants, who had NYHA class I to III heart failure symptoms, and the treatment achieved at least 90 % reduction in serum TTR concentration by day 28, which was sustained through 4–6 months follow-up. Later phase trials are ongoing with this totally novel single-shot therapy, which is likely to have considerable appeal among the older patient population that accounts for most cases of ATTR-CM.

4.6. Antibody-mediated removal of ATTR amyloid

Whilst development of various treatments designed to inhibit amyloid formation has been truly extraordinary, none target the existing amyloid deposits and there remains a major unmet need for therapy that enhances their naturally very slow clearance. For unknown reasons, amyloid deposition appears to evoke very little reaction in the tissues, and amyloid fibrils are known to be very stable and resistant to enzymatic degradation in vitro. The potential for antibody mediated elimination of amyloid has been pursued for some time with regard to CNS Abeta amyloid in Alzheimer disease, with a notably chequered history, but its plausibility in systemic ATTR amyloidosis has lately gained much support from two seminal studies. A phase 1 double-blind placebo-controlled randomized trial of NI006 [58], a recombinant human IgG1 antibody that binds all non-soluble conformations of TTR, was conducted in 40 patients with ATTR-CM; whilst there were some adverse effects, there was a promising indication of efficacy suggested by decreases in serum cardiac biomarkers, cardiac uptake of bone tracers and myocardial ECV values, which would be consistent with a reduction in cardiac amyloid load [58]. Further evidence suggesting a therapeutic role for anti-amyloid antibodies emerged from mechanistic investigations of three unique ATTR-CM patients in whom unprecedented spontaneous recovery occurred in association with near complete clearance of their cardiac amyloid deposits [59]. Circulating polyclonal IgG antibodies specific for the ATTR amyloid fibril conformation were present in each patient. Moreover and very significantly, elimination of amyloid was accompanied by remodeling of their hearts back towards normal with regards to both structure and function, and without fibrosis. These findings compellingly suggest that ATTR-CM is a truly reversible disorder, bringing hope for patients even with advanced disease.

5. Monitoring treatment response with multimodality cardiac imaging

Echocardiography and CMR studies represent the most commonly used imaging technologies to monitor patients with amyloid cardiomyopathy, although notably CMR can detect early changes in myocardial structure compared to echocardiography. In the HELIOS-A trial in patients with hereditary ATTR-PN, treatment with the 3 monthly administered RNAi agent vutrisiran was associated with a trend toward stabilisation in structural and functional echocardiographic parameters

in patients with co-existing cardiomyopathy, but no meaningful changes were identified using this relatively insensitive imaging technique [60]. At 18 months, patients receiving vutrisiran had unchanged NT-proBNP serum concentrations compared to baseline and more frequently showed reduced myocardial uptake in serial bone scintigraphy compared to those receiving placebo. It is important to note that at this time, the mechanism and significance of reduced bone tracer uptake is not known.

A recent study using CMR with ECV mapping has demonstrated an unanticipated potential for regression AL amyloid deposits in the heart evidenced by reduction or normalization of myocardial ECV value among patients achieving rapid complete response or very good partial response (i.e., precursor protein concentration of <40 mg/L, but still detectable) as early as 6 months following initiation of chemotherapy [18]. The results of this study further confirmed that amyloid deposition is a dynamic process that results from the relationship between amyloid formation and amyloid clearance [61]. Amyloid infiltration occurs when the rate of amyloid formation exceeds that of amyloid clearance [18,61]. *In vivo* evidence of cardiac amyloid regression has been also demonstrated in a group of 16 'real-world' patients with ATTRv amyloidosis and a mixed phenotype (i.e., cardiomyopathy and neuropathy); after 12 months of treatment, patients demonstrated lower ECV values, coupled with reduced NT-proBNP concentrations and improved exercise capacity on the 6MWT [62].

6. Conclusion

Over the last 10 years, many traditional dogmas in amyloidosis have been refuted through many exciting and very substantial advances in diagnosis, management and treatment of patients with ATTR-CM. The future is bright with numerous therapeutics now in phase 2 and 3 clinical trial, whilst knowledge is accumulating at an ever-increasing pace with regard to mechanisms of amyloid formation, epidemiology, sex differences and applications of advanced cardiac imaging for diagnosis and informing clinical management. However, there remains much to learn about patient-tailored treatment strategies as well as defining clinically meaningful criteria for treatment response and failure, let alone the potential and role for combination amyloid inhibitor and depleter therapies.

Declaration of Competing Interest

Declarations of interest: none related to the topic discussed in the present work.

Outside of the present work: Gianfranco Sinagra reports personal fees for educational activities (Biotronik, Boston Scientific, Astra Zeneca, Novartis, Dompé, Menarini, and Vifor Pharma) outside the submitted work. Julian D. Gillmore has consulting income from Ionis, Alexion, Eidos, Intellia, Alnylam and Pfizer. Marianna Fontana has consulting income from Intellia, Novo-Nordisk, Pfizer, Eidos, Prothena, Alnylam, Alexion, Janssen, Astrazeneca, Attralus, Lexeo and Ionis. Philip Hawkins has consulting income from Alnylam. The remaining author (Aldostefano Porcari) has nothing to disclose.

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