Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy

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One sentence summary

This consensus document from an international expert panel recommends a set of clinically feasible tools for the long-term monitoring of patients with transthyretin amyloid cardiomyopathy (ATTR-CM), including meaningful thresholds for defining disease progression and the frequency of measurements.

Abstract:

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening condition with a heterogeneous clinical presentation. The recent availability of treatment for ATTR-CM has stimulated increased awareness of the disease and patient identification.

Stratification of patients with ATTR-CM is critical for optimal management and treatment; however, monitoring disease progression is challenging and currently lacks best-practice guidance. In this report, experts with experience in treating amyloidosis and ATTR-CM developed consensus recommendations for monitoring the course of patients with ATTR-CM and proposed meaningful thresholds and frequency for specific parameters.

A set of 11 measurable features across three separate domains were evaluated: (1) clinical and functional endpoints, (2) biomarkers and laboratory markers and (3) imaging and electrocardiographic parameters. Experts recommended that one marker from each of the three domains provides the minimum requirements for assessing disease progression.

Assessment of cardiac disease status should be part of a multiparametric evaluation in which progression, stability or improvement of other involved systems in ATTR should also be considered. Additional data from placebo arms of clinical trials and future studies assessing ATTR-CM will help to elucidate, refine and define these and other measurements.

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening condition that is characterised by deposits of amyloid protein in the extracellular space of the myocardium, causing progressive infiltrative cardiomyopathy (1, 2). ATTR-CM is characterised by increased left ventricular (LV) wall thickness and diastolic dysfunction, with around a third of patients showing a restrictive filling pattern (3).

ATTR-CM presents in two predominant phenotypes: variant ATTR-CM (ATTRv), which is a hereditary form of the disease caused by mutations in the transthyretin (*TTR*) gene that can present as a multisystem disease in people from early middle age onwards; and wild-type ATTR-CM (ATTRwt), which predominantly affects the heart in isolation and typically affects men over 60 years of age, but is also found in women (3, 4). The early stages of the disease manifest as heart failure (HF) with preserved ejection fraction (5) and may mimic hypertensive heart disease (3) or hypertrophic cardiomyopathy (6). The natural history of ATTR-CM is variable (7), particularly in hereditary forms where genotype influences the likelihood (and predominance) of cardiac involvement (7) but prognosis, if untreated, is poor with a median survival time from diagnosis of 3.6 years (4), and 2.6 years for patients with V122I-genotype (8).

Traditionally, ATTR-CM has been considered to be a rare disease; however, recent data suggest that the prevalence may be substantially higher than previously assumed (2, 9, 10). Historical underdiagnosis means that the natural history of the disease remains uncertain, with data limited to small observational cohorts and latterly to the placebo arm of clinical trials (11). Nevertheless, it is clear that the disease progresses silently and that diagnosis often follows presentation with late-stage cardiac manifestations (8, 9, 12). It is hoped that with improved diagnosis and heightened awareness, ATTR-CM can be detected earlier, allowing more precise patient stratification and profiling with regards to disease progression at all stages.

Several red flags that support ATTR-CM suspicion and techniques that facilitate earlier diagnosis have been identified and these have assumed greater importance with the availability of disease-modifying treatments that improve clinical outcomes (13, 14). Parameters that change with

ATTR-CM disease progression span several domains, such as functional capacity, quality of life (QoL), laboratory biomarkers and cardiac imaging, and these require multidisciplinary expertise for their interpretation (7). However, there is a lack of guidance on the use of potential disease markers in monitoring disease progression. Several models using independent measures for estimating prognosis in ATTR-CM are available (4, 15, 16) (Table 1) but they are limited by inter-subject variability and were not designed to monitor progression.

To address this unmet need, a group of international experts in cardiac amyloidosis elaborated a series of recommendations for the monitoring of patients with ATTR-CM. The document is based on two surveys and two expert panel discussions, in which the experts provided experience-based opinions on the tests and biomarkers that they felt to be most useful and feasible for long-term assessment of ATTR-CM patients. This report summarises the group's recommendations, including the thresholds for defining disease progression.

Methods/selection of tools

A panel of experts from Europe (Austria, France, Germany, Italy, Portugal, Spain and UK), Japan and the USA were convened in sponsored meetings. No participant was appointed by a national society or by a regulatory authority.

The experts were asked to complete two surveys and to agree on a final list of recommended clinical parameters deemed to be feasible and clinically meaningful when monitoring disease progression in ATTR-CM. In survey one, experts were asked to list key measurable clinical features for longitudinally assessing disease status in patients with ATTR-CM that they either used or would recommend. In survey two, experts were asked to rank the list of features and to outline the tools/techniques/investigations they would use to measure change in each clinical feature; they were also asked to describe the frequency and threshold for minimally important change for each measurement. Following completion of the surveys, panel discussions were held in which experts explored the value of individual parameters and achieved consensus on the clinical indicators and thresholds that inform on change in ATTR-CM. Subjectivity, standardisation and sensitivity were considered, particularly where lack of standardisation and inter- and intra-subject variability could impact consistency. To the best of our knowledge, this is the first time that a set of measurement tools has been defined with the explicit objective of characterising, in detail, the progression of ATTR-CM in diagnosed patients.

Results

The surveys identified many candidate clinical features for monitoring patients with ATTR-CM, which are listed in the Appendices. During consensus discussions, the list was refined and defined using thresholds and frequency of measurements (Appendices 1–3). By consensus, this set of 11 measurable features, was recommended across three separate domains: (1) clinical and functional endpoints, (2) biomarkers and laboratory markers and (3) imaging and electrocardiographic parameters (Table 2). While a change in each clinical feature was considered meaningful, worsening in any single marker was insufficient to define disease progression and at least one marker in each of the three domains was required.

(1) Clinical and functional endpoints

Heart failure-related hospitalisations

The number of HF decompensation-related hospitalisations (17) requiring intravenous diuretic treatment (18) is a meaningful indication of disease progression and is used as a common endpoint in HF and ATTR-CM trials (14). The recommended threshold for this parameter is one or more hospital admission during a 6-month period, while the absence of any hospitalisations is considered stabilisation of ATTR-CM during this period. The panel acknowledged that other reasons for hospitalisations – including pacemaker implantation due to rhythm disturbances and arrhythmias/ syncope (if related with arrhythmias on ECG/Holter) are well-established markers of progression. As hospitalisation for arrhythmic/conduction would qualify under two domains, the panel aimed to avoid overestimation of a single parameter. While the experts agreed that the use of intravenous diuretic therapy (in both inpatient and outpatient settings) was a better indicator of disease progression than an increase in the use of oral diuretics, the dose of diuretic is a strong predictor of outcome in HF studies (20) and an independent predictor of mortality in ATTR-CM patients (16); moreover, peripheral oedema, observed as an increase in weight or ankle, leg and foot circumference, is a significant change that patients can monitor daily (21), in addition to assessments at any hospital visits.

NYHA functional class/HF class

The NYHA classification categorises patients into one of four groups, based on the degree of exertion required to produce symptoms. Considered a cornerstone of clinical assessment of HF status, the NYHA classification is commonly used to determine eligibility status in clinical trials (19).

Although easily implemented in everyday practice, HF is more complex and multifactorial than the four classes described by this tool. Subjectivity and a lack of detail have meant that use of the NYHA classification to assess disease status has been questioned (19, 20). NYHA classification depends on patient self-reporting and physician examination, and its use is associated with risks of inter- and intra-subject variability (20, 21). Although NYHA class has been shown to be prognostic in ATTR-CM (19, 22), the group decided that it lacks sensitivity as a standalone tool for detecting subtle progression of ATTR-CM in individual patients, and therefore should be interpreted in a multiparametric approach with other markers (20); it was also recommended that NYHA measures should be made after 30 days of stability, as defined by stable symptoms. In ATTRv patients with overlapping phenotypes, NYHA class classification may be limited in the assessment of motor disabilities caused by polyneuropathy.

QoL tools

QoL assessment, using tools such as EuroQol five dimensions (EQ-5D), the Kansas City Cardiomyopathy Questionnaire (KCCQ) is an established chronic disease measure (23) that is considered an essential indicator of response in HF treatment (24). The Hospital Anxiety and Depression Scale (HADS) provides valuable patient insight, although it has not been validated specifically in the ATTR-CM population. In addition to being important endpoints for treatment trials, QoL assessments provide valuable learnings for patient engagement and education and may also to help guide thresholds and cut-offs for different markers.

The KCCQ includes domains of physical and social limitations, symptoms and self-efficacy, using either an improvement or a reduced decline in QoL, this tool has been employed in randomised controlled trials (RCTs), including a recent evaluation of tafamidis in ATTR-CM (11, 14). A

significant reduction in KCCQ decline was found in tafamidis-treated patients versus placebo in the ATTR-ACT study (14); in the placebo arm of this study, KCCQ decline was greater in ATTRv patients than ATTRwt patients, and the placebo group also demonstrated higher mortality and increased N-terminal pro-brain natriuretic peptide (NT-proBNP) levels over time in ATTRv compared with ATTRwt (11).

In isolation, QoL measurements are subjective, and defining thresholds using these measures for patient management is a challenge; therefore, experts proposed that QoL should be used in concert with other measures to confirm stability or progression and, in this way, facilitate earlier detection of ATTR-CM progression. It should be noted that without the dedicated teams and resources provided in a research setting, routine QoL assessments may be too time-consuming for a typical clinic and patients may tire of repeated questionnaires. The KCCQ provides patient-centric data and can be used to monitor changes in disease status but training is required to improve physicians' understanding of the instrument (25) and where possible, disease-specific QoL tools should be used.

Physical function/functional capacity

Physical assessments such as the number of meters walked in 6 minutes (6MWT) are an objective way to detect disease severity, progression and treatment effects (11, 26): for example, in the ATTR-CT study, 6MWT showed a reduced decline in tafamidis-treated patients compared with those receiving placebo (14). However, because of logistical constraints, these tests tend to be performed in research settings more than routine clinical practice (11, 26).

Frailty is an important domain, particularly in elderly and multi-comorbidity patients; it is associated with higher risk of mortality and hospitalisation in older patients with chronic HF (27). While the inclusion of additional frailty assessments may be challenging to incorporate into routine clinics, the 6MWT – particularly if already being performed to assess physical function – may be helpful for stratifying frailty in ATTR-CM patients and determining prognosis (27). Because formal frailty measurements are currently difficult to incorporate into routine clinics, these were not part of the recommended criteria in Table 2; however, they form an important part of patient examination.

(2) Biomarkers and laboratory markers

NT-proBNP

NT-proBNP measurement is a reference biomarker for determining the probability of HF (28); moreover, owing to its low cost and easily interpretable results it is feasible in routine clinical practice. NT-proBNP measurements are also deemed to be useful measures of disease progression (15) – as demonstrated in the placebo arm in the ATTR-ACT trial (11) and amyloidosis-staging systems (4). Where NT-proBNP measurements are not possible, B-type natriuretic peptide (BNP) can also be used to determine risk and predict outcomes in HF with reduced EF. It should be noted, however, that these peptides present in different ratios, with NT-proBNP levels more than six times higher than BNP in patients with HF with reduced EF and that BNP has been less studied in ATTR-CM (29).

Caution is advised when measuring NT-proBNP, as increased levels occur with renal failure and atrial fibrillation (30, 31), which could impact on the interpretation of changes as evidence of ATTR-CM progression. In this regard, it should be noted that the relationship between NT-proBNP and eGFR is complex, reflecting a combination of cardiac and renal factors (15). Given that analytical variability and biological variability affect the precision of this marker (32), the panel recommended using both relative (30%) and absolute (300 pg/mL) increases in NT-proBNP to ensure that progression can be detected in both early-stage and more advanced patients. Proposed thresholds for NT-proBNP variation may be updated as more information becomes available The experts stressed that biomarker measurements should be interpreted following 30 days of clinical stability, without a change in diuretic dose, and under the same heart rhythm (i.e., sinus or atrial fibrillation) as when previously examined. Otherwise, NT-proBNP should be interpreted accordingly.

Troponin and biomarker stage

Persistent elevation of cardiac troponin levels is suggestive of myocardial damage and may have prognostic value for ATTR-CM (33). The standardisation of absolute cardiac troponin levels, however, is an ongoing issue – generations of troponin assays developed by different manufacturers have confounded its use, with different centres preferring particular assays (15).

Furthermore, the association between absolute troponin value changes and changes in disease status is unknown, making it unclear what constitutes significant change. As patients with ATTR-CM

are often clinically stable for years (7), and because troponin levels may be in the reference range for long durations, a step change may not be suitable for patients with early stages of the disease. Therefore, this panel of experts believes that a 30% relative increase, using a high-sensitivity assay, would be a better indication of ATTR-CM progression than a pre-specified absolute level. Nevertheless, reduced troponin clearance in patients with concomitant HF and chronic kidney disease suggests that troponin measurements are also affected by renal function (34, 35), underpinning the need for caution in interpreting such data, particularly in multimorbid patients.

Staging systems

Advanced clinical staging systems (Table 1) allow documentation of changes and associations between biomarker levels, clinical and physical functioning, and QoL. Because the Mayo Clinic staging system was derived only for ATTRwt patients and the Columbia system includes functional parameters that are separately evaluated in the functional domain, the group agreed that these staging systems were less suited for monitoring progression of ATTR-CM. Moreover, the NAC system described by Gillmore et al (15) is currently the only staging system that has been shown to predict survival throughout the natural history of ATTR-CM (36) and comprises features from only the "biomarkers and laboratory markers domain", therefore it was agreed that a change in the NAC score would be a helpful indication of disease progression in ATTR-CM (4, 15, 36).

(3) Imaging and electrocardiographic parameters

Echocardiography

Due to low costs, as well as ease of image acquisition and interpretation, echocardiography is the universal imaging tool for cardiac amyloid assessment and plays a crucial role in monitoring disease progression (1); however, there is a need for clear and objective thresholds with regards to ATTR-CM progression criteria. Experts recommended that trends in disease progression should be identified and defined using serial measurements, and that findings should be interpreted in the context

of other clinical examinations. RCT data may help to define thresholds for disease progression when long-term data on responders versus non-responders becomes available.

Due to the capacity for serial measurements, the panel recommended that physicians simultaneously collect a range of echocardiography parameters that provide meaningful indications of ATTR-CM worsening; for example, stroke volume, inferior vena cava diameter, Doppler assessment including E/e' and transmitral flow, global longitudinal strain and pericardial effusion.

Based on clinical trial data in which 8% of patients experienced ≥2 mm increase in LV wall thickness (37), experts agreed that this threshold was suggestive of disease progression, whereas changes of a lesser magnitude may represent measurement error. However, such changes occur slowly and so are less likely to be useful in guiding short-term management decisions. Confounders such as systemic hypertension should also be considered when assessing LV wall thickness. Routine measurement of LV systolic function should be assessed with ≥5% decreases in LV ejection fraction or ≥5ml decrease in stroke volume indicative of disease progression, as determined from the ATTR-ACT trial data (14). Indeed, these measures may be better indicators of ATTR-CM progression than LV wall thickness. LV global longitudinal strain (GLS) has also been shown to diagnose LV dysfunction in ATTR-CM at the early stages of the disease (38) and to be diagnostically accurate when differentiating cardiac amyloidosis from other aetiologies (39). Based on linear extrapolations of findings from the APOLLO trial and ATTR-ACT, the panel recommended that a ≥1% increase in GLS was indicative of disease progression (14, 37). Diastolic dysfunction in conjunction with wall thickening leads to restrictive cardiomyopathy (40); therefore, echocardiographic detection of diastolic worsening should be routinely performed, with the caveat that it may be altered by changes in fluid status, heart rate and heart rhythm.

The value of different echocardiographic parameters varies according to disease stage; for example, early disease markers include LV strain and low-grade diastolic dysfunction, whereas late markers comprise LV ejection fraction, right ventricular systolic function, restrictive LV filling, reduced myocardial contraction fraction, increased LV mass and LV wall thickness (41, 42). The

recommended testing frequency of 6–12 months using echo agrees with published consensus statements on ATTR-CM imaging (43).

Electrocardiogram (ECG)

Using a standard 12-lead ECG, ATTR-CM can be characterised by a "pseudo-infarct" pattern of Q-wave or T-wave changes or low-QRS voltage (1, 22). The development of atrioventricular (AV) block – particularly advanced AV block, and PR interval prolongation >20 ms–were considered meaningful changes in patients with ATTR-CM that signal disease progression (44) and may appear in isolation or together with bundle branch block pattern. The appearance of left branch bundle block or trifascicular block may also be indicative of disease worsening, however, because conduction disturbances are often present before diagnosis (45), these measures may be inconclusive in isolation. Moreover, 24-hour ambulatory ECG monitoring was considered a pragmatic recommendation for the detection of AF and conduction disturbances. In some individual patients with paroxysmal symptoms suggesting arrhythmia, more prolonged monitoring may be appropriate (46, 47). Indications for permanent pacing, such as sinus node dysfunction, atrial fibrillation with a slow ventricular response and AV block also indicate disease progression.

Cardiovascular magnetic resonance (CMR) and radionuclide imaging (nuclear cardiology)

As a pivotal diagnostic tool in ATTR-CM, CMR using native T1 mapping and T1 with late gadolinium enhancement (LGE) is used for tissue characterisation and measurement of extracellular volume (ECV (48). Cine CMR is also more reproducible and accurate for measuring both LV geometry and functional parameters than echo measurements (7, 49, 50). ECV has prognostic value in ATTR-CM (51, 52), but its use as a measure of treatment response requires validation. Although CMR is contraindicated with some pacemakers, new conditional devices enable imaging where necessary. However, based on costs, availability, and the lack of serial data in ATTR-CM, CMR was not included in the progression criteria. When available, long-term treatment data will clarify a future role for CMR and it is likely that interval scanning may be an important aspect of disease monitoring, for example,

recently a biennial CMR screening was recommended in a consensus recommendations document for ATTR-CM (43).

Cardiac scintigraphy with bone avid tracers

Quantitative cardiac single photon emission computed tomography/positron emission tomography (SPECT/PET) using bone avid radiotracers, ^{99m}Tc-pyrophospate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) and ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) are robust non-invasive diagnostic tools that are currently embedded in routine ATTR-CM diagnosis (53-55). Recent findings demonstrated suboptimal sensitivity of DPD scintigraphy in patients carrying the early-onset Val50Met (formerly Val30Met) variant and other rarer genotypes like Phe64Leu, suggesting that the accuracy of the technique may be influenced by the ATTRv genetic variant (56, 57).

Although these tools play an important role in identifying early ATTR-CM, their value in assessing the progression of ATTR-CM is not fully elucidated, and therefore the expert group did not make a recommendation for their use in disease monitoring (7). The same is true for other amyloid-specific radiotracers, such as 11C- Pittsburgh-Compound B and 18F-florbetapir (58-62).

Discussion

General considerations for monitoring ATTR-CM in identified patients

There remains a need for practical clinical evaluation tools that are feasible to conduct every 6–12 months; for example, CMR, radionuclide imaging and QoL measures may be more challenging to perform, whereas clinical examination, NYHA functional class assessment, ECG and circulating biomarkers are more practical. Nevertheless, the entire battery of tests should be performed yearly in patients with diagnosed ATTR-CM, with some tests performed twice during this period. Attempts should be made to coordinate specialists to minimise the number of hospital visits.

Accurate baseline levels are crucial; this includes the initial disease staging and knowledge of relevant markers for early versus late stage of ATTR-CM. Reproducibility of certain measures, such as NT-proBNP, echocardiography and CMR has not been demonstrated in ATTR-CM, so parameters that

are evaluated over multiple timepoints may be more meaningful than those used at specific cut-off values.

The experts highlighted that ATTR-CM phenotype (ATTRv versus ATTRwt) and disease stage may impact the feasibility or reliability of the measurements used to monitor cardiac disease progression in ATTR-CM patients, supporting the importance of a multiparametric approach that includes clinical variables, questionnaires, laboratory biomarkers, and imaging.

Consideration of clinical variables that influence criteria defining progression in ATTR-CM

Physical frailty and biological age, and the patient's own perception of disease worsening were generally not considered to influence the measurement tools. However, it was noted that elderly people frequently present with degenerative conduction diseases such as AV blocks (even in the absence of amyloidosis), which may complicate the interpretation of ECG findings.

Treatment effects and ATTR-CM progression

An additional factor when considering meaningful change is the potential delay in treatment effect, and this should be taken into account whilst the disease stabilises, particularly during the initial 6–12-month interval after starting treatment. This recommendation underpins the importance of robust measures to discern between cardiac remodelling or lack of efficacy in patients with advanced-stage disease, and it is believed that imaging parameters may play a key role in this distinction in the future.

Currently, long-term data in treated ATTR-CM patients are lacking, so clear endpoints indicating disease progression or stability are unknown. Findings from phase 3 trials, such as the ATTR-ACT study may provide relevant endpoints for treatment goals (14) and long-term data will also inform these decisions. The panel stressed that where these tools indicate ATTR-CM progression, measurements should not be interpreted as a recommendation to discontinue disease-modifying therapies.

Future studies

To improve the management of patients with ATTR-CM, several studies assessing the relationship between patient outcome and progression help inform therapeutic decisions (Table 3). Therefore, a set of parameters measuring physical function, biomarkers and imaging should be categorised into different ATTR-CM disease stages based on their relationship with progression and survival. Data from placebo arms of RCTs will provide an opportunity to observe progressive changes in cardiac geometry and will allow a comparison of progressive changes in treated versus untreated ATTR-CM patients (11). Another area of future research includes the validation of systemic ATTR biomarkers for the production and plasma concentration of circulating TTR and unstable TTR. These include kinetic and peptide biomarkers that selectively bind to misfolded pathogenic oligomers in the serum; however, these are in the early stages of clinical investigation (63).

The experts propose that long-term studies in patients with ATTR-CM should explore global measurements of frailty, stratifying patients by age, severity and ATTR-CM phenotype. Ideally, multidimensional assessment of frailty should be incorporated into ongoing holistic assessment of ATTR-CM patients, but further studies are required to understand better how different frailty phenotypes influence disease progression. In a similar vein, owing to the typical late-stage diagnosis, the data to support these measures of progression tend to be from older patients, it is hoped that with improved diagnosis and awareness, disease progression in early stage patients can be characterised. Assessment of cardiac progression in mixed ATTRv phenotype should be part of a multisystemic evaluation, in which progression, stability or improvement of other involved organs (i.e. peripheral neuropathy, kidneys and the autonomic system) should also be considered as they contribute to the overall interpretation of the disease course (64).

This report also highlights the need for more research validating imaging parameters for ATTR-CM progression, including CMR, T1 mapping and ECV changes, and radionuclide imaging with SPECT and PET. A recognised limitation of the study was the lack of patient engagement for selecting relevant endpoints, it is hoped that future studies that focus on such endpoints, including patient surveys and patient-reported outcomes studies will gain perspective on what matters most to patients.

Conclusions

A minimum set of parameters should be used to detect disease progression in patients diagnosed with ATTR-CM and these measures should be performed in a relatively short timeframe (6–12 months) after diagnosis or commencing treatment for ATTR-CM. Parameters should include the following:

1. Quantitation of functional decline (clinical and functional endpoints)
2. Quantitation of disease severity by biomarkers and laboratory markers
3. Quantitation of disease severity by imaging and electrocardiographic parameters

Upcoming data on non-treated patients will help to elucidate, refine and define these measurements.

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Tables

Table 1: Clinical Staging systems for ATTR-CM

Grogan et al, 2016 (Mayo) (4) ATTRwt		**Gillmore et al, 2018 (NAC) (15)** ATTRv & ATTRwt		**Cheng et al, 2020 (Columbia) (16)** ATTRv & ATTRwt	
Staging parameters: Troponin T > 0.05 ng/mL NT-ProBNP > 3,000 pg/mL		Staging parameters: eGFR < 45ml/min NT-ProBNP > 3,000 pg/mL		Scoring parameters: Mayo or NAC Score (0 to 2 points) Daily dose of Furosemide or equivalent: 0 mg/kg (0 points), >0-0.5 mg/kg (1 point), >0.5-1 mg/kg (2 points), and >1 mg/kg (3 points) NYHA class I-IV (1 to 4 points)	
Stage	**Median survival**	**Stage**	**Median Survival**	**Score**	**Mean Survival**
Stage I (0 parameters)	66 months	Stage I (0 parameters)	69.2 months	Score 1–3	78 months
Stage II (1 parameter)	40 months	Stage II (1 parameter)	46.7 months	Score 4–6	48 months (Mayo) 45.6 months (NAC)
Stage III (2 parameters)	20 months	Stage III (2 parameters)	24.1 months	Score 7–9	26.4 months (Mayo) 22.8 months (NAC)

ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant ATTR-CM; ATTRwt, wild-type ATTR-CM; HF, heart failure; NAC, UK National Amyloidosis Centre

Table 2: Recommended measurement tools for detecting transthyretin amyloid cardiomyopathy progression in treated patients

Tool and domain	Clinical feature	Threshold indicating disease progression	Recommended frequency of measurement
Clinical and functional			
Clinical and medical history	Cardiovascular-related hospitalisations	Worsening indicated by any hospitalisation (related to HF decompensation) in a 6-month period	6 months
HF class: NYHA class	Stepwise class change (plus or minus) should indicate progression or amelioration/ improvement, respectively	One class increase (note: must be measured during a 30-day period of stability)	6 months
QoL: EQ-5D tool and KCCQ	Description of measurements	Five-point decrease in KCCQ represents deterioration; Ten-point decrease in KCCQ represents moderate deterioration; 10% decline in EQ-5D score represents deterioration	6–12 months
Functional capacity	6MWT	Decrease of 30–40 m every 6 months (in the	6 months

		absence of obvious non-cardiovascular cause)	
Biomarkers and laboratory markers			
Biomarkers and laboratory markers	NT-proBNP	30% increase with 300 pg/mL cut-off. To be measured during a 30-day period of clinical stability and under same atrial rhythm.	6 months)
	Troponin (high-sensitivity) assay	30% increase	6 months
	Clinical staging system	Advance in NAC staging score	6 months
Imaging parameters and ECG			
Echocardiography	LV measures wall thickness/mass	≥2-mm increase in LV wall thickness	6–12 months
	Systolic function measurements	≥5% decrease in LV ejection fraction decrease; ≥5ml decrease in stroke volume and ≥1% increase in LV global longitudinal strain	12 months
	Diastolic dysfunction worsening; e.g., using diastolic functioning grade	Stepwise increase in diastolic functioning grade; consistent deterioration in diastolic function	12 months

ECG/ Holter ECG	New-onset of Arrhythmic/conduction disturbances	New-onset bundle branch block. New-onset AV block (of any degree). Sinus pauses, sinus node dysfunction, AF with a very slow ventricular response without pharmacologic treatment (<50 bpm)	6 months

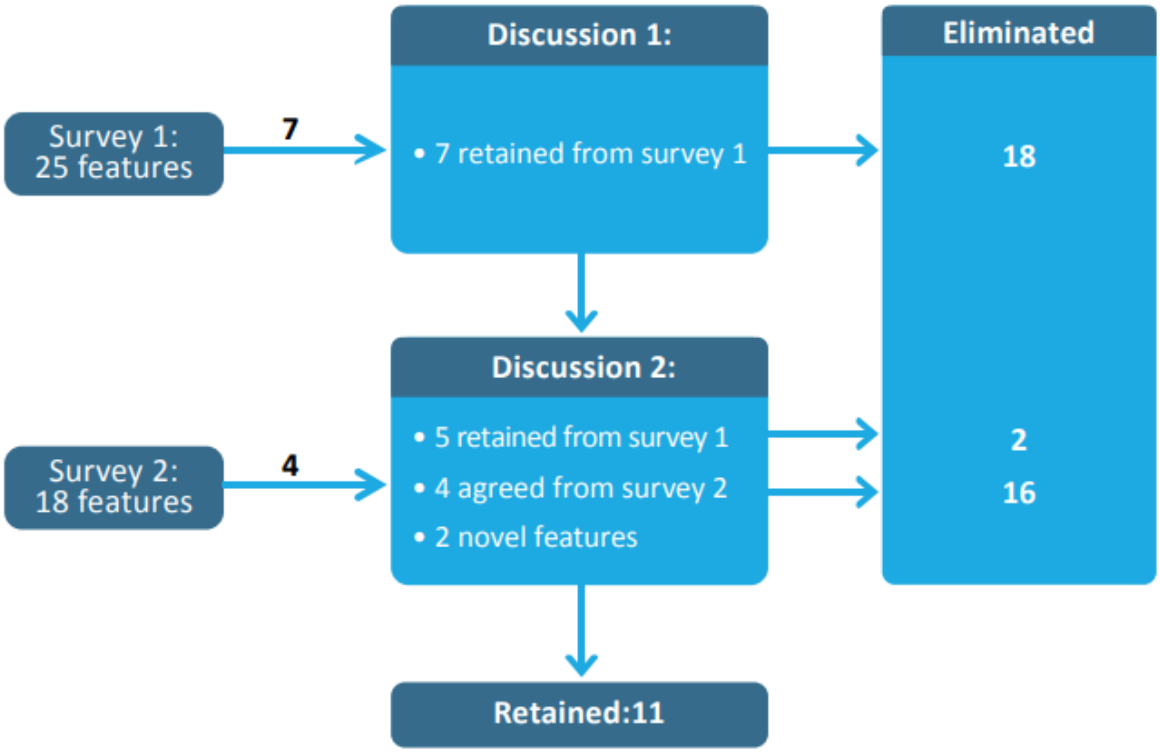
AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiography; EQ-5D, EuroQol five dimensions; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; NT-proBNP, N-Terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life; 6MWT, number of meters walked in 6 minutes

Table 3: List of proposed studies to improve the understanding of disease progression in patients with ATTR-CM

1	Multiparametric evaluation to characterise disease progression and predict survival for different stages of ATTR-CM (early vs late) and for disease severity
2	Pooled analyses of RCT data, using placebo arms to define changes in cardiac geometry and compare of progressive changes with those in treated ATTR-CM patients
3	Studies validating systemic ATTR biomarkers for determining the production and plasma concentration of circulating TTR and unstable TTR, such as kinetic and peptide biomarkers
5	Long-term studies exploring global measurements of frailty, stratifying patients by age, severity and ATTR-CM phenotype to assess its influence on disease progression
6	Assessment of cardiac progression in mixed ATTRv phenotype to determine the stability or improvement of other involved organs (i.e. peripheral neuropathy, kidneys and the autonomic system)
7	Validation of imaging parameters for ATTR-CM progression, including CMR, T1 mapping and ECV changes, and radionuclide imaging with SPECT and PET
8	Patient engagement studies that include relevant patient-centric endpoints, such as surveys and patient-reported outcomes

Appendices

Appendix 1: Flow chart of consensus process



Appendix 2

25 clinical features identified by the experts in survey 1
6-minute walk test (6MWT)/functional capacity
Body composition monitoring (BCM)
Conduction abnormalities
CV-related hospitalizations/ hospitalisation for HF
E/e'
eGFR
Extracellular volume (ECV)
LV Global Longitudinal Strain
hs-Troponin T
Interventricular septum (IVS) thickness
Liver congestion (laboratory evaluation)
LV ejection fraction (LVEF)
LV mass and wall thickness
Mean pulmonary arterial pressure (mPAP)
Native T1 Times
Need for IV therapy to treat HF (emergency department - no hospitalization)
NT-proBNP
NYHA Class/heart failure class
Peripheral edema/Need for diuretics to treat heart failure
Physical function
Quality of life/EQ-5D
Quantitative myocardial uptake of amyloid-binding PET radiopharmaceuticals
RV function/ Right ventricular ejection fraction (RVEF)
Spiroergometry
TTR levels

Appendix 3

16 clinical features identified by the experts in survey 2
LV mass and wall thickness
LV strain
Interventricular septum (IVS) thickness
T1 mapping
E/e’
12-lead electrocardiogram (ECG)
Extracellular volume (ECV)
LV global longitudinal strain
High-sensitivity (hs) troponin T
Onset of persistent atrial fibrillation
24-hour Holter monitor
Requirement of pacemaker
Posterior wall thickness
Diuretics requirement
Renal function
Onset or progression of neuropathy in hereditary ATTR-CM