Amyloidosis The FORUM

Great Room, US Food and Drug Administration
Wednesday, October 22, 2025. 8:30-4:00pm EST

2025 Amyloidosis Forum Annual Meeting

CROSS STAKEHOLDER WORKING GROUP PROJECTS TO ACCELERATE DRUG DEVELOPMENT IN AL AND ATTR AMYLOIDOSIS

Amyloidosis Research Consortium

INTRODUCTION

The Amyloidosis Forum

About the Forum

The Amyloidosis Forum, a public private partnership, was launched in 2019 with the goal of bridging the gaps in drug discovery and development in AL and ATTR amyloidosis through multi-stakeholder collaboration.

> *How do we make the next 10 years truly transformational for patients?*
>
> *When we partner, we deliver the speed, precision and hope that patients deserve...The forum represents what is possible...working towards one goal.*
>
> **— Isabelle Lousada, CEO and Founder, Amyloidosis Research Consortium (ARC)**

> *There is an upbeat vibe in the room - very different from the early days.*
>
> *No one person can do this.*
>
> *This community has delivered reliable evidence of clinical benefit...patients are better off for this.*
>
> **— Norman Stockbridge, MD, PhD, Consultant, S & S Consulting Partners LLC**

The Forum has organized 3 working groups – each focused on one of 3 areas that have been prioritized as representing key scientific and regulatory challenges to drug development in AL and ATTR amyloidosis:

- Standardization of Imaging
- Prognostic Factors
- Clinical Trial Endpoints

This report summarizes the working group updates and discussions that occurred during the 2025 Annual Forum Meeting.

INTRODUCTION

Thank You

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OVERVIEW

Amyloidosis Research at a Crossroads

From Current Challenges to Innovative Solutions

Moderators: Mat Maurer, MD, New York-Presbyterian Hospital, Columbia University Medical Center, USA; Ashutosh Wechalekar, MD, University College London, UK

Dr Maurer presented an overview of the challenges in ATTR cardiac amyloidosis – once considered a rare, underdiagnosed, and untreatable condition, but now known to be not uncommon and to present with a heterogeneous phenotype (diverse LVEF, LV thickness and ECG findings). The possibility of a non-invasive diagnosis on a single day in the majority of patients represents a major advance, and this together with increased awareness and a range of available effective therapies have resulted in improved outcomes. Questions remain that physicians face every day in the clinic - can the choice of initial therapy be matched to a particular patient profile? When should therapies be switched, stopped or combined? Should non-symptomatic patients be treated? How should disease progression be assessed? Moreover, while having multiple therapies with distinct MOAs is undoubtedly beneficial for the patient, decisions about which option to choose for which patient are currently made in the absence of head-to-head data, and such comparative effectiveness trials are unlikely. Real world evidence from observational trials and registries represent a potential source of information on comparative effectiveness and are extremely valuable for drug development programs – and a number of lessons have been learned – FDA and other regulatory bodies should be engaged early, and data collection must be performed in a standardized fashion. Importantly, to make the most the data collected, it must be shared. While the barriers are understandable, the sharing of data should be incentivized and encouraged. Finally, the design of clinical trials and the identification of a treatment effect is complex in a disease such as ATTR amyloidosis that is multi-systemic and consequently heterogeneity is the norm.

Dr Wechalekar discussed the situation in AL amyloidosis, and while there have been real advances in this rare disease, the landscape is very different to that of ATTR amyloidosis. Treatments are faced with addressing 3 targets – the abnormal plasma clone, the abnormal proteins produced that are themselves toxic, and the deposition of the proteins into organs and the subsequent damage. In contrast to the treatment options for ATTR amyloidosis, there is only one formally licensed treatment regimen for AL amyloidosis (daratumumab, cyclophosphamide, and dexamethasone [Dara-CyBorD]). Targeting the underlying plasma cell dyscrasia has proved successful, with survival improving over the last 25 years (2.5 years to 7.3 years)-largely driven by an improvement in the depth of the hematologic response, with deeper responses translating to improved overall survival. The rapid and deep responses obtained with daratumumab and other drugs now being studied in clinical trials have meant response criteria must be redefined to capture the early treatment benefits. As patients are living longer overall survival becoming a challenging endpoint to achieve. Adoption of novel endpoints could include evaluations of treatment impact on organ (biomarkers), QoL, imaging, and will face the challenge of validation where registry data will play a key role. The success of Dara-CyBorD in the front-line setting has also led to a significant unmet need-how to treat patients who progress or who have an inadequate response. On the horizon for patients with AL amyloidosis are an ever-expanding range of range of targets for plasma cell therapies, together with advances in amyloid -stabilizers and agents that target amyloid removal. Learning from completed trials is vital, and consequently (as with ATTR amyloidosis), the hurdles associated data sharing must be overcome.

A number of common challenges remain

- **Data sharing – there are obvious barriers, but patients want their data to be shared to enable drug development.**
- **Patient heterogeneity – makes designing and running a clinical trial difficult.**
- **Maintaining a patient focus in terms of endpoints– moving away from purely survival and towards how patients feel. Could a PRO be a primary endpoint?**

Finally, although the focus of the discussion was ATTR and AL amyloidosis, there was an acknowledgment that much rarer forms of amyloidosis need to be addressed. Are these patients being left behind? How do we move the needle in term of patient identification and treatment? Registry data and interrogation of electronic health records (AI driven) will be vital – and again, the sharing of data will be imperative as no one Center will have enough patients with very rare forms of disease.

WORKING GROUP

Standardization of Imaging

Moderators: Sharmila Dorbala, MD, Brigham and Women's Hospital, Harvard Medical School, USA; Ahmad Masri MD, MS, Oregon Health and Science University, USA

Dr Soman (University of Pittsburgh) discussed the available imaging modalities in cardiac ATTR amyloidosis that have proved transformative for the field by elucidating the true prevalence of the disease (not considered rare anymore) and making trials significantly easier (no need for a biopsy for diagnosis). Despite this, imaging endpoints have not been used in clinical trials – a reflection of gaps in our understanding of the disease, including a lack of an imaging metric that reflects amyloid burden and the complexity between cardiac function and symptoms/outcomes (i.e., how the patient is feeling). In addition, Tc-based scans (Tc-PYP, HMDP, DPD), are simple procedures that have proved transformative (used in 1000s of patients), however knowledge gaps still exist. What is the real-world sensitivity of scintigraphy? What exactly are we imaging? The significance of changes in cardiac update within Tc-based scintigraphy remains uncertain. The decreases in Tc-based imaging do not correlate with a change in cardiac structure or a response to treatment. In contrast, the PET tracers directly bind to amyloid, are highly specific tracers which may potentially image small amounts of amyloid, helping with early diagnosis. The ability to identify very early disease leads to an important question – how do we manage patients with a small amount of amyloid but no symptoms? How can we identify those patients who will progress vs. those who will not? This is a particularly important question given the cost of treatment. Further study is required to understand the lack of concordance between changes in amyloid burden and cardiac structure/function that is often observed with Tc-based scans? Clearly, as we move forward, results from imaging will be considered in concert with other metrics. While the focus is clearly on cardiac involvement, we need to evaluate uptake outside the heart. What is the utility of non-cardiac imaging? Finally, as we consider the possibility of imaging being used as a primary endpoint in clinical trials, it will be important for sponsors to engage early with imaging experts in trial design.

Dr Slivnick (University of Chicago) then discussed the opportunities to integrate artificial intelligence (AI) into cardiac imaging technology (with a focus on ECHO cardiography). The use of AI to expand access to imaging (through the identification of potential patients) and improve image-based screening has obvious implications for early diagnosis. Many questions remain including – what is the real-world performance of AI in this setting? How should AI be integrated with established clinical risk markers? What is the optimal workflow and what is the ideal reimbursement model? How can we overcome mistrust of new technology and manage the ramifications of AI-driven disease misclassification? The use AI with imaging technology also has the potential to improve the efficacy of image interpretation and enhance measurement accuracy and reproducibility for monitoring of treatment response.

Dr Fredrick Ruberg (Boston University) reported on a proposed ECHO reproducibility study developed by the Imaging Working Group. ECHO was selected based on the global availability of the technology, and the safety and (relatively) low cost. Funding is being pursued for the study.

A number of common challenges remain

- **Tc-based scintigraphy (PYP, DPD, HMDP) has enabled the identification of cardiac involvement in ATTR amyloidosis without the need for a biopsy. However, Tc-based scintigraphy does not correlate with a change in cardiac structure or a response to treatment.**
- **In contrast, the PET tracers do bind to amyloid and have the ability to identify very early disease.**
- **The integration of AI into cardiac imaging technology has implications for early diagnosis, together with the potential to improve the efficacy of image interpretation and enhance measurement accuracy and reproducibility for monitoring of treatment response**

WORKING GROUP

Prognostic Factors

Moderators: Mat Maurer, MD, New York-Presbyterian Hospital, Columbia University Medical Center, USA; Ashutosh Wechalekar, MD, University College London, UK

Dr Chakraborty (Columbia University Irving Medical Center) reviewed the prognostic factors in AL amyloidosis, including disease-specific parameters (plasma cell clone related and organ related) and patient-specific parameters (e.g., 6MWT, PRO instruments). While these are mostly static prognostic factors, there are dynamic factors that can be followed during treatment and are indicators of the depth of hematologic response (e.g., dFLC) and MRD status. This has resulted in validated staging systems. Biomarkers of progression and response to therapy should include functional capacity and markers of cardiac, renal, and hepatic function.

Dr Vaishnav (Johns Hopkins University Comprehensive Amyloidosis Center) reviewed the situation in ATTR amyloidosis where better outcomes have been achieved with early diagnosis and disease modifying treatments. Prognostic factors – tools to assess prognosis and progression-include clinical markers, biomarkers, assessments of functional capacity, PRO, imaging, and combined scores. While markers are available to assess disease progression in ATTR CM (functionality and QOL, ECHO LV strain, cardiac biomarkers), the proposed criteria for disease progression in CM are not in widespread use in routine clinical practice and there no current guidelines or consensus on what the clinically meaningful thresholds of change are. Multicenter collaborative studies are needed to develop robust guidelines. Similarly, there are no current guidelines or biomarker thresholds for ATTR-PN, although Nfl does seem to correlate with disease severity and disease progression.

Dr Wechalekar (University College London) discussed the AL-International Staging System (AL-ISS) that uses GLS with cardiac biomarkers to identify patients with stage 3C AL amyloidosis – an ultra-poor-risk cohort of patients. The original AL amyloidosis staging system (Mayo 2004) used NT-proBNP and Hs-TnT) and was subsequently revised by the addition of dFLC (Mayo 2012). The European modification of the Mayo 2004 system was also published and used an absolute value of NT-proBNP. Survival of poor risk patients has improved with advances in treatment, with the poorest risk patients better identified by the European system. As treatment options progressed with the arrival of daratumumab, outcomes have improved for the poor risk patient. However, there is a clear need to better define the poorest-risk patient group in terms of clinical trial design and ultimately the development of novel therapeutic options. GLS (LS%) represents a sensitive and specific marker in cardiac patients, with those with an LS% between 0 to -9% having poorer outcomes – and it is this group of patients who need novel treatment options. At the time of the meeting, a validation of the new system was underway to confirm GLS as an independent prognostic marker with final data in 2493 patients in UK, Europe, and the US. It should be noted that at the time of the meeting, the data was embargoed as per ASH rules however results were subsequently presented at the 67th ASH Annual Meeting (December 6-9, 2025) and have been published (Khwaja J, Kirkwood AA, Milani P, et al. New Validated Staging System for Light Chain [AL] Amyloidosis With Stage IIIC Defining Ultra-Poor Risk: AL International Staging System. J Clin Oncol. 2026;44(4):311-320. doi:10.1200/JCO-25-02558). Early data have demonstrated that the new system can separate patients with stage 3 AL amyloidosis into 3A, 3B, and 3C. Importantly, those patients with stage 3B (as per current classification which includes the ultra-poor risk stage IIIC) – although they have better outcomes – are currently excluded from clinical trials. This new system,

using the additional of a single marker, would allow their identification and inclusion AL-ISS stage IIIB should be included clinical trials. Moreover, GLS can be tracked over time. While there is a question about using GLS within a large trial conducted at a large number of sites, data indicate that GLS is sufficiently different in 3C patients so as to overcome any site-to-site variability. The question is now – can GLS data be incorporated into clinical development programs? Also- what is the role for automation of assessments using AI to ensure reproducibility and give the drug developers/regulators some confidence to overcome the variability in GLS measurements.

Within both AL and ATTR amyloidosis, could staging systems ever be used as primary endpoints within a scenario where patients move from one stage to another with treatment? Trials would have to be designed with that in mind, and as the items within staging systems are essentially biomarkers, the major question – will regulators accept changes in biomarkers as evidence of effectiveness? Could they be used for accelerated approvals? Fundamental to this is the need to understand how the magnitude of an effect on a biomarker is expected to translate into the clinical outcomes of interest.

Dr Bampatsias (Columbia University Irving Medical Center, New York) presented clinical data (including patient marker and QoL) as a framework to monitor disease progression in ATTR-CM amyloidosis. While tools are available to monitor progression and guide patient management, it is not clear which tool is the best use and how to implement into the design of a clinical trial. Moreover, as progression can occur in different domains, there is a need for a multidimensional approach. Data was presented from a study in 158 ATTR-CM amyloidosis patients from the Columbia Cardiac Amyloid Registry – all patients were on disease modifying therapy and baseline, and follow-up assessments were obtained. Most patients (69%) met at least one criterion of progression, with 36% meeting 2 or more markers. Only 31% were stable at all follow-ups in all domains. As the proposed model includes patient-centered outcomes and functional outcomes to score progression across multiple domains, there is a clear need for a multicenter collaboration to validate the scoring, and a weighted analysis must be developed to determine significance of each domain within the model.

With a focus on patient-centric assessments, physicians are often asked the question - when will I start to feel better? Fatigue is a major issue so any model must include this assessment. Frailty is another an important item to consider, especially in the elderly ATTR population. Importantly, assessments of disease progression are performed in the context of existing comorbid conditions (e.g., age, medications), so which assessment values can be assigned to amyloidosis vs. other issues. While a laudable goal would be to have a single lab value that could be used to follow disease progression, the nature of amyloid necessitates that many measures will be incorporated into a system. At the end of the day, if we assess that disease has progressed, we must be able to offer potential solutions to the patients. This is particularly important in advanced disease stages where transplant is the only option for these patients, and many are not eligible.

A number of common challenges remain

- Prognostic factors are available in AL amyloidosis, including disease-specific parameters and patient-specific parameters.
- Dynamic factors can be followed during treatment and are indicators of the depth of hematologic response and MRD status (e.g., dFLC). This has resulted in validated staging systems.
- Prognostic factors in ATTR amyloidosis include clinical markers, biomarkers, assessments of functional capacity, PRO, imaging, and combined scores.
- Proposed criteria for disease progression in ATTR-CM amyloidosis are not in widespread use in routine clinical practice and there no current guidelines or consensus on what the clinically meaningful thresholds of change are needed.
- The AL-International Staging System (AL-ISS) using GLS with cardiac biomarkers can stratify patients with stage 3 AL amyloidosis into stage 3A, 3B, and 3C. Patients with AL-ISS stage 3B, typically excluded from clinical trials, can now be identified and included.
- As amyloidosis can progress in multiple domains, models proposed to follow disease progression should include patient-centered outcomes and functional outcomes to score progression across multiple domains.

WORKING GROUP

Endpoint Development

Moderator: Angela Dispenzieri, MD, Mayo Clinic, USA

Dr Grodin (University of Texas Southwestern Medical Center, Dallas, TX) discussed the potential for AI-enabled ECG to track disease progression and response to treatment for patients with ATTR CM amyloidosis. There are currently no established surrogates for ATTR-CM treatment efficacy, and while biomarkers or imaging can be used to follow progression, studies demonstrating their utility for FDA approval are lacking. ECG is routine and inexpensive and requires little technical expertise. There are now number of AI-based ECG assessments that may be able to track disease. The working group has proposed a trial design that involves the post hoc analysis of baseline and longitudinal data from previously conducted trials in which extensive ECG data are available. As discussed previously regarding AI-driven assessments of cardiac evaluations, regulators and physicians will want to know what the error rate is and subsequently the rate of misclassifications. Such technology will also have the potential to act as an enrichment tool for a particular population for trial enrolment.

Dr. Keeney (IQVIA) discussed how the KCCQ had been used to define endpoints in ATTR-CM clinical trial populations. The working group has reviewed the literature regarding KCCQ use as an endpoint measure in clinical trials and evidence of the psychometric properties in this population. Twenty-three trials were identified that used KCCQ as primary, secondary, or exploratory endpoint measure with use increasing over time. While the majority used KCCQ as a secondary endpoint measure, it was important to note that inconsistent terminology was frequently used to describe KCCQ scores. Moreover, studies that described the psychometric properties typically presented only preliminary data; importantly limited evidence of meaningful change thresholds hinders evaluation and interpretation of change in trials. Consequently, it will be essential to establish content validity in ATTR-CM amyloidosis and to conduct further validation studies. Additionally, efforts are needed to identify which KCCQ versions and scores are best suited to ATTR-CM amyloidosis clinical trials and apply them in a consistent manner.

For regulatory bodies, the question is - what is a clinically meaningful response on the KCCQ scale? This becomes very important as we try to use KCCQ as a primary endpoint measure, and this is in the context of trial populations being healthier compared to previous populations. Given this, should we consider a different PRO – one that is simpler and more sensitive to change? Additional discussion emphasized the need to identify anchors that conceptually align with KCCQ scores, as well as the importance of gathering supportive qualitative data from patients to confirm anchor relevance and determine what level of change they would consider meaningful.

Dr Dispenzieri (Mayo Clinic) discussed the progress of the working group regarding hematologic dFLC variability and definitions of disease progression. Two challenges face this work. First, AL amyloidosis is a heterogenous disease, and there is a dependency of organ response and overall survival on hematologic response (hematologic response is essential). Second, the existing definition of hematologic progression is no longer adequate in the current era of plasma cell directed therapies. Hematologic progression was originally defined about 20 years ago in an age of very limited treatment options. A major part of the hematologic progression criteria is dependent on a minimum increase of dFLC: “a 50% increase with a minimum of 10 mg/dL,” which was fine in 2005; however, with more effective and more numerous treatment options, that

minimum is too high to be accepted by most practitioners/ investigators prompting a change in therapy before the "hematologic progression" criterion is met. These actions translate into "missed opportunities" for "events" in clinical trials, making trials lengthier and more expensive. A better definition of progression is needed, which is validated by clinical data; this is a work in progress. Finally, she touched upon the importance of regulatory body consensus regarding organ response and progression criteria, as novel agents are under development that target amyloid fibrils in organs and/or stabilizers of circulating FLCs. Contenders include proteinuria, NT-proBNP, and patient reported outcomes.

How do we get from endpoints routinely used in the clinic/academia to what regulatory bodies want (e.g., OS, 6MWT, MOD-PFS, hospitalization/death)? This issue is especially important as OS is no longer feasible for most patients given the increasing overall survival with more effective therapies. Complete hematologic response is a valid endpoint (as long as the drug is not toxic) and composite endpoints using hospitalization only work for the sickest patients. Indeed, composite/hierarchical endpoints are potentially useful, but the components need to be acceptable to all. While NT-proBNP is currently not a validated endpoint and cannot be part of a hierarchal composite endpoint, it has always proved predictive of survival. There are significant amounts of data to evaluate - another reminder about the need for data sharing, and if there is a large treatment effect on NT-proBNP, a trial could be designed and powered to confirm the benefit and validate the NT-proBNP as a surrogate endpoint. Regulatory bodies favor functional endpoints, so more data is required regarding KCCQ and 6MWT among patients with AL amyloidosis. Concerns that for the majority of patients with milder cardiac involvement, that 6MWT will not detect differences and more strenuous functional cardiac tests may be required.

Dr Leung, MD (Mayo Clinic) reviewed renal involvement in amyloidosis. Of the 42 types of amyloid proteins identified in humans to date, 14 are known to clinically involve the kidney. Amyloid targeting treatments are available for 3 types (AL, ATTR, AA), with renal response criteria available for just one (AL). There are no renal response criteria for ATTR amyloidosis, although proteinuria is typically present after cardiac and neuropathic symptoms. This is important, as data (from the NAC in London) demonstrates that a decline in kidney function in ATTR amyloidosis is associated with decreased OS (vs. stable kidney function), and while kidney function is a predictor of OS, studies often do not include proteinuria data, and few have eGFR data/ measurements. This is in spite of the fact that treatments do alter the projection of kidney function (function seems to improve on siRNA therapy, but not on stabilizers). In summary, while renal involvement in ATTR amyloidosis is becoming more recognized, future clinical studies trials should incorporate assessments of kidney function. Nephrologists must look for kidney involvement.

Dr Muchtar (Sheba Medical Center) presented data regarding tracking renal recovery and progression in AL amyloidosis, evaluating the roles proteinuria and eGFR dynamics. Historically, renal response has been primarily defined by the degree of proteinuria reduction with preservation of serum creatinine. A transition has occurred from a binary system (no response/response) to a 4-level renal response framework (CR, VGPR, PR, NR). Although renal response and progression are dependent on hematologic response, there is also a co-dependency on baseline renal factors, including age, gender, light chain isotype, baseline eGFR and proteinuria levels. Data to date would suggest that renal response is largely dependent on reduction in proteinuria while renal progression is more accurately tracked by eGFR kinetics. For example, an increase in 24-hour urine in the absence of a decline in eGFR does not predict for renal or overall survival. In contrast, a greater than 25% decline in eGFR from nadir is associated with poorer renal and overall survival. In the ongoing multicenter REWARD study, longitudinal data is being collected over a 5-year period from initiation of treatment, with the aim of evaluating dynamic interplay between eGFR and proteinuria to further identify predictors of renal response and progression in contemporary AL amyloidosis cohorts.

A number of common challenges remain

- AI-enabled ECG has the potential to track disease progression and response to treatment for patients with ATTR CM amyloidosis.
- KCCQ has been primarily used as a secondary endpoint in ATTR clinical trials. A major issue is the limited evidence of meaningful change thresholds that hinders evaluation and interpretation of change in trials.
- Given the improved median OS observed in AL Amyloidosis and the increasing number of potential treatments, OS a trial endpoint is no longer feasible for most populations.
- For plasma cells directed therapies, hematologic response and progression are important endpoints, but with improvements in outcomes with immunotherapies, a better definition of hematologic response and progression are needed.
- In addition, as novel agents are under development that do not address the clone, it is essential to develop definitions for organ response and progression incorporating using biomarkers in AL amyloidosis patients.
- While kidney function is a predictor of OS, there are no renal response criteria for ATTR amyloidosis. Renal involvement is becoming more recognized, and future clinical studies trials should incorporate assessments of kidney function.
- An ongoing study is collecting longitudinal data over a 5-year period from initiation of treatment for AL amyloidosis, with the aim of evaluating dynamic changes in both proteinuria and eGFR over time to better identify predictors of renal response and progression.

The next annual Amyloidosis Forum meeting is planned for September 30, 2026.

Amyloidosis The FORUM

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