

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT



Proposed Cardiac End Points for Clinical Trials in Immunoglobulin Light Chain Amyloidosis: Report From the Amyloidosis Forum Cardiac Working Group

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ABSTRACT: Immunoglobulin light chain amyloidosis is a rare, multisystemic, phenotypically heterogeneous disease affecting cardiovascular, renal, neurological, and gastrointestinal systems to varying degrees. Its underlying cause is a plasma cell dyscrasia characterized by misfolding of monoclonal immunoglobulin light chains which leads to aggregation and deposition of insoluble amyloid fibrils in target organs. Prognosis is primarily dependent on extent of cardiac involvement and depth of hematologic response to treatment. To facilitate development of new therapies, a public-private partnership was formed between the nonprofit Amyloidosis Research Consortium and the US Food and Drug Administration Center for Drug Evaluation and Research. In 2020, the Amyloidosis Forum launched an initiative to identify novel/composite end points and analytic strategies to expedite clinical trials for development of new therapies for the primary hematologic disorder and organ system manifestations. Specialized working groups identified organ-specific end points; additional working groups reviewed health-related quality of life measures and statistical approaches to data analysis. Each working group comprised amyloidosis experts, patient representatives, statisticians, and representatives from the Food and Drug Administration, the UK Medicines and Healthcare Products Regulatory Agency, and pharmaceutical companies. This review summarizes the proceedings and recommendations of the Cardiac Working Group. Using a modified Delphi method, the group identified, reviewed, and prioritized cardiac end points relevant to immunoglobulin light chain amyloidosis in the context of an antiplasma cell therapy. Prioritized cardiovascular end points included overall survival, hospitalization, N-terminal pro-B-type natriuretic peptide level, 6-minute walk test, Kansas City Cardiac Questionnaire, and cardiac deterioration progression-free survival. These recommended components will be further explored through evaluation of clinical trial datasets and formal guidance from regulatory authorities.

Key Words: amyloidosis ■ clinical trial ■ immunoglobulin light chains ■ prognosis ■ progression-free survival

IMMUNOGLOBULIN LIGHT CHAIN AMYLOIDOSIS AND CARDIAC INVOLVEMENT

Immunoglobulin light chain (AL) amyloidosis is a rare, multisystemic, and phenotypically heterogeneous disorder, affecting cardiac, renal, neurological, and gastrointestinal

systems to varying degrees in different patients. AL amyloidosis is caused by a monoclonal plasma cell disorder characterized by misfolding of monoclonal immunoglobulin light chains which leads to aggregation and deposition of insoluble amyloid fibrils in target organs.^{1,2} Deposition of amyloid fibrils in target organs and chemotherapeutic regimens to treat the underlying plasma cell dyscrasia

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Nonstandard Abbreviations and Acronyms

6MWT	6-minute walk test
ACE	angiotensin-converting enzyme
AL	immunoglobulin light chain
ARB	angiotensin receptor blocker
ARNIs	angiotensin receptor neprilysin inhibitors
HRQOL	health-related quality of life
MCIDs	minimally important clinical differences
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PFS	progression-free survival

significantly and broadly impact health-related quality of life (HRQOL).³⁻⁷

AL amyloidosis is the most common type of systemic amyloidosis seen in specialized centers with an estimated annual incidence between 3 and 12.7 per million person-years and annual prevalence ranging between 20 and 58 per million person-years.² The median age at diagnosis is ≈65 years.^{8,9} The impact of AL amyloidosis is often devastating.¹⁰ For the estimated 76% of patients with cardiac involvement,⁹ the ability to perform daily activities is impaired both by symptoms related left heart failure (eg, orthostatic hypotension, syncope, progressive shortness of breath and pulmonary edema) as well as symptoms related to right heart failure (eg, hepatic and intestinal vascular engorgement and peripheral edema). Many standard treatments for congestive heart failure (eg, β -blockers, ACE [angiotensin-converting enzyme] inhibitors, ARB [angiotensin receptor blocker], and ARNIs [angiotensin receptor neprilysin inhibitors]) are either contraindicated or poorly tolerated in patients with AL amyloidosis, especially at high doses. Cardiac damage may be irreversible and contribute to ongoing morbidity and mortality despite achieving a complete hematologic response.¹¹ The median overall survival of patients with advanced cardiac involvement is <12 months.

Delays in diagnosis contribute to worsened outcomes. Delays may prevent the use or limit the effectiveness of plasma cell-directed therapies, including chemotherapy, immunotherapies, and high-dose melphalan followed by autologous stem cell transplant.^{12,13} Daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone have been used in the clinical setting of AL amyloidosis patients across different stages of the disease, including those with advanced cardiac disease. Based on clinical trial data, the Food and Drug Administration granted accelerated approval to daratumumab/hyaluronidase in combination with bortezomib, cyclophosphamide, and dexamethasone in newly diagnosed patients and noted it is not recommended for the treatment of patients with AL amyloidosis who are Mayo Stage IIIB or who are New York Heart Association functional

class IIIB or class IV outside of controlled clinical trials.¹⁴ Institutional practices with respect to this recommendation may vary given the lack of alternative therapies in advanced cardiac amyloidosis patients.

Overall, patient prognosis is primarily dependent on the extent of cardiac involvement and the depth of hematologic response to treatment. There is a high need to have treatments that not only halt disease progression but also reverse organ damage, improve HRQOL, and are safe to use in patients with cardiac involvement. The evolving treatment landscape is shifting from targeting the underlying plasma cell disorder only to also targeting the AL amyloid deposits directly at the organ level (ie, antiamyloid treatments), which may impact the current definitions of organ response based on the different mechanisms of action. Likewise, clinical trials must be designed with clinically meaningful end points that will ensure participant safety as well as engagement, and measure and capture improvement in cardiac function over time.

THE AMYLOIDOSIS FORUM

In 2019, a public-private partnership was formed between the nonprofit Amyloidosis Research Consortium (www.arci.org) and the US Food and Drug Administration Center for Drug Evaluation and Research. The goal of this public-private partnership is to identify and bridge the scientific gaps that pose barriers to novel drug development for the treatment of AL amyloidosis.¹⁵ This public-private partnership seeks to leverage the expertise and resources of all stakeholders (academia, industry, patients, and regulatory agencies) for the conduct of mutually beneficial scientific activities in the precompetitive domain to support bringing new, safe, and efficacious therapies to patients with AL amyloidosis.

The Amyloidosis Forum subsequently launched a series of virtual workshops to focus on the development of novel, patient-relevant end point components and analytical strategies for clinical trials in AL amyloidosis (Figure 1).

APPROACH TO DEVELOPMENT OF A NOVEL MULTIDOMAIN END POINT FOR AL AMYLOIDOSIS TRIALS

In 2020, the Amyloidosis Research Consortium-Food and Drug Administration public-private partnership convened a series of specialized working groups in the areas of cardiac, hematologic, renal, and other (gastrointestinal, neurological, hepatic, and autonomic) organ systems to identify organ-specific end point components as the next step toward development of a novel multidomain composite end point for trials in AL amyloidosis. Additional working groups reviewed potential HRQOL measures and statistical approaches to analysis of clinical trial data.

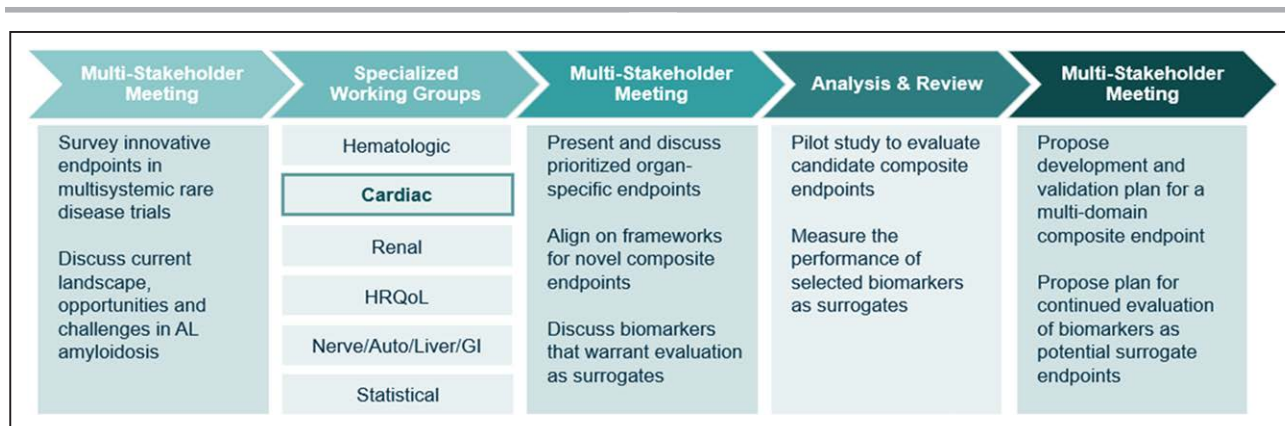


Figure 1. A community approach to development of a novel multidomain end point in immunoglobulin light chain (AL) amyloidosis.

The Amyloidosis Forum set out to develop a novel multidomain composite end point and analyses methods for use in clinical trials for AL amyloidosis. Specialized working groups identified and prioritized organ-specific and health-related quality of life (HRQoL) end points; an additional working group focused on statistical approaches to analysis of clinical trial data. From these recommendations and post hoc analysis of available clinical trial data, the Amyloidosis Forum will develop and evaluate candidate composite end points and potential surrogate end points to facilitate drug development in AL amyloidosis. Auto indicates autonomic; and GI, gastrointestinal.

The Cardiac Working Group was comprised a patient representative, a statistician, and a panel of experts in cardiology and hematology representing academia, industry, and regulatory agencies (Food and Drug Administration and MHRA) and used a modified Delphi process to reach consensus recommendations. The Cardiac Working Group chairperson (M. Maurer) conducted a literature review (including review of registrational AL amyloidosis clinical trials) to identify known and potential cardiac end points. A series of meetings followed over a 3-month time period during which the Cardiac Working Group iteratively reviewed these source materials. At a follow-up meeting of the Amyloidosis Forum held on January 22, 2021, the Cardiac Working Group reported their findings and recommendations for potential cardiac end point components to be considered for future AL amyloidosis clinical trials (available at: <https://amyloidosisforum.org>). This review summarizes the proceedings of the Cardiac Working Group.

PRIORITIZED CARDIAC END POINTS

All outcome measures considered by the Cardiac Working Group are summarized in Table 1. For each end point candidate, the Cardiac Working Group was asked to consider: (1) clinical relevance, (2) available natural history data and clinical experience, (3) relevant time horizon to detect change based on natural history and timing of impact of effective treatment, (4) meaningful thresholds/minimally important clinical differences (MCIDs), and (5) gaps in knowledge regarding that end point. For this initial effort, potential cardiac end points were considered in the context of treatment with plasma cell reduction agents, with the recognition that the relative utility of the various end point components might be different in the context of a trial evaluating an antiamyloid therapy (ie, a therapy targeting the removal

of amyloid fibril deposits). Summary characteristics of the prioritized cardiac end point components are shown in Table 2 and discussed briefly below.

Overall Survival

Overall survival is recognized as an objective and clinically meaningful end point by regulatory authorities. The degree of cardiac involvement in AL amyloidosis has a primary impact on overall survival and, therefore, represents a clear, objective outcome for interventional trials.^{22–24,29} For those with advanced cardiac involvement (ie, Mayo Stage IIIb or IV), antiplasma cell therapy may not result in cardiac improvement; therefore, high mortality due to disease progression has been observed in 12 months or less, depending on the extent and rapidity of hematologic response.^{11,25,26} It was the opinion of the Cardiac Working Group that overall survival could be a viable outcome measure in those with advanced cardiac involvement because of the high expected event rate. Conversely, a mortality end point in those with early stage disease would likely contribute relatively little in an early Mayo Stage population in whom anticipated survival could be years.

Agreement was reached that a 15% relative risk reduction in mortality would be the MCID for a new therapy. From a regulatory point of view, this would be acceptable, in that no beneficial effect on mortality that is convincingly demonstrated with statistical significance is too small to matter. The estimated median survival for the population under study will vary by Mayo stage and degree of cardiac involvement; the absolute extension of survival (in months) corresponding to a 15% risk reduction is an important consideration in discerning meaningful treatment effect.

The Working Group considered whether the cause of death should be restricted to cardiovascular mortality or

Table 1. Summary of Candidate Cardiac End Points in AL Amyloidosis

Cardiac end points considered	Prioritized
Mortality	
All-cause and cardiovascular-related	✓
Hospitalizations	
All-cause and cardiovascular-related	✓
Heart failure hospitalizations	
Hospital-free time	
Days alive out of hospital	
Home days	
Biomarkers	
NT-proBNP	✓
Troponin	
Cardiac deterioration	
Cardiac progression-free survival	✓
Imaging	
Global longitudinal strain	
Extracellular volume fraction mapping	
Functional measures	
6-minute walk test	✓
Short physical performance battery	
Actigraphy	
Frailty measures	
Health-related quality of life	
Kansas City Cardiomyopathy Questionnaire	✓
New York Heart Association Classification	

AL indicates immunoglobulin light chain; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

if all-cause mortality is more appropriate given the multisystemic nature of AL amyloidosis. In a pivotal trial of tafamidis for the treatment of transthyretin-mediated amyloidosis (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial [ATTR-ACT]), the primary efficacy end point was a Finkelstein-Schoenfeld Analysis of all-cause mortality and frequency of cardiovascular-related hospitalizations. From that trial, 29.5% of tafamidis-treated subjects died, as opposed to 42.9% of placebo-treated subjects.³⁰ Total cardiovascular-related deaths were reported for 20.1% and 28.2% of subjects in the tafamidis and placebo treatment arms, respectively.³¹ Thus, in ATTR-ACT, cause-specific death would have contributed less to the overall trial mortality outcome than was achieved using all-cause mortality as a component of the primary end point.

Given the additional element of direct light chain myotoxicity present in AL amyloidosis, it is possible cardiovascular death may be more predominant in AL amyloidosis with cardiac involvement. Data from implanted monitors suggest that bradyarrhythmias, not tachyarrhythmias, are more often the cause of sudden cardiac death in AL amyloidosis.³² Additionally, results from a chemotherapy trial suggest sudden death is a relatively

rare event in these patient populations.³³ Thus, the Working Group did not recommend including sudden cardiac death as a specific end point in AL cardiac amyloidosis trials given the potential rarity of this end point coupled with the inability to accurately discern if a death was sudden based on retrospectively obtained data.

Additional considerations include the occurrence of extracardiac organ failures in AL amyloidosis, as well as noncardiac toxicities, associated with drugs administered to treat the underlying plasma cell dyscrasia. Considering all these elements, the Cardiac Working Group favored the inclusion of all-cause mortality as an efficacy outcome measure (with secondary assessment of cardiovascular mortality).

Another issue related to mortality that was considered by the Cardiac Working Group was the necessity of adjudication of the cause of death (as opposed to accepting the investigator's determination as to the cause of death). In some trials where blinding of investigators to treatment assignment is not feasible, blinded adjudication of cause-specific death may be a reasonable approach. However, if all-cause mortality is the choice for inclusion into an end point composite for primary efficacy, adjudication becomes less of an issue. In addition, the need for cause-specific death adjudication does not appear to be supported by recent experience. Specifically, a comparison of death adjudication by investigators versus a central end point committee in a randomized, placebo-controlled study concluded adjudication did not significantly change the final trial result compared with investigator judgment and that the benefits of an adjudication committee warrant reconsideration.³⁴ In a randomized, active-controlled trial, use of investigator-determined rather than adjudication committee-determined cause of death would have resulted in more events contributing to the primary outcome and a statistically significant primary end point.³⁵

The Working Group noted limitations to stringent prospective death adjudication criteria which may not account for the interpretation of confounding factors by the attending physician and could result in removal of events from a primary outcome analysis. Furthermore, it was recognized that adjudication committees are resource intensive, and in rare diseases, it may be preferable to redirect those resources into enrolling larger numbers of subjects. The Working Group acknowledged that opinions on this subject by regulators may vary by region but felt that this was an issue worthy of exploration.

Finally, the Cardiac Working Group anticipates that a hierarchical/ranked analysis approach may be particularly relevant to trials in AL amyloidosis to enhance statistical power with survival as a component of the primary end point hierarchy. Additional statistical analysis is needed to discern the utility of survival as part of a ranked hierarchical analysis (eg, Finkelstein-Schoenfeld analysis) or if there is value in using restricted mean survival times compared with traditional metrics.¹⁶

Table 2. Prioritized Cardiac End Points for Clinical Trials in AL Amyloidosis

Characteristic	Survival	Hospitalization	Biomarker (NT-proBNP)	6-Minute walk test	Kansas City Cardiomyopathy Questionnaire	Cardiac progression-free survival
Objective	Yes	Yes	Yes	Yes*	Yes*	Yes
Clinically relevant	Cardiac involvement and mortality common ^{9,10}	Valid measure of morbidity in heart failure	Employed in clinical practice to prognosticate and monitor response to therapy	Recognized standard measure of function that is employed in other rare disease for regulatory approval	Recognized measure in heart failure that has defined response criteria	Cardiac progression predictive of survival
		Related to survival ¹⁶	Predictor of survival ¹⁷⁻²⁰			
Meanful threshold	15% relative risk reduction in mortality	20% relative risk reduction	>30% and >300 ng/L if baseline >650 ng/L	Threshold of ≥300 meters associated with improved survival	5-point change ²¹	Progression: NT-proBNP increase >30% and >300 ng/L if baseline >600 pg/mL
				33-meter improvement as used in other cardiopulmonary disorders ⁵ is independent predictor of survival		
Time horizon	<1 to >4 y dependent on: Disease stage Depth of hematologic response	Dependent on disease stage	As early as 3 mo but often at 6 mo	Only data at 12 mo	Not established	Not established ²⁰
			Early indicator	Dependent on therapy duration/side effects		
Natural history	Yes ²²⁻²⁶	Limited data	Yes	Yes ^{27,28}	Unknown	Unknown
Potential limitations	Requires longer time to achieve outcome	Hospitalizations cluster before mortal event	Labile/variable in measurement	May deteriorate during treatment before improving	No data in AL amyloidosis	Exploratory
	Deprioritizes comorbidity and patient journey	Variable clinical practice internationally	Influenced by other factors (eg, dietary indiscretion, steroid use, anemia, etc)	Not routinely used in clinical practice	Dependence on stage of cardiac involvement not understood	Not known if predictive of survival/hospitalization
				Limited data from single-center study		
				Utility only after 12 mo		Component of progression not yet defined

AL indicates immunoglobulin light chain; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*In the context of a double-blind trial.

Hospitalization

Reduction in hospitalization (both all-cause and cardiovascular-related) is a highly relevant, recognized clinical end point of morbidity in heart failure.³⁶ Hospitalizations are quantifiable and potentially objective albeit limited by geographic, regional, and investigator practice variability.³⁷⁻³⁹ However, within the confines of a blinded trial where homogeneity in randomization can be assured, regional practice variability should not be a source of problematic bias. There is precedent for assessment of all-cause mortality, followed by frequency of cardiovascular-related hospitalizations according to the Finkelstein-Schoenfeld method.³⁰ Agreement was reached that a 20% relative reduction in hospitalization would be clinically meaningful in patients with AL cardiac amyloidosis.

Of particular importance for patients and a reflection of the patient journey is the duration of life outside of hospital (ie, days alive out of hospital or home days), as a meaningful measure related to both mortality and hospitalizations.^{16,40-42} A retrospective study evaluated risk-adjusted 30-day home time (out of a hospital or facility) as a hospital level quality metric among patients discharged after hospitalization for heart failure, and this was found to be associated with 30-day readmission, 30-day mortality, and 1-year mortality outcomes.⁴³ To date, hospitalization data from large multicenter trials in AL amyloidosis have not been systematically investigated for days alive and out of hospital. Hospitalizations

also tend to cluster near mortality. While meaningful, the Working Group concluded days out of the hospital are not appropriate for inclusion as a primary end point and requires more data to be considered as part of a composite but may have benefit as a pharmacoeconomic outcome. Alternative end points that reflect outpatient interventions (eg, unscheduled visits to health care provider or administration of intravenous diuretic) may also reflect clinically important worsening symptoms.³⁶ Such encounters, which are defined as urgent heart failure visits, have been included in ongoing Phase 3 trials for transthyretin cardiac amyloidosis as part of the primary end point. Hospitalization-associated end points inclusive of other relevant health care utilization should be prospectively defined with input from regulatory bodies.

Biomarkers: Pathophysiological Role and Predictive Value in AL Amyloidosis

The Working Group reviewed available evidence from the literature for troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as relevant biomarkers in AL amyloidosis and considered utility in clinical practice (Table 1). High sensitivity cardiac troponin and changes in NT-proBNP have been shown to correlate with outcome,⁴⁴ and troponin in combination with NT-proBNP improves the prognostic staging of patients with AL

amyloidosis.⁴⁵ However, there are currently no data on the use of cardiac troponin (including high sensitivity) in defining cardiac response criteria, particularly in the context of a prospective interventional clinical trial.

Of the circulating biomarkers considered, NT-proBNP is currently the cardiac biomarker best positioned as an end point. Available data from numerous retrospective and prospective studies suggest NT-proBNP could be considered a surrogate for survival in AL amyloidosis in response to antiplasma cell therapy.^{17,19,46} In non-AL amyloidosis heart failure, multiple mechanisms may influence NT-proBNP levels, and these may not be causally related to the pathobiology of the condition (Figure 2). These multiple mechanisms play a role in influencing the NT-proBNP plasma levels in cardiac AL amyloidosis as well, but other mechanisms such as toxic free light chain injury are possibly the main determinants of NT-proBNP elevation. It has been postulated that NT-proBNP levels in AL cardiac amyloidosis reflect, in addition to the mechanisms found in non-AL amyloidosis heart failure, cardiac damage due to direct insult to ventricular cardiomyocytes by toxic light chains or amyloid fibrils, thereby providing biologic plausibility as a relevant biomarker.^{19,47} Reductions in NT-proBNP levels in patients with AL

cardiac amyloidosis follow the achievement of hematologic response and are not sustained in the absence of a very good partial or complete hematologic response.¹⁸

Multiple streams of evidence support NT-proBNP as a surrogate biomarker in AL cardiac amyloidosis. In clinical practice, NT-proBNP is also used to guide patient management. Elevated NT-proBNP in AL amyloidosis patients without cardiac involvement at diagnosis is predictive of subsequent cardiac involvement.⁴⁸ NT-proBNP levels correlated with the mean SF-36 score. In a longitudinal evaluation of HRQOL in patients with AL amyloidosis, an association between risk of death and baseline SF-36 physical component summary scores has also been shown.⁴⁹ Among patients with an NT-proBNP response, the improvement was seen in physical function, social roles, global mental health, and anxiety. Among patients with an NT-proBNP progression, worsening was seen with anxiety, depression, sleep, and global mental health.⁵⁰ A prospective cohort study in newly diagnosed patients showed improvement in Patient Reported Outcomes Measurement Information System (PROMIS Global Health v1.2 and PROMIS-29 Profile v2.0) measures at 1 year which were associated with changes in NT-proBNP levels. In a contrast enhanced

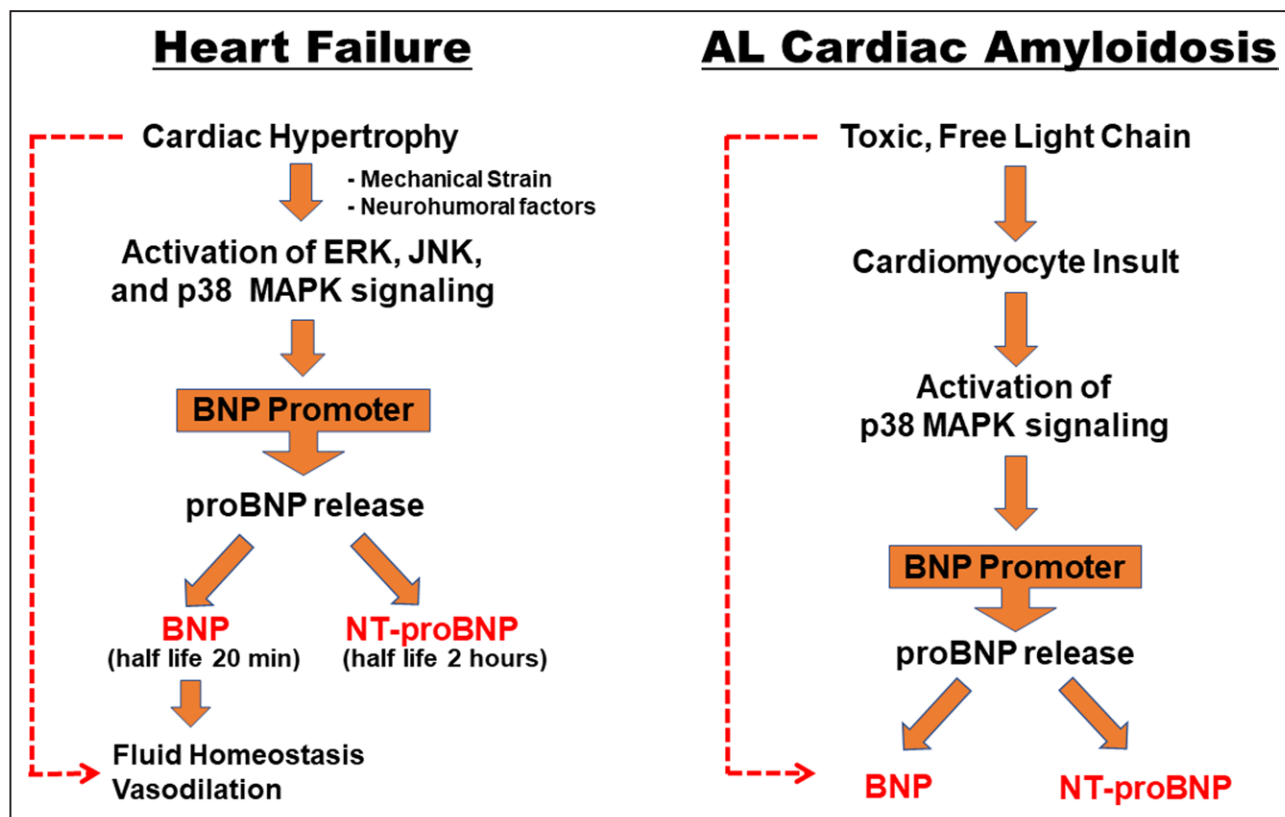


Figure 2. Pathophysiology and biologic plausibility of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a relevant biomarker in immunoglobulin light chain (AL) amyloidosis.

In non-AL amyloidosis heart failure, multiple pathways influence biochemical response to cardiac stress; NT-proBNP release is primarily related to myocardial stress (**left**). In AL amyloidosis, elevations of NT-proBNP levels directly reflect cardiomyocyte insult by toxic light chains (**right**) in addition to stress induced by extracellular amyloid fibrils. BNP indicates B-type natriuretic peptide; ERK, extracellular-signal regulated kinase; JNK, c-Jun N-terminal kinases; and P38 MAPK, 38-kDa mitogen-activated protein kinase.

cardiac magnetic resonance imaging study, NT-proBNP correlated with indicators of myocardial amyloid burden such as left ventricular mass, late-gadolinium enhancement, and extracellular volume.^{51,52}

The kinetics of cardiac response are well defined after hematologic complete response. NT-proBNP levels have been shown to be predictive of response and overall survival in multiple trials (Table 3).^{17,20,44,53–57} Although the cardiac response evaluated using NT-proBNP was validated at 3 and 6 months, in the original international multicenter study,¹⁷ 2 recent international phase 3 trials showed that cardiac response can be reliably compared at 6 months.^{19,46,58} In the ALChemistry study, a prospective nonrandomized cohort study of patients with AL amyloidosis undergoing chemotherapy in the United Kingdom, NT-proBNP at 12 months was associated with survival.^{59,60} This suggests that timing and type/duration of therapy are critical aspects to take into consideration.⁶¹

Cardiac response criteria based on NT-proBNP changes with plasma cell reduction therapy have been defined by a multicenter collaboration¹⁷ and have been shown to be useful in both retrospective and prospective studies (Table 3). Meaningful thresholds are established for both response (decline of >30% and >300 ng/L if baseline >650 ng/L) and for progression (increase of >30% and >300 ng/L if baseline >650 ng/L). Graded response criteria of NT-proBNP have also been further delineated to provide additional prognostic information¹⁸: no response (<30% reduction in NT-proBNP from baseline), partial response (31% to 60% reduction in NT-proBNP from baseline), very good partial response (>60% reduction in NT-proBNP from baseline to a nadir >350 pg/mL), and complete response (nadir NT-proBNP <400 pg/mL). An international study is ongoing to validate the graded cardiac response criteria using NT-proBNP.¹⁸

Measures of NT-proBNP are variable and affected by noncardiac issues, including renal function, anemia, activation of the sympathetic and renin-angiotensin-aldosterone system, atrial fibrillation, obesity, and medications, including steroids. Given the multisystem nature of amyloidosis (>60% have cardiac and renal involvement), NT-proBNP levels in amyloidosis are likely reflective of more than just cardiac involvement, which may be one of the reasons it has performed so well in this as a method to risk stratify patients and follow disease progression and response in the context of antiplasma cell therapy. In the setting of a multicenter clinical trial, variability around measurement may be addressed by use of a central laboratory for quantification, and with sampling at multiple time points to ensure the durability of a significant change in NT-proBNP levels. Recommended response criteria should be sufficient to detect meaningful changes. Landmark analyses, slope of change, or area under the concentration curve may also prove beneficial and warrant additional exploration.

Functional Measures: 6-Minute Walk Test

Of the functional measures reviewed (Table 1), the 6-minute walk test (6MWT) is a standardized functional measure⁶² recognized by regulatory bodies, has been used to garner approval in other rare diseases for new therapies, and is familiar to cardiologists. Most hematologists do not use the 6MWT in practice; therefore, training is required in the clinical trial setting. The 6MWT has been shown to correlate strongly with other prognostic factors including Eastern Cooperative Oncology Group performance status and the New York Heart Association Classification of Heart Failure.⁶³

In a large, single-center study, a baseline 6MWT distance of 300 meters, independent of Mayo staging, was associated with overall survival; inability to perform the 6MWT was an indicator of extremely poor prognosis.²⁸ An improvement of 33 meters is generally considered clinically meaningful in cardiopulmonary disorders.^{27,64} In patients with AL amyloidosis, preliminary data suggest a 33-meter improvement was independent of hematologic response in predicting survival and improvement at 12 months was only observed in patients who achieved complete hematologic response.²⁸

Data on the temporal evolution of the 6MWT in AL amyloidosis is limited. Notably, the 6MWT distance in patients receiving antiplasma cell therapy fell significantly by 6 months and then rose again by 12 months.²⁸ Thus, timing of assessments may be problematic due to treatment toxicities obviating early improvements. A 12-month landmark may be reasonable, with earlier improvements possible based on tolerability and mechanism of drug action, although available data suggest earlier testing may not show improvements.

Potential limitations include confounding comorbidities (eg, neuropathy) that may preclude an individual from performing the 6MWT. In the clinical trials setting, the inability to perform a 6MWT should be documented on the case report form and should be accounted for in the analysis. Furthermore, the 6MWT has a strong motivational component and is inherently subject to both physician and patient bias, necessitating effective blinding to interpret its results. Additional prospective multicenter data is required to further qualify this functional outcome and its utility as an end point in trials of AL amyloidosis.

Patient-Reported Outcomes: Kansas City Cardiac Questionnaire

The Kansas City Cardiac Questionnaire (KCCQ) is an objective, standardized measure recognized by regulatory bodies and familiar to cardiologists. Data specifically in AL cardiac amyloidosis is not available, but in ATTR cardiac amyloidosis, tafamidis was associated with better scores on KCCQ-12 than placebo,⁶⁵ and the instrument

Table 3. Summary of Clinical Trials Demonstrating That NT-proBNP or BNP Response Predicts Clinical Outcome

Reference	Population (N)	Median age, y	Cardiac involvement (%) [*]	Median survival	
				NT-proBNP responder [†]	NT-proBNP nonresponders
Palladini et al ⁵³	No prior treatment (51)	63	100	>80% at 40 mo	≈13 mo
Kastritis et al ⁵⁴	Newly diagnosed and prior treatment (94)	62	73	>80% at 36 mo	≈12 mo
Palladini et al ⁴⁴	Newly diagnosed (171)	64	70	>80% at 60 mo	8 mo
Palladini et al ¹⁷	Newly diagnosed (test cohort: 816)	63	69	>65% at 48 mo	≈10 mo
	(Validation cohort: 374)	64	84	>75% at 48 mo	≈15 mo
Kastritis et al ⁵⁵	Newly diagnosed (85)	67	67	≈45 mo	≈10 mo
Rezk et al ⁵⁶	Newly diagnosed with renal and cardiac involvement (318)	66	100	Highly significant (protective) predictor of death (HR, 0.24 [0.12–0.51]; <i>P</i> <0.001)	NT-proBNP progression highly significant predictor of death (HR, 3.67 [1.79–7.53]; <i>P</i> <0.001)
Lillness et al ⁵⁷	Newly diagnosed (94)	59	100	>60% at 120 mo [‡]	34 mo [‡]

BNP indicates B-type natriuretic peptide; HR, hazard ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

^{*}Cardiac involvement = percentage of patients with New York Heart Association class ≥2.

[†]Median survival not reached.

[‡]Used BNP (or BNP progression).

Adapted from Merlini et al¹⁹ with permission. Copyright ©2016, Springer Nature.

performed well in transthyretin cardiac amyloidosis (ATTR-CA) trials.³⁰

A 5-point change is considered the MCID; meaningful thresholds of 5, 10, and 20 points represent small, moderate-to-large, and large-to-very large clinical changes.²¹ The natural history in AL amyloidosis has not been delineated sufficiently to establish the relevant time horizons for meaningful change and treatment modification; a reasonable estimate of 6 months may be extrapolated from ATTR-CA.³⁰

It is not known how the KCCQ performs in AL cardiac amyloidosis, or in patients with AL amyloidosis absent cardiac involvement. The Cardiac Working Group recommended further validation of the KCCQ in patients with AL amyloidosis and cardiac involvement. Given the multisystemic nature of AL amyloidosis and the lack of existing data in the indication, consideration of a general measure such as the SF-36 may be a complementary HRQOL outcome tool in future research.⁶⁶ A separate HRQOL Working Group was also formed to perform an in-depth assessment of available patient-reported outcomes and relevance to patients with AL amyloidosis.

Exploratory End Points: Cardiac Deterioration Progression-Free Survival

Progression-free survival (PFS) is commonly used in oncology trials to measure time until disease recurrence/worsening or death from any cause. Using clearly defined criteria, PFS is likely most useful in setting where a survival trial would impractical, such as early or intermediate-stage AL amyloidosis. This approach is clinically relevant given (1) cardiac involvement is the primary determinant of survival and (2) cardiac deterioration/progression is a predictor of survival.

Although there are no existing cardiac deterioration PFS criteria defined in AL amyloidosis, a phase 3 clinical trial applied major organ deterioration PFS as a composite key secondary end point.⁶⁷ Major organ deterioration PFS was defined as any one of the following events (whichever came first): death; cardiac deterioration (requiring cardiac transplant, left ventricular assist device or intraaortic balloon pump); end-stage renal disease requiring hemodialysis or renal transplant; or hematologic progression per consensus guidelines.⁶⁸ However, the Cardiac Working Group noted that the major organ deterioration PFS included cardiac events that are very rare (use of mechanical circulatory support and transplant) and are highly dependent on the experience of the center, thereby limiting their broad utility.

The Cardiac Working Group proposed meaningful thresholds for cardiac deterioration PFS based on available NT-proBNP data in AL amyloidosis whereby progression would be defined as a >30% and >300 ng/L increase in NT-proBNP levels assuming a NT-proBNP of at least 650 ng/mL at baseline.

The concept of cardiac deterioration PFS is exploratory, there are no prospective data in AL amyloidosis using this metric to show meaningful change. The delayed timing of organ recovery following antiplasma cell therapy is a consideration in using this end point. In one study, time to cardiac response among hematologic responders was 9.4 months.¹⁸ Additional work is needed to develop cardiac response/PFS criteria to assess whether there is added value to the prediction of definitive outcomes (survival and hospitalizations).

OTHER END POINTS CONSIDERED

Other functional, patient-reported outcomes, and biomarkers were not considered further at this time primarily

because of either lack of sufficient data in the setting of AL amyloidosis (Table 1). The Cardiac Working Group also discussed multiple imaging variables (Table 1).

Imaging

Global longitudinal strain is a strong prognostic marker but limited in evaluating the impact of an antiplasma cell-directed therapy due to poor signal to noise ratio, high inpatient variability, and a long time horizon to show meaningful change (MCID: 1.5%–2% change in newly diagnosed patients) of at least 1 year.⁶⁹ By contrast, in an open-label trial, patients with relapsed/refractory AL amyloidosis and cardiac involvement, improvements in global longitudinal strain and NT-proBNP were observed in as little as 12 weeks following administration of an investigational monoclonal antibody therapy targeting light chain amyloid fibrils.⁷⁰

Cardiac magnetic resonance has lately emerged as a robust technique that can provide unique information about tissue composition. Cardiac magnetic resonance can visualize, with late-gadolinium enhancement,⁷¹ and measure, with T1 mapping, the continuum of cardiac amyloid deposition. T1 mapping, before the administration of contrast,^{72,73} can measure the intrinsic signal from the myocardium (native myocardial T1), while T1 maps preadministration and postadministration of gadolinium-based contrast can be used to calculate the myocardial extracellular volume.^{74,75} Both native myocardial T1 and extracellular volume have been extensively validated in cardiac amyloidosis as surrogate markers of infiltration.^{52,71,73–75} Native myocardial T1 provides a composite signal from the intra and extracellular spaces, a signal potentially influenced by other pathophysiological mechanisms beyond simple amyloid load, while extracellular volume measurements enables us to isolate the signal from the extracellular space and is, therefore, considered a more specific measure of amyloid infiltration. Myocardial extracellular volume by cardiac magnetic resonance can track amyloid regression in cardiac AL amyloidosis,⁷⁶ and likely would be most relevant as an end point in evaluating antiamyloid therapies to demonstrate activation of the pathway of interest and removal of amyloid. A MCID of 5% absolute difference was suggested for this parameter. Programs aimed at standardization across centers are in progress and likely to define biochemical and structural abnormalities caused by AL amyloid fiber deposition, the reversal of which may be useful as end points in future clinical trials.

The timing of imaging assessments to assess treatment response may vary based on the therapeutic mechanism of action (ie, antiplasma cell or antiamyloid). For example, in the context of antiplasma cell therapy, which does not directly target existing deposits, a long-time course (6–12 months) may be required to demonstrate meaningful changes. For these reasons, imaging

modalities were considered to be more suitable for proof-of-concept measures in phase 1 and 2 studies and to evaluate mechanisms of action as part of pivotal phase 3 programs.

In general, the group agreed on importance of establishing mechanisms to ensure rigor and reproducibility in imaging modalities to assess structural cardiac changes (eg, extracellular volume and global longitudinal strain) for use in pivotal multicenter trials. Core labs with expertise in these modalities will be critical. The Working Group strongly supported investigation of imaging in smaller mechanistic studies throughout a drug development program and emphasized the importance and utility of imaging in all clinical trials to delineate drug mechanism of action, durability of response, and optimal treatment duration in the case of antiamyloid therapies.

FUTURE DIRECTIONS AND POTENTIAL LIMITATIONS

Given the systemic, multiorgan, heterogeneous nature of AL Amyloidosis, the Amyloidosis Forum is working toward identifying appropriate end points and analytical methodologies for use in clinical trials investigating novel therapies. Cardiac end points are critical components of a multidomain end point given the devastating impact of cardiac involvement for patients with AL amyloidosis. The Cardiac Working Group sought to identify and prioritize cardiac end points as the next step toward development of a novel multidomain end point for trials in AL amyloidosis. Overall, consensus was reached with respect to thresholds for clinically meaningful changes and timeframes for each prioritized end point component.

The Cardiac Working Group identified 6 potential end points, and graded their utility based on disease stage (Table 4). The delineation by disease stage was pragmatic and based on established natural history. For example, a trial in early stage disease with a mortality end point would have few events and would, therefore, have a long duration. Similarly, as mortality and hospitalizations are not common in early stage disease, these end points are more appropriate in patients with advanced disease.

Table 4. Utility of Selected End Points by Disease Stage of Trial Population

Cardiac end point	Early stage	Intermediate stage	Late stage
Overall survival/mortality reduction	±	++	+++
Hospitalizations (all-cause/cardiovascular)	+	++	+++
Biomarker (NT-proBNP response)	++	+++	+++
Functional measure (6MWT distance)	+	++	++
Health-related quality of life (KCCQ)	±	++	++
Cardiac progression-free survival	?	?	?

6MWT indicates 6-minute walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Mortality and some measure of cause-specific hospitalization were identified as important key end points for trials conducted in late-stage patients. In the context of all AL amyloidosis trials, all deaths and life-threatening events occurring in the context of a sponsored clinical trial must be thoroughly documented. Causes of death, whether from progressive heart failure (which is common), or sudden cardiac death (which is less common), and interventions such as placement of pacemakers, implantable cardioverter-defibrillators, and other cardiac procedures/therapies should be systematically ascertained throughout a trial and reported to inform the natural history of the patient population under study.

NT-proBNP was identified as a useful outcome measure across the spectrum of AL amyloidosis Mayo Stages. Specifically, the Cardiac Working Group identified NT-proBNP as an integral end point that should be examined in all interventional trials conducted in patients with AL cardiac amyloidosis. In AL cardiac amyloidosis, NT-proBNP correlates with both improvement and progression in vast majority of patients.¹⁹ Despite variability in the context of both retrospective and prospective trials, NT-proBNP response criteria have been shown to predict survival. The Working Group agreed that the evidence establishes NT-proBNP as a relevant biomarker in AL amyloidosis based on disease pathophysiology—toxic light chains stimulate myocellular production of NT-proBNP.

The Cardiac Working Group emphasized the specific importance of NT-proBNP in AL amyloidosis and will seek formal advice from regulatory agencies as to the most efficient pathway with which to gain acceptance for the use of NT-proBNP as the basis for accelerated approvals for treatments of AL amyloidosis without regard to precedent in unrelated indications.^{77–79}

Data on 6MWT and KCCQ in AL amyloidosis are limited, but it was the sense of the working group that they would be more useful as end points for intermediate or late cardiac stage patients than earlier stage patients (Table 4). For example, there is limited data on 6MWT results in patients with AL amyloidosis obtained postintervention.²⁸ Therefore, the timing of assessments to date precludes it from showing an earlier indication of benefit. Prospective data from earlier time points would be needed to demonstrate the utility of early assessment with the 6MWT. Development of a Cardiac Progression-Free Survival end point is considered exploratory—the initial components are depicted in Figure 3. The working group will further explore its potential utility in the setting of AL amyloidosis trials.

While there are challenges in designing trials with newly diagnosed patients, the study of patients with relapsed/refractory AL amyloidosis presents additional challenges. Established response criteria, median overall survival, and cardiac and renal response/progression criteria were all defined using reference data from the first-line therapy setting¹⁷ and may not be applicable to second- or third-line therapy in relapsed/refractory patients. More work is required to understand the utility of these end points in the context of drug development trials conducted in the relapsed/refractory setting.

For clinical trials conducted in patients with AL amyloidosis at risk of cardiac failure, the Cardiac Working Group recommends inclusion of both clinical outcomes (death, cardiovascular hospitalizations, and urgent outpatient visits for heart failure) and biomarker-based outcomes (NT-proBNP) as appropriate for the intervention and population under study (Figure 3). The Cardiac Working Group has summarized the evidence and recommended

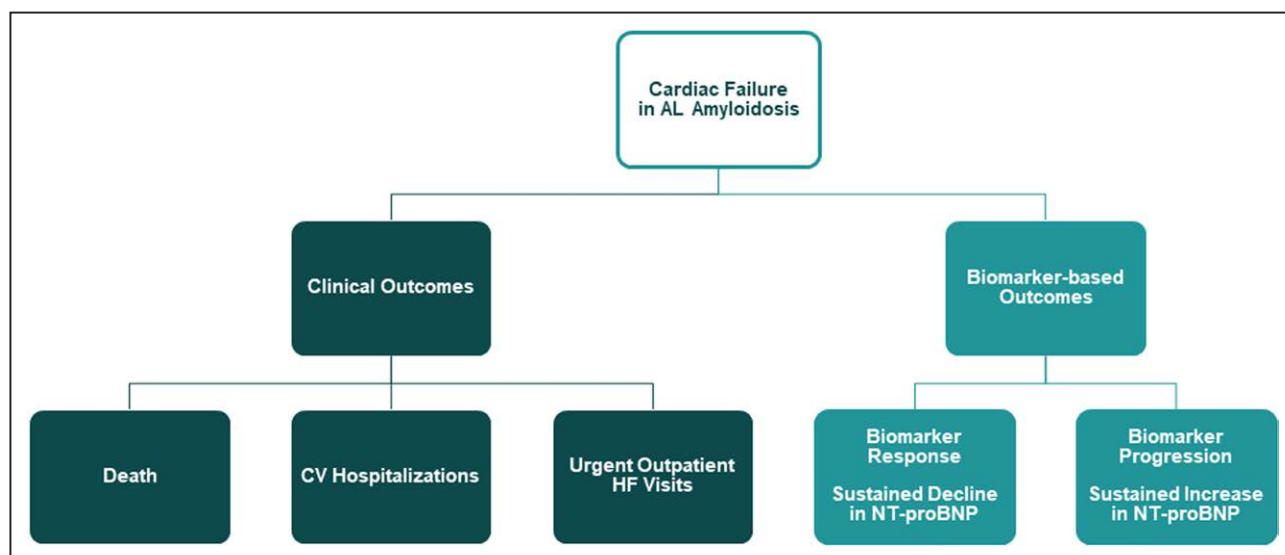


Figure 3. Proposed components of progression in cardiac immunoglobulin light chain (AL) amyloidosis.

Proposed components of a composite heart failure outcome for use in AL amyloidosis clinical trials. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been demonstrated to be a surrogate for cardiac death. Meaningful thresholds are established for both response (decline of >30% and >300 ng/L if baseline >650 ng/L) and for progression (increase of >30% and >300 ng/L if baseline >650 ng/L). CV indicates cardiovascular; and HF, heart failure.

implementation of NT-proBNP as an informative prognostic biomarker and potential surrogate to assess either response or progression.

The working group agreed that further qualification of these prioritized end points is required across multicenter trial datasets in early and intermediate-stage disease. The group has identified the lack of available prospective data for supporting several cardiac candidate end points as a key limitation to their use in clinical trials. The Cardiac Working Group will seek to obtain and analyze data sets from prospective interventional trials to further qualify these end points with respect to the timing and population baseline severity for which changes in these measures will be most predictive of response to therapy and clinical outcomes. The community of patients with AL amyloidosis and the physicians who treat them stand ready to support further studies to this end.

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