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Development of Imaging Endpoints for Clinical Trials in AL and ATTR Amyloidosis:

Proceedings of the Amyloidosis Forum

Sharmila Dorbala, MD, MPH, MASNC[a], **Rosalyn Adigun, MD, PHARMD, MS**[b], **Kevin M. Alexander, MD**[c], **Michela Brambatti, MD, MS**[d], **Sarah A.M. Cuddy, MB, BCH, BAO**[a], **Angela Dispenzieri, MD**[e], **Preston Dunnmon, MD, MBA**[f], **Michele Emdin, MD, PHD**[g], **Omar F. Abou Ezzeddine, MD, CM, MS**[e], **Rodney H. Falk, MD**[h], **Mariana Fontana, MD, PHD**[i], **Justin L. Grodin, MD, MPH**[j], **Spencer Guthrie, MPH, MBA**[k], **Michael Jerosch-Herold, PHD**[a], **A. Alex Hofling, MD, PHD**[b], **Kristen Hsu, BS**[l], **Grace Lin, MD, MBA**[e], **Ahmad Masri, MD, MS**[m], **Mathew S. Maurer, MD**[n], **Clemens Mittmann, MD**[o], **Krishna Prasad, MD**[p,†], **Cristina C. Quarta, MD, PHD**[q], **Jean-Michel Race, MD**[r], **Joseph G. Rajendran, MD**[b], **Frederick L. Ruberg, MD**[s], **Vandana Sachdev, MD**[t], **Vaishali Sanchorawala, MD**[s], **James Signorovitch, PHD**[u], **Christophe Sirac, PHD**[v], **Prem Soman, MD, PHD**[w], **Jens Sorensen, MD, PHD**[x], **Brett W. Sperry, MD**[y], **Andrew W. Stephens, MD, PHD**[z], **Norman L. Stockbridge, MD, PHD**[b], **John Vest, MD**[aa], **Jonathan S. Wall, PHD**[bb], **Ashutosh Wechalekar, MBBS, MD, DM**[i], **Cynthia Welsh, MD**[b], **Isabelle Lousada, MA**[l]

[a]Brigham and Women's Hospital, Boston, Massachusetts, USA

[b]U.S. Food and Drug Administration, Silver Spring, Maryland, USA

[c]Stanford University, Stanford, California, USA

[d]Ionis Pharmaceuticals, Inc, Carlsbad, California, USA

[e]Mayo Clinic, Rochester, Minnesota, USA

[f]Janssen Research and Development, Raritan, New Jersey, USA

[g]Scuola Superiore Sant'Anna, Fondazione G. Monasterio, Pisa, Italy

[h]Harvard Medical School, Boston, Massachusetts, USA

[i]University College London, London, England, United Kingdom

[j]University of Texas Southwestern Medical Center, Dallas, Texas, USA

[k]Attralus, Inc, San Francisco, California, USA

[l]Amyloidosis Research Consortium, Newton, Massachusetts, USA

ADDRESS FOR CORRESPONDENCE: Ms Isabelle Lousada, Amyloidosis Research Consortium, 320 Nevada Street, Suite 210, Newton, Massachusetts 02460, USA. ILousada@arci.org.

†Dr Prasad passed away before manuscript publication.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

[m]Oregon Health and Science University, Portland, Oregon, USA

[n]Columbia University Irving Medical Center, New York, New York, USA

[o]Federal Institute for Drugs and Medical Devices, Bonn, Germany

[p]UK Medicines and Healthcare Products Regulatory Agency, London, England, United Kingdom

[q]Alexion Pharmaceuticals, Inc, Boston, Massachusetts, USA

[r]Agence nationale de sécurité du médicament et des produits de santés, Saint Denis, France

[s]Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts, USA

[t]National Heart, Lung, and Blood Institute, Bethesda, Maryland, USA

[u]Analysis Group, Boston, Massachusetts, USA

[v]University of Limoges, Limoges, France

[w]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[x]Uppsala University, Uppsala, Sweden

[y]Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA

[z]Life Molecular Imaging, Berlin, Germany

[aa]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA

[bb]University of Tennessee Graduate School of Medicine, Knoxville, Tennessee, USA

Abstract

Light chain amyloidosis and transthyretin amyloidosis are rare protein misfolding disorders characterized by amyloid deposition in organs, varied clinical manifestations, and poor outcomes. Amyloid fibrils trigger various signaling pathways that initiate cellular, metabolic, structural, and functional changes in the heart and other organs. Imaging modalities have advanced to enable detection of amyloid deposits in involved organs and to assess organ dysfunction, disease stage, prognosis, and treatment response. The Amyloidosis Forum hosted a hybrid meeting to focus on the use of imaging endpoints in clinical trials for systemic immunoglobulin light chain amyloidosis and transthyretin amyloidosis. Stakeholders from academia and industry, together with representatives from multiple regulatory agencies reviewed the use of imaging biomarkers with a focus on cardiac amyloidosis, described applications and limitations of imaging in clinical trials, and discussed qualification of imaging as a surrogate clinical outcome. Survey results provided important patient perspectives. This review summarizes the proceedings of the Amyloidosis Forum.

Keywords

amyloidosis; cardiac imaging; clinical trial endpoints

The Amyloidosis Forum was formed in 2019 as a public-private partnership between the nonprofit Amyloidosis Research Consortium[1] and the U.S. Food and Drug Administration

(FDA) Center for Drug Evaluation and Research to advance innovation in drug development for the treatment of systemic amyloidosis.[2] Initially, the Amyloidosis Forum focused on clinical trial endpoints and analysis methodologies to address complexities in the development of new therapies for systemic immunoglobulin light chain (AL) amyloidosis.[3–6] A consistent theme discussed at previous forums was the role of imaging in clinical trials, clinical practice, and patient perspectives for both AL and transthyretin (ATTR) amyloidosis.[2,5] The Amyloidosis Forum has expanded its initiatives to assess the role of imaging in development of new therapies for both AL and ATTR amyloidosis.

This review summarizes the proceedings of the Amyloidosis Forum meeting held on the FDA campus, Potential Pathways for Development of Imaging Endpoints for Clinical Trials in AL and ATTR Amyloidosis.[7] Stakeholders from academia and industry, along with representatives from U.S. and multiple European health authorities reviewed the current use of imaging biomarkers in AL and ATTR amyloidosis and discussed the role of imaging in diagnosis, assessment of response to therapy, and applications/limitations of use in clinical trials. Survey results provided important patient perspectives on imaging.

DISEASE BACKGROUND: AL AMYLOIDOSIS AND ATTR AMYLOIDOSIS

Systemic amyloidoses are rare, multisystem, and phenotypically heterogeneous protein misfolding disorders characterized by deposition of amyloid fibrils in the heart and various organs, with amyloidosis type determined by the specific type of misfolded precursor protein.

AL amyloidosis is a monoclonal B-cell disorder associated with misfolded monoclonal immunoglobulin light chains affecting the cardiac, renal, neurological, and gastrointestinal systems and soft tissues to varying degrees in different patients.[3,8] The multisystemic nature and nondescript presentation of AL amyloidosis often leads to delays in diagnosis.[9,10] Diagnosis of AL amyloidosis typically requires biopsy proof of a plasma cell dyscrasia and amyloid formation. Prognosis has improved with available therapies but remains primarily dependent on the extent of cardiac involvement, which may be irreversible despite complete hematologic response.[11,12]

ATTR amyloidosis exists in 2 forms determined by the sequence of the TTR gene: hereditary ATTR (ATTRv; also known as ATTRh, previously referred to as familial amyloidosis) or the wild-type form (ATTRwt, previously referred to as “senile” amyloidosis), which typically is a disease of aging.[13] As with AL amyloidosis, cardiac amyloid deposition is usually the determinant of morbidity, and ultimately mortality, in these patients.[14] ATTRv can exist as a cardiomyopathy (denoted ATTR-CM), neuropathy, or a mixed phenotype; available therapies have been shown to slow progression of neuropathy,[15–18] and in patients with ATTR-CM, there is currently one FDA-approved therapy that prolongs survival and reduces hospitalizations due to heart failure.[19] However, even asymptomatic patients with ATTR-CM progress to heart failure and, if an appropriate candidate, may be considered for cardiac transplantation.[19,20] Diagnosis of ATTR amyloidosis is delineated based on screening for the presence of monoclonal protein,

followed by biopsy of the clinically involved organ (if ≥1 abnormality) or bone scintigraphy and genetic testing as indicated.[21]

Available therapies target precursor proteins for AL[11] and ATTR amyloidosis;[16,17,19] the treatment landscape is evolving to also target amyloid deposition at the organ level (ie, anti-amyloid, amyloid-depleting, amyloid-clearing, or fibril-degrading treatments).

Despite advances in treatment, there is still an unmet medical need for assessment of organ-level treatment response for patients with AL amyloidosis or ATTR amyloidosis. Imaging biomarkers have the potential to detect organ amyloid deposition, capture changes in cardiac function over time in response to targeted amyloid treatments, and play an important role in patient selection and to guide therapy. Ultimately, disease staging from imaging could be used to develop dynamic adaptive therapy guidelines to inform clinical treatment decisions in systemic amyloidosis.

EMERGING PRECLINICAL ANIMAL MODELS OF AMYLOIDOSIS

BACKGROUND.

The Amyloidosis Forum reviewed the status of emerging preclinical models of AL and ATTR amyloidosis. Preclinical models could help to further elucidate the pathophysiology of disease, rapidly develop novel drug candidates, establish proof of concept, and potentially contribute confirmatory evidence to the support of effectiveness in drug development programs.[22] Animal models may also provide a basis for preclinical evaluation of new molecular tracers and biodistribution studies of therapeutic molecules targeting amyloid deposits. Currently, in AL amyloidosis, a transgenic mouse model produced a high amount of a human free light chain and upon seeding, developed amyloid deposits in heart/spleen/kidney, but not organ dysfunction.[23] In ATTR-CM, a transgenic mouse model with human TTRS52P[24] is characterized by substantial ATTR amyloid deposits in the heart and tongue upon seeding.

FORUM PANEL DISCUSSION.

The panelists discussed the potential for these experimental models under development to allow further investigations of the factors that influence human AL and ATTR amyloid deposition and the development of new treatments. Well-established animal models that fully recapitulate AL and ATTR amyloidosis are limited and form a major barrier to drug development. Thus, currently, in vivo imaging in patients with amyloidosis remains the primary pathway for drug development studies to assess changes in organ-level amyloid burden.

IMAGING-BASED BIOMARKERS

BACKGROUND.

Understanding the pathophysiology of amyloidoses and the ability to measure disease status and progression are foundational for building the capability to assess responses to amyloid-specific therapies. To introduce the concept of imaging-based biomarkers, the Forum reviewed the differences among diagnostic, prognostic, and response biomarkers

using the FDA–National Institutes of Health Joint Leadership Council's BEST (Biomarkers, EndpointS, and other Tools) Resource,[25] and the requirements for surrogate endpoints per the Prentice Criteria.[26]

FORUM PANEL DISCUSSION.

Although the operational criteria of surrogate endpoints in clinical trials, ie, Prentice Criteria,[26] have long been regarded as the standard to define and validate a surrogate endpoint, the Forum discussed views suggesting that these criteria are conceptually appealing, but may be generally impractical because of high stringency that is almost never satisfied.[27] With this contextual framework, the Forum members reviewed the current state of imaging modalities in AL and ATTR amyloidoses with a focus on cardiac amyloidosis.

CRITICAL ASSESSMENT OF IMAGING MODALITIES

Advanced imaging allows for quantitative assessment of changes in cardiac structure, cardiac function, and myocardial tissue characteristics from amyloidosis. Recently, imaging criteria for diagnosis of ATTR and AL cardiac amyloidoses have been recommended.[28,29] Direct quantification of amyloid infiltration in the heart and the various organs, the relationship to functional status, and prognostic value are emerging (Central Illustration). Multiple imaging modalities were critically reviewed at the Forum, along with the potential for each modality to diagnose disease and act as a surrogate for disease progression. Technical and clinical feasibility of tracking a change over time, at the scale that would be required for a multicenter trial, was discussed.

ECHOCARDIOGRAPHY: AL AND ATTR AMYLOIDOSIS

BACKGROUND.

Echocardiography is usually the first test performed when cardiac amyloidosis is suspected. Classical abnormalities of amyloid infiltration on echocardiography are well described in the published reports.[30] Evaluation of myocardial deformational metrics using speckle tracking is quantitative and has multiple advantages over "standard" echocardiography parameters. Myocardial deformation metrics have extensive support in the published reports for early diagnosis and prognostication in cardiac amyloidosis[31,32] and the ability to evaluate all 4 cardiac chambers.[32]

In cardiac AL amyloidosis, abnormal left ventricular longitudinal strain (LV-GLS) (Figure 1A) as well as myocardial stroke volume index are strong prognostic markers.[33] Lower LV-GLS has been shown to be associated with worse survival.[34] Moreover, hematologic response has been associated with improvement in longitudinal strain, and patients with improved longitudinal strain had improved overall survival (Figure 1B).[34–36] In ATTR amyloidosis clinical trials, structural echocardiography markers (left ventricular [LV] wall thickness, mass, volumes, cardiac output, and stroke volume) and deformation (LV-GLS) have shown stabilization or a nominal change following therapy with TTR-stabilizing or -silencing drugs.[19,37,38] Myocardial work index and myocardial efficiency are emerging as novel load-independent echocardiography parameters to evaluate response to TTR-stabilization therapy (Figure 2).[39]

FORUM PANEL DISCUSSION.

Echocardiography plays a central role in human drug development because of its simplicity, wide access, and ease of use in large studies. Despite simplicity and appeal of use of echocardiography in multicenter clinical trials, the panel discussed limitations. LV-GLS as a clinical outcome variable in clinical trials poses certain challenges,[34,40] including inter-manufacturer variability and limited precision. Assessment of LV-GLS is dependent on vendor selection, well-trained sonographers, standardized equipment, and interpretation by a central laboratory and/or artificial intelligence (AI). With current precursor protein–directed treatments, the magnitude of changes in cardiac structure and function are generally small, limiting the usefulness of echocardiography. Compared with tomographic imaging modalities, echocardiography does not provide insights into disease burden in other systemic organs such as the lungs, liver, spleen, or kidney.

KEY POINTS.

The general consensus of the Forum was that with standardized protocols, training, and central vendors or AI technology to read and interpret echocardiography, LV-GLS assessed by speckle tracking echocardiography has the potential to emerge as a reproducible endpoint in multicenter clinical trials. The Forum also discussed the potential of creating a virtual core lab for the amyloid community to globally validate echocardiography technique and presentation of results.

CARDIAC MAGNETIC RESONANCE IMAGING: AL AND ATTR AMYLOIDOSIS

BACKGROUND.

Cardiac magnetic resonance (CMR) imaging provides tomographic imaging (ie, 3-dimensional) with accurate assessment of cardiac structure and function and myocardial tissue characteristics. Late gadolinium enhancement on CMR may provide high accuracy.[41] Moreover, native T1 mapping, before the administration of gadolinium-based contrast,[42,43] as well as T1 maps post-administration of gadolinium-based contrast for estimation of extracellular volume (ECV) fraction mapping,[44,45] provide quantitative measures of tissue characteristics. ECV offers a promising utility to quantify changes in amyloid load and to track treatment response.

In cardiac AL and ATTR amyloidosis clinical trials, both native myocardial T1 and ECV have been studied as surrogate markers of cardiac amyloid infiltration.[41,43–46] In AL amyloidosis, statistically significant drug-induced changes in amyloid regression in the heart[47] have been shown to correlate in a larger study with clinical outcomes (Figure 3).[48] CMR-derived ECV mapping also demonstrated regression of AL amyloid in the liver and spleen that correlated with ^{123}I-SAP scans, biomarker changes, and predicted prognosis.[49] Data are emerging to evaluate ECV in systemic organs in AL amyloidosis and thus CMR may provide insights into disease burden and changes with therapy in the heart and other organs, notably the liver and spleen.[46,50] In ATTR-CM, CMR ECV has been shown to stabilize with TTR-stabilization therapy (Figure 4);[51] however, these data are limited by imbalanced sample size and overlap of the data between groups, limiting the results of this single-center study.

FORUM PANEL DISCUSSION.

Although data are promising, most data are from single-center studies and there was no clear consensus. Forum panelists also discussed the need for additional multicenter long-term studies to obtain data on the standardized use and analysis of native T1, ECV, and late gadolinium enhancement and to establish the prognostic relevance of these CMR variables as surrogates of clinical response to therapy. As with echocardiography, reproducibility requires standardized protocols, similar scan manufacturer, mapping protocols, field strength, unified contrast protocols, and central reading center/core lab (or AI) to increase quality. Programs aimed at standardization of CMR methods across centers are in progress and are likely to define biochemical and/or structural abnormalities caused by amyloid deposition, the reversal of which may be useful as endpoints in future clinical trials. Access to CMR is limited in certain parts of the world and CMR expertise for amyloidosis imaging remains limited. The use of CMR as a key determinant in clinical trials requires exclusion of patients with impaired renal function or implanted cardiac devices, and the procedure may have limited tolerability for certain patients (eg, multiple breath holds, duration). Thus, the panelists discussed that the greatest utility for the use of CMR in clinical trials is in the early stages of development (ie, phase 1–2 or substudy in phase 3).

KEY POINTS.

The panelists concluded that CMR performance requires technical expertise, and standardization would benefit from using the same scanner, T1 acquisition protocols, magnetic field strength, contrast agent, accurate standardized post-contrast protocols, and an experienced core lab.

MOLECULAR IMAGING OF AMYLOIDOSIS–SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY: ATTR AMYLOIDOSIS

BACKGROUND.

Single-photon emission computed tomography (SPECT) with ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) bone-avid radiotracers has emerged as a highly specific means to diagnose ATTR-CM[52,53] in the setting of imaging suspicious for cardiac amyloidosis and a negative work-up for a plasma cell disorder. This technique has been increasingly adopted in clinical practice, minimizing need for invasive endomyocardial biopsy for a diagnosis of ATTR-CM. In treatment trials, a decrease in cardiac radiotracer uptake (^{99m}Tc-PYP/DPD/HMDP) has been reported with both TTR-stabilizing[54–56] and -silencing therapies[38,55,57] (Figure 5). One study showed that the cohorts of patients with a decrease in ^{99m}Tc-DPD retention index (> median vs < median decrease) had improved left ventricular ejection fraction (LVEF);[51] whether this portends better long-term cardiac structural and functional improvements and clinical outcomes is not yet known. Absolute quantitation of myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP using SPECT/computed tomography (CT) technology is an advancement that has potential to identify early cardiac amyloidosis, predict prognosis,[58,59] and detect changes in response to therapy.

FORUM PANEL DISCUSSION.

The panelists agreed that for clinical trial application, the utility of bone-avid tracer cardiac SPECT or SPECT/CT as a diagnostic test for ATTR-CM is widely accepted. This procedure is noninvasive with relatively low radiation exposure; SPECT technique and interpretation is relatively easy to train, and therefore amenable to implementation and scale in a clinical trial setting for diagnostic purposes. However, most panelists concurred that additional education was needed given the high incidence of false positives (eg, due to error in ^{99m}Tc-PYP technique or interpretation) or the failure of clinicians to order or properly interpret monoclonal protein studies and immunoglobulin free light chain testing. Lower sensitivity of this technique, especially in certain hereditary forms of ATTR-CM was discussed. Also, the Forum panel agreed that quantitation of ^{99m}Tc-bone-avid tracer SPECT/CT uptake has potential use as a surrogate biomarker, although more data are needed with respect to standardization of methodologies and optimal frequency/changes in uptake over time, as well as a thorough assessment of the risk for adverse clinical outcomes.

KEY POINTS.

The panelists concluded that molecular tracers for SPECT imaging are highly specific and useful for diagnosis and patient selection for clinical trials. There is a need to use established standardized methods for image acquisition, processing, and analysis. Quantitative SPECT/CT imaging is helpful in assessing repeat studies and more data are needed.

MOLECULAR IMAGING OF AMYLOIDOSIS-POSITRON EMISSION TOMOGRAPHY: AL, ATTR, AND RARE FORMS OF AMYLOIDOSIS

BACKGROUND.

Positron emission tomography (PET) technology affords high specificity as well as nano- or pico-molar sensitivity, high temporal and spatial resolution, absolute quantitation, and hybrid imaging to localize myocardial or organ uptake. A number of PET-based amyloid-binding molecular tracers (beta-amyloid tracers: ^{11}C-Pittsburgh B compound (PiB),[60] ^{18}F-florbetapir,[61] ^{18}F-florbetaben,[62] ^{18}F-flutemetamol,[63] and ^{124}I-evuzamitide[64]) are now available. Beta-amyloid tracers bind to beta sheets of amyloid fibrils (eg, beta-amyloid tracers) and iodine ^{124}I-evuzamitide[65] binds to charged components of amyloid, the glycosaminoglycans, and surface of various forms of amyloid fibrils. Notably, being a whole-body tomographic imaging modality, PET offers evaluation of systemic amyloid burden in the heart and other involved organs (Figure 6).[66,67] Myocardial uptake of amyloid PET tracers correlated with cardiac biomarkers and functional outcomes,[64] suggesting an emerging role as a surrogate for clinical outcome. Multiple single-center studies show the emerging prognostic value of PET tracers in patients with greater myocardial amyloid burden estimated by ^{11}C-PiB[68,69] and ^{18}F-florbetapir (Figure 7).[70]

FORUM PANEL DISCUSSION.

Panelists agreed the high specificity of amyloid PET tracers independent of the precursor proteins makes them ideal for noninvasive diagnosis of amyloidosis including early

disease[60,71] and for assessment of response to therapy. However, they felt that the current data are from small single-center studies and larger multicenter studies are much needed. Emerging data from a recent multicenter test-retest repeatability study have shown excellent interclass correlation for ^{124}I-evuzamitide,[72] but variability of other PET amyloid tracers with repeat measurements is not well described. PET amyloid tracer use in multicenter clinical trials may be limited by access to PET scanners, lack of FDA-approved amyloid imaging tracers for cardiac amyloidosis, and cost. With further understanding of tracer pharmacokinetics and biodistribution, amyloid PET tracers hold promise for quantitative PET imaging to characterize amyloid burden and changes in response to therapy.

KEY POINTS.

Amyloid-binding PET tracers are highly specific for amyloid in the heart and can image systemic organ amyloidosis. A clear understanding of amyloid PET radiotracer biodistribution in healthy adults may be particularly important to define organ involvement. These agents are currently not approved for clinical use in cardiac amyloidosis.

NOVEL CONCEPTS IN IMAGING AND IMAGING ENDPOINTS FOR FUTURE CLINICAL TRIALS IN AMYLOIDOSIS

Several novel concepts were identified for further evaluation in clinical trials. The Forum recognized that as opposed to precursor protein–directed therapies, which showed no substantial changes with standard echocardiographic measures, new fibril-directed therapies for AL and ATTR amyloidosis directly targeting cardiac structure may demonstrate larger magnitude of structural and functional improvements with echocardiography and/or CMR imaging, and possibly at earlier time points after therapy. The Forum also discussed novel imaging measures including evaluation of myocardial work index and myocardial efficiency as novel load-independent echocardiography parameters that have been used to evaluate response.

There is an emerging recognition that patient-reported outcomes may represent information that is currently not captured by cardiac biomarker or imaging metrics and is prognostic. This is an important endpoint accepted by the FDA for approval of some of the new amyloidosis therapies. Moreover, although 6-minute walk distance (6MWD) has the value of large validation, simplicity of use, and universal applicability, it has some limitations and may require large sample sizes. The Forum discussed a more objectively measured metric on cardiopulmonary exercise testing may be helpful at least in small cohorts as secondary endpoints as performed in the hypertrophic cardiomyopathy clinical trials. The discussion concluded that the correlation of changes in cardiac structure and function identified on imaging with functional outcomes such as cardiopulmonary exercise testing or disease-specific patient-reported outcomes, such as the recently developed ATTR-QoL (Transthyretin Amyloidosis Quality of Life) questionnaire,[73] warrants further exploration.

To facilitate drug development for the treatment of AL and ATTR amyloidosis, the Forum also discussed formation of a consortium to perform observational studies focused on the development of standards for imaging in clinical trials and in clinical practice. A

key question would focus on understanding the timing of imaging analysis for response assessment. Most available data are based on survivors (ie, 6–12 months post intervention). Knowledge of changes at an early time point (eg, 2–3 months after initiation of therapy) is critical to capture changes in disease status for both responders and nonresponders. With several effective approved therapies for AL and ATTR amyloidosis, alternate therapy may be considered in non-responders to improve their outcomes.

SUMMARY OF FORUM PANEL DISCUSSION ON IMAGING

Following review of available data on imaging modalities, the Forum discussed the potential pathway for the use of imaging as a predictive biomarker, ie, a validated surrogate for clinical outcomes in amyloidosis trials, with perspectives from multiple regulatory authorities. Currently, no imaging modality meets all criteria to establish a clear surrogate outcome in amyloidosis, although evidence supports further development for use in clinical trials. Most phase 3 treatment trials to date have evaluated echocardiography as a secondary or exploratory endpoint.[19,37,74] These results provided no consistent or significant signal of improvement in cardiac structure or cardiac function assessed by echocardiography. Emerging studies report on the use of technetium-99m bone-avid tracer cardiac SPECT as a secondary endpoint.[38,75] These studies have reported a significant decline in myocardial uptake of bone-avid tracers after therapy with TTR-silencing drugs as well as TTR-directed antibodies in the context of no significant change in cardiac structure or function. This discordance is perplexing, especially given lack of clear understanding of the mechanism of myocardial uptake of technetium-99m bone-avid compounds and needs to be better understood. Newer ongoing clinical trials, including trials of antibodies against amyloid fibril, are using cardiac MRI-based extracellular volume as a secondary endpoint and these results are awaited.

The emphasis was on the need to demonstrate that statistically significant drug-induced improvement of an imaging biomarker is causal (largely attributable) to a statistically significant improvement of a clinical outcome, while accounting for the variability of both measurements. The Forum panelists then discussed the standardization of each imaging modality and the importance of establishing test-retest criteria and meaningful changes in patients. Overall, the Forum agreed prospective standardization of each of these modalities is required to minimize variability, with acceptance of a reasonable degree of variability. Although real-world data have appeal, meta-analysis of available imaging data would be inherently challenging due to variability in methodology (even for within-patient change). Reproducibility and repeatability of measures of echocardiography, CMR, and SPECT and PET amyloid imaging, specifically in cohorts of patients with amyloidosis, needs to be established. This is highly relevant for multicenter trials to establish meaningful changes with amyloid-directed therapy.

CONNECTING IMAGING TO FUNCTIONAL MEASURES AND PATIENT PERSPECTIVES

BACKGROUND.

Measures of health-related quality of life (HRQoL) are critical for advancing the management of AL and ATTR amyloidosis. In AL amyloidosis, the underlying disease and current therapeutic regimens have profound negative impacts on functional capacity[76] and HRQoL as measured by multiple patient-reported outcomes.[77–83] The Amyloidosis Forum has updated a conceptual model to describe these impacts and identified the SF-36v2 Health Survey (SF-36v2; QualityMetric Incorporated, LLC) and Patient-reported Outcomes Measurement Information System-29 Profile (PROMIS-29; HealthMeasures) as instruments relevant to patients with AL amyloidosis.[5] HRQoL measures correlated strongly with functional status and cardiac biomarkers in AL amyloidosis, and with low to moderate but significant correlations with amyloid burden measured by ^{18}F-florbetapir PET/CT. These findings suggest that functional status and HRQoL metrics capture multiple aspects of the disease status beyond simple cardiac alterations from amyloid accumulation. Notably, both HRQoL and functional capacity predicted outcomes independent of the Mayo Stage.[84] Although imaging-based outcomes were observed at 6 to 12 months, improvements in HRQoL were generally slower to change (≥12 months), suggesting imaging and HRQoL are temporally independent predictors of survival.[36,76]

In ATTR amyloidosis, patients often present with impairments in cardiac functional capacity (Kansas City Cardiomyopathy Questionnaire Overall Summary Score) and 6MWD at the time of diagnosis, the degree of which is prognostic for survival.[19] In ATTRv neuropathy, significant improvements have been reported in functional capacity and neuropathy quality of life following TTR-silencing therapies.[15–18] Following treatment for ATTR amyloidosis, particularly with TTR-silencing therapies, improvements in some echocardiography parameters,[37] and ECV and LV mass by CMR,[57] have been observed, as well as improvements in 6MWD, N-terminal pro–B-type natriuretic peptide, and reduction in death/cardiovascular events.[19] In both AL and ATTR amyloidosis, cardiac amyloid burden measured by ^{124}I-evuzamitide PET/CT correlated moderately to strongly with HRQoL.[64]

FORUM PANEL DISCUSSION.

Additional research is needed to identify imaging markers that correlate with baseline HRQoL and functional capacity (and changes with treatment), and their temporal relationship, in ATTR amyloidosis.

KEY POINTS.

Development of HRQoL measures specific to amyloidosis is much needed.

PATIENT PERSPECTIVES: THE VALUE OF IMAGING

In ATTR amyloidosis, the introduction of advanced imaging modalities (CMR and bone-avid tracer cardiac scintigraphy) has transformed the noninvasive diagnostic pathways and

has been associated with a diagnosis at an earlier disease stage with associated improved survival from the time of diagnosis.[85] A key component of the Amyloidosis Research Consortium's contributions to the Amyloidosis Forum is the incorporation of patient perspectives and an emphasis on patient-focused drug development.[77,86] To that end, an informal online survey was conducted (October 20, 2022, through November 1, 2022) to characterize patient experiences and preferences in imaging for monitoring amyloidosis (Table 1).

Of the 653 respondents, most (64%) were diagnosed ≥2 years ago, and approximately 80% reported use of imaging for either diagnosis or monitoring of their disease. Patients with ATTRwt amyloidosis most commonly reported experience with imaging, 90% of whom were diagnosed by imaging. Patients with AL amyloidosis were the least likely to have experience with imaging procedures; 33% reported never having had imaging. Yet compared with patients with ATTR amyloidosis, they more commonly reported that imaging was used to monitor their disease. Roughly 19% of respondents reported having undergone either a heart or kidney biopsy. Open-ended responses suggest patients place a preference for imaging relative to biopsy; the highest importance was placed on being able to "see" the impact of treatment (mean score 4.46) and use of imaging in understanding disease status (mean score 4.43) (Figure 8).

PATHWAY TO QUALIFICATION OF IMAGING MEASURES AS CLINICAL OUTCOME SURROGATES

To lay the groundwork for the discussion of qualifying imaging data as a potential clinical outcome surrogate, the Forum reviewed a case study from another rare disease: the approval of mavacamten for the treatment of patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM). Before 2022, medical treatment of oHCM was based on observational data and expert opinion with no available medications to target the underlying pathobiology.[87,88] In the double-blind, placebo-controlled EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) trial, echocardiographic measures were components of eligibility criteria, a secondary efficacy endpoint (LV outflow tract gradients), and safety monitoring (LVEF).[89] Parallels were drawn between oHCM and amyloidosis, the role of imaging, and the development of new interventions to directly address the underlying pathophysiology, particularly in the face of earlier identification of ATTR-CM and the decreasing traditional hard outcomes event rate.

REGULATORY CONSIDERATIONS: IMAGES AS PREDICTIVE BIOMARKERS (TRIAL ENDPOINT SURROGATES)

Nine panelists representing multiple divisions of the FDA (United States), Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom), and the European Medicines Agency (EMA, Germany, France) provided their perspectives on current discussions within health authorities relating to imaging biomarkers as trial endpoint surrogates.

FDA representatives discussed the value of bio-markers for diagnosis, enrollment/enrichment, and evaluating response. Emphasis was placed on identification of disease-relevant biomarkers and the compilation of supportive evidence; data sharing was encouraged. Standardization and technical validation of imaging processes are necessary to optimize the quality of imaging data. Although standardization of imaging is important in routine clinical practice for reliable assessment of imaging, standardization becomes essential when imaging is used as an endpoint in clinical trials intended to support approval of drugs for marketing. Standardization optimizes the quality of imaging data obtained in clinical trials by reducing variability and improving interpretability of data across study subjects, study sites, and study protocols. In comparison with clinical practice, trial-specific imaging standards generally provide greater assurance that the imaging methods for the assessment of a trial endpoint are well defined and reliable. The 2018 FDA Guidance for Industry titled, “Clinical Trial Imaging Endpoint Process Standards,”[90] describes imaging acquisition, display, archiving, and interpretation process standards regarded as important to optimize the quality of imaging data obtained in clinical trials.

The assessment of an imaging endpoint in a trial of an investigational therapeutic drug might require the investigational use of an imaging device or imaging drug. If it is anticipated that such imaging will be required for the safe and effective use of the therapeutic drug post-approval, parallel development of the required imaging products for approval at the same time as the therapeutic drug would likely be needed.

MHRA representatives postulated whether, in the context of a multisystem disease, cardiac imaging and/or 1 marker would be sufficient to represent the entire disease severity spectrum and enable regulatory decision making. The need for evaluation of the patient as a whole and systemic disease burden was highlighted. Emphasis was placed on an understanding of the investigational medicinal product’s mechanism of action. Within MHRA, there is potential to take forward a multimarker concept. At present, all imaging modalities presented require additional qualification.

Based on input from EMA representatives, a conditional marketing authorization is an option for earlier availability of a medicinal product for debilitating or life-threatening diseases in the European Union under certain conditions. Available data must be sufficient to conclude a positive benefit-risk balance. To which degree imaging data can contribute in this context to the overall data package will be a case-by-case decision.

Imaging-based endpoints can provide valuable information for proof of concept and dose selection for phase 3 and may support extrapolation of results from a population with an established positive benefit-risk balance to a related population or to subgroups not sufficiently represented yet. Obstacles to the use of imaging as a primary endpoint in pivotal trials pertain to validation, establishment of the predictive value for a specific medicinal product, and the correlation between changes in imaging markers and clinical benefit for the overall population and for subgroups as defined by patient characteristics, clinical condition, and baseline amyloidosis-targeted therapy.

FUTURE DIRECTIONS

The goal of the Amyloidosis Forum Imaging Meeting was to identify the activities required over the next 5 to 10 years to enable regulatory decisions based on imaging/composite endpoints, with a focus on patient-focused drug development in AL and ATTR amyloidosis. To that end, the Forum also initiated an exploration of the HeartShare Study[91] and BioData Catalyst[92] programs. HeartShare is a National Heart, Lung, and Blood Institute phenomics program to conduct large-scale analysis of phenotypic data, including images, in patients with heart failure with preserved ejection fraction.[93] The Forum discussed the potential to leverage these programs for ancillary studies to look for heart failure patients with amyloidosis and will explore this possibility. The Forum emphasized the importance of data sharing as a key to success and encouraged research centers to obtain consent to share data from patients using platforms/tools like RDCA-DAP (Rare Disease Cures Accelerator Data Analytics Platform) to facilitate this goal. The Amyloidosis Forum is focused on maximizing the impact of limited resources and encouraging collaboration and sharing of existing data. The Steering Committee of the Forum will identify work-streams moving forward to address gaps in the use of imaging in drug development for systemic amyloid disorders in the precompetitive domain.

CONCLUSIONS

Amyloidosis is a systemic disease and characterization of whole-body amyloidosis burden is increasingly recognized as central for optimal patient management. Imaging advances have revolutionized the detection and diagnosis of cardiac amyloid, which has translated to a beneficial impact on patient care. With additional standardization, imaging has the potential to become a powerful tool to delineate efficacy of drug therapy, durability of treatment response, and optimal treatment duration in the case of anti-amyloid therapies, especially for cardiac amyloidosis. Establishing rigor, reproducibility, and accuracy of imaging modalities is paramount to assess cardiac structural and functional changes and amyloid load for use in pivotal multicenter trials. Imaging core labs with technical and interpretive expertise will be critical, and the expanded application of AI methodologies to various imaging modalities holds promise. Continued investigation of imaging in natural history studies and smaller mechanistic studies throughout drug development is likely to improve clinical outcomes in patients with amyloidosis.

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ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walk distance
AI	artificial intelligence
AL	systemic immunoglobulin light chain amyloidosis
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloidosis-cardiomyopathy
CMR	cardiac magnetic resonance
ECV	extracellular volume fraction

LV	left ventricular
LVEF	left ventricular ejection fraction
LV-GLS	left ventricular longitudinal strain
PET	positron emission tomography
SPECT	single-photon emission computed tomography

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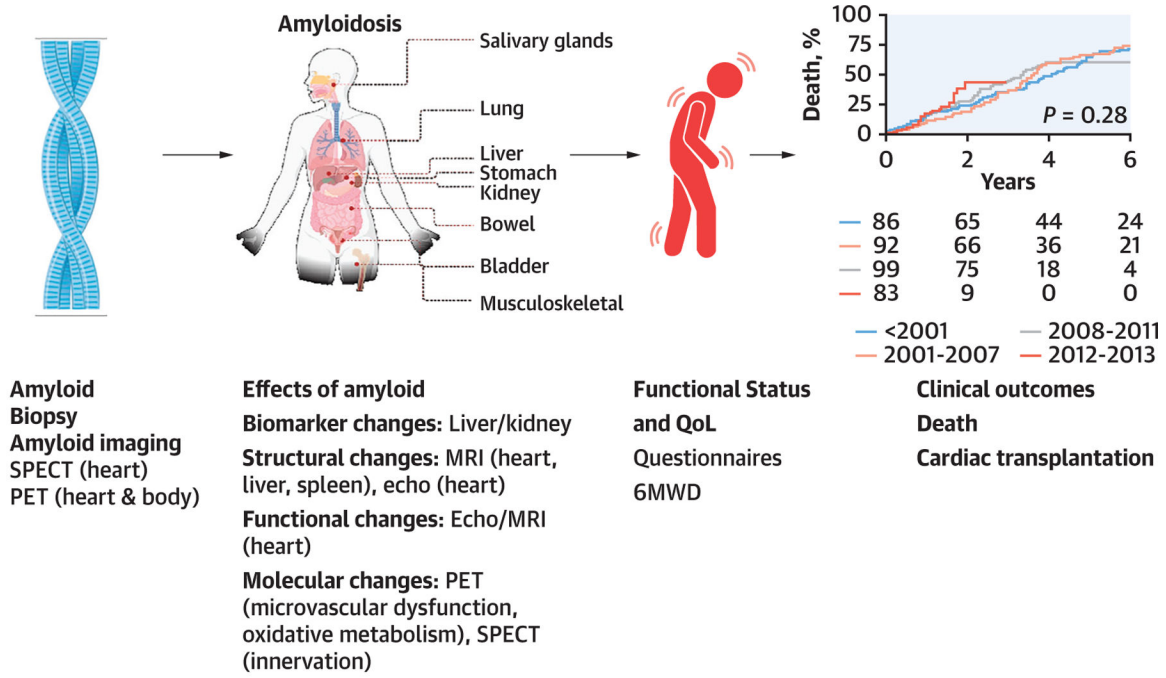
HIGHLIGHTS

- Systemic amyloidoses are characterized by deposition of misfolded proteins as amyloid fibrils in various organs.
- Novel therapies for amyloidosis are emerging, but noninvasive assessment of organ response remains challenging.
- The Amyloidosis Forum reviewed imaging endpoints in clinical trials for AL and ATTR amyloidosis.
- Standardization of imaging is critical for acceptance of imaging endpoints in pivotal multicenter clinical trials.



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CENTRAL ILLUSTRATION. Imaging Targets and Potential Imaging-Based Surrogate Endpoints

Misfolded precursor proteins deposit as amyloid fibrils in various organs including the heart, disrupting organ structure (heart and other organs), causing organ dysfunction, and poor clinical outcomes. Bone-avid SPECT tracers provide a highly specific signal for amyloid, especially ATTR amyloid, in the heart. Amyloid-binding PET tracers image a molecular signal of amyloid, including AL, ATTR, and other types, in the heart and in systemic organs. Echocardiography visualizes structural and functional changes in the heart. MRI characterizes changes in the tissues from amyloid deposition in the heart as well as in the liver and spleen. Amyloid deposition impacts functional status and health-related quality of life, ultimately resulting in the need for cardiac transplantation or death. The survival curve is reproduced with permission from Grogan et al.[14] 6MWD = 6-minute walk distance; AL = immunoglobulin light chains; ATTR = transthyretin; MRI = magnetic resonance imaging; PET = positron emission tomography; QoL = quality of life; SPECT = single-photon emission computed tomography.

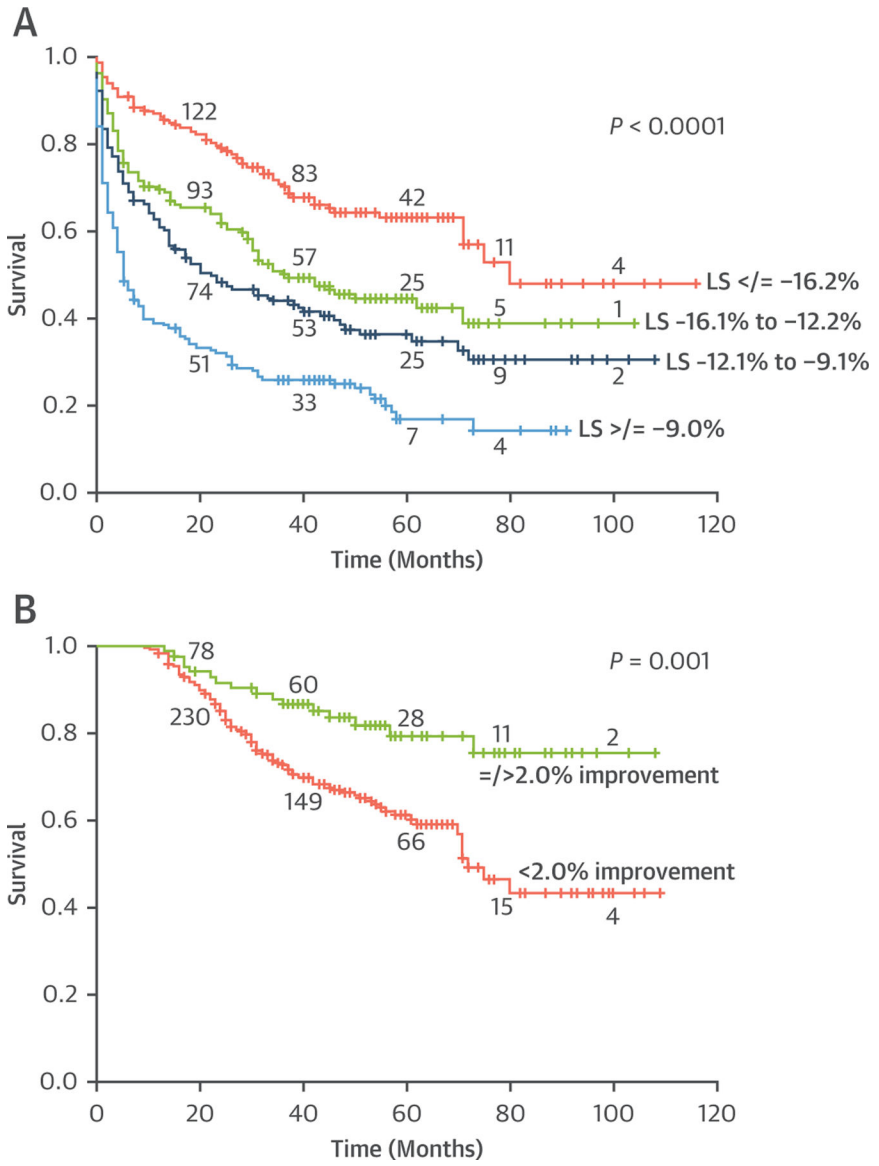

FIGURE 1. Prognostic Value of Baseline Longitudinal Strain in AL Amyloidosis and Changes With Therapy

Prospective observational study of newly diagnosed patients (N = 915) with AL amyloidosis chemotherapy (ALCHEMY) seen at the UK National Amyloidosis Centre (NAC) (February 2010–August 2017). (A) Overall survival by baseline longitudinal strain showing a highly significant worsening of overall survival with worsening longitudinal strain category: longitudinal strain ≤−16.2%: 80 months, −16.1% to −12.2%: 36 (95% CI: 20.9–51.1) months, −12.1% to −9.1%: 22 (95% CI: 9.1–34.9) months, and ≥−9.0%: 5 (95% CI: 3.2–6.8) months ($P < 0.0001$). (B) Overall survival by ≥2.0% longitudinal strain response at 12 months showing patients with a <2.0% longitudinal strain improvement, overall survival was not reached at 50 months, compared with a median survival of 72.0 (95% CI: 64.8–79.2) months. Reproduced with permission from Cohen et al.[34] AL = systemic immunoglobulin light chain amyloidosis.

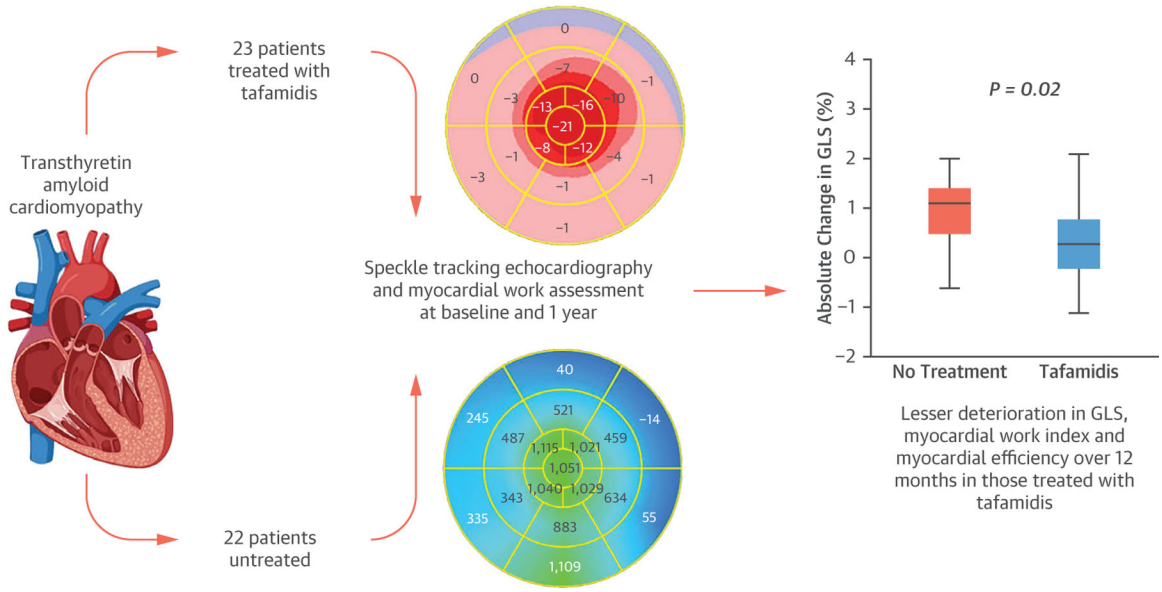

FIGURE 2. GLS and Myocardial Work by Echocardiography as Indicators of Disease Stability in ATTR-CM

In a study of 23 patients with ATTR-CM treated with tafamidis for at least 1 year compared with 22 control subjects with ATTR-CM who did not receive therapy, global longitudinal strain (GLS) and myocardial work index at 1 year worsened less in the tafamidis cohort, suggesting stabilization of amyloidosis. Reproduced with permission from Giblin et al.[39] ATTR-CM = transthyretin amyloidosis–cardiomyopathy; CMR = cardiac magnetic resonance; ECV = extracellular volume fraction.

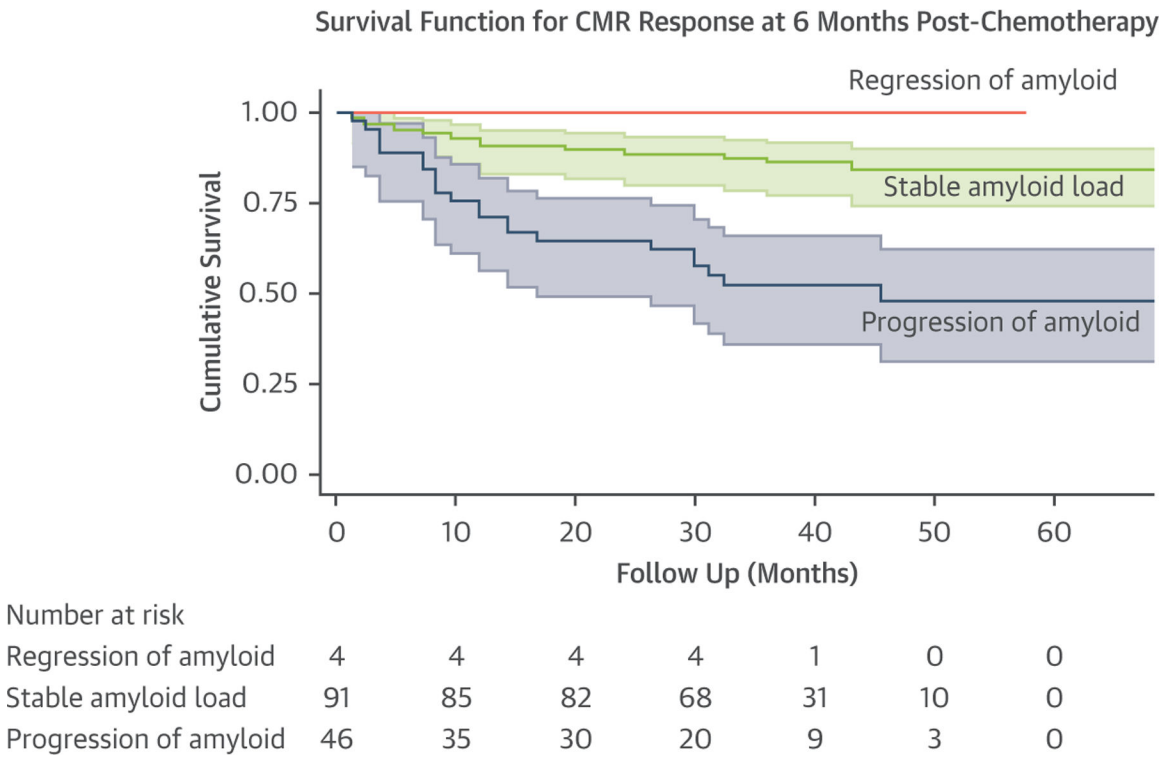

FIGURE 3. Changes in ECV on CMR Imaging as an Indicator of Disease Response in AL Amyloidosis

Kaplan-Meier survival curves, with shaded 95% confidence regions, displaying survival in all patients according to change in amyloid burden (measured by the change in extracellular volume on follow-up CMR) after 6 months. Reproduced with permission from Martinez-Naharro et al.[48] Abbreviations as in Figures 1 and 2.

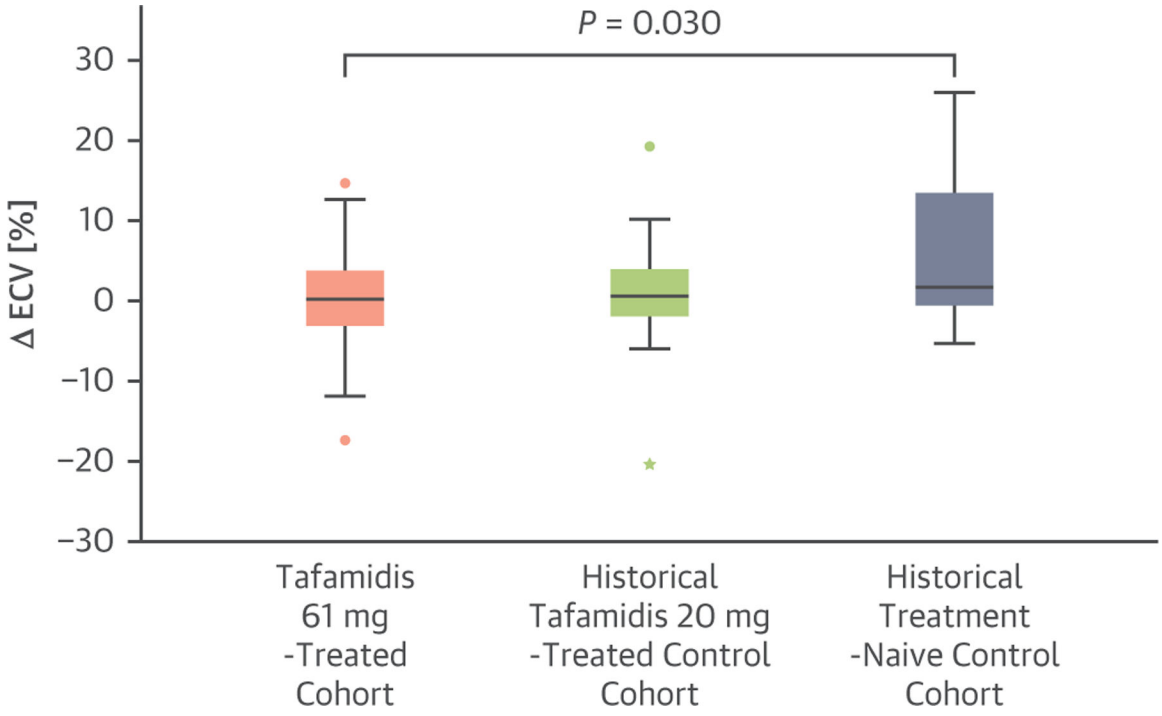

FIGURE 4. ECV on CMR Imaging as an Indicator of Disease Stabilization in ATTR-CM

Longitudinal changes in modified look-locker inversion recovery sequence-derived ECV. In a group of 35 patients treated with tafamidis (61 mg every day) for a median of 9 months (green bar), compared with 19 historical control treatment naive patients (red bar), the progression of interstitial ECV expansion worsened less in the tafamidis cohort. Reproduced with permission from Rettl et al.[51] SAP = serum amyloid P; other abbreviations as in Figures 1 and 2.

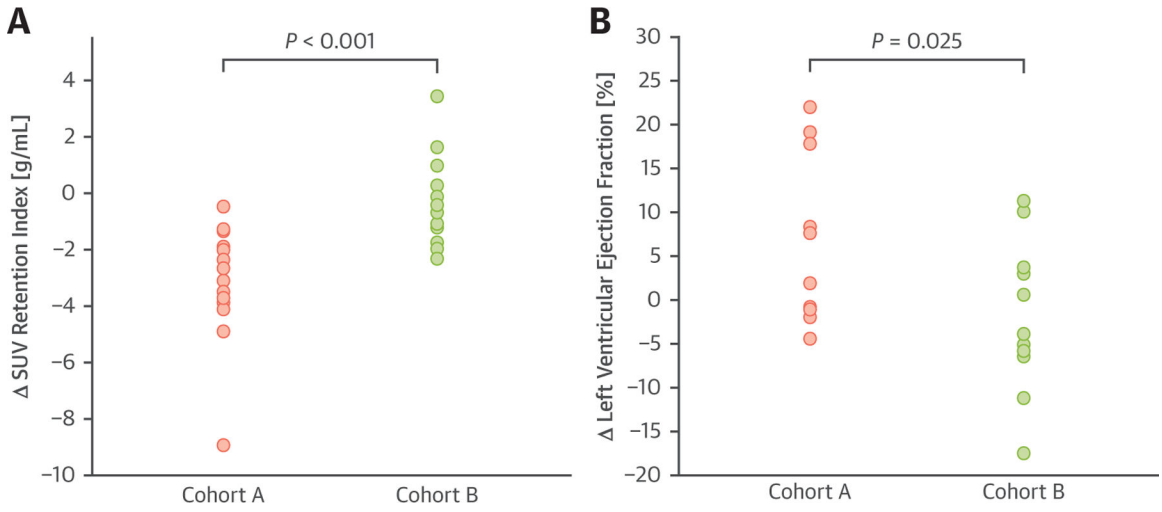

FIGURE 5. Changes in Quantitative Cardiac Uptake of ^{99m}Tc-DPD Using SPECT/CT as an Indicator of Disease Stabilization in ATTR-CM

In 40 patients who received tafamidis for a median of 7 months, those with greater than median improvement in myocardial DPD SUV retention index (A) demonstrated a small but statistically significant improvement in LVEF on CMR (B). Reproduced with permission from Rettl et al.[54]

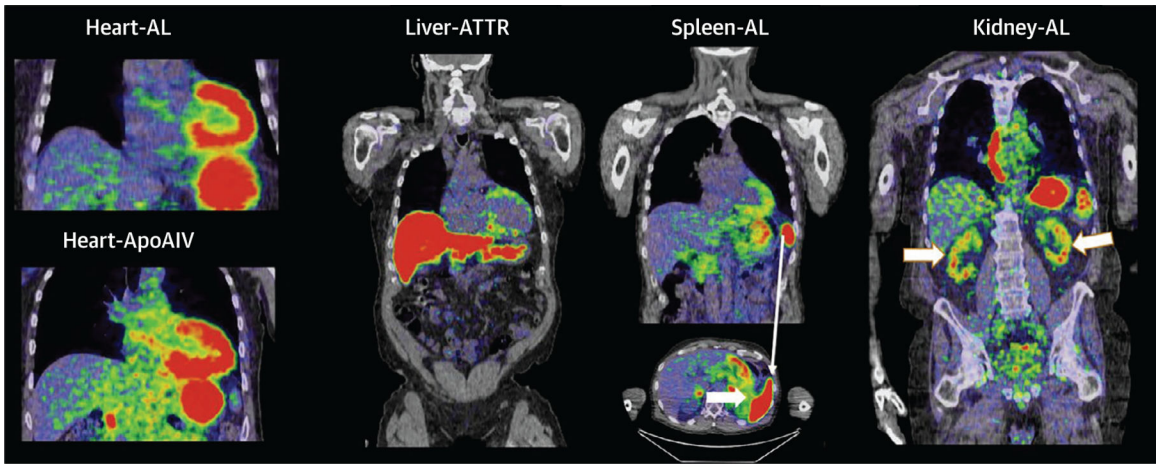

FIGURE 6. PET to Quantify Amyloid in the Heart and Multiple Organs

Demonstration of the value of ^{124}I-evuzamitide PET/CT to image amyloid in the heart and various organ systems. %ID = percent injected dose; CAA = cardiac amyloid activity; PET = positron emission tomography; other abbreviation as in Figure 5.

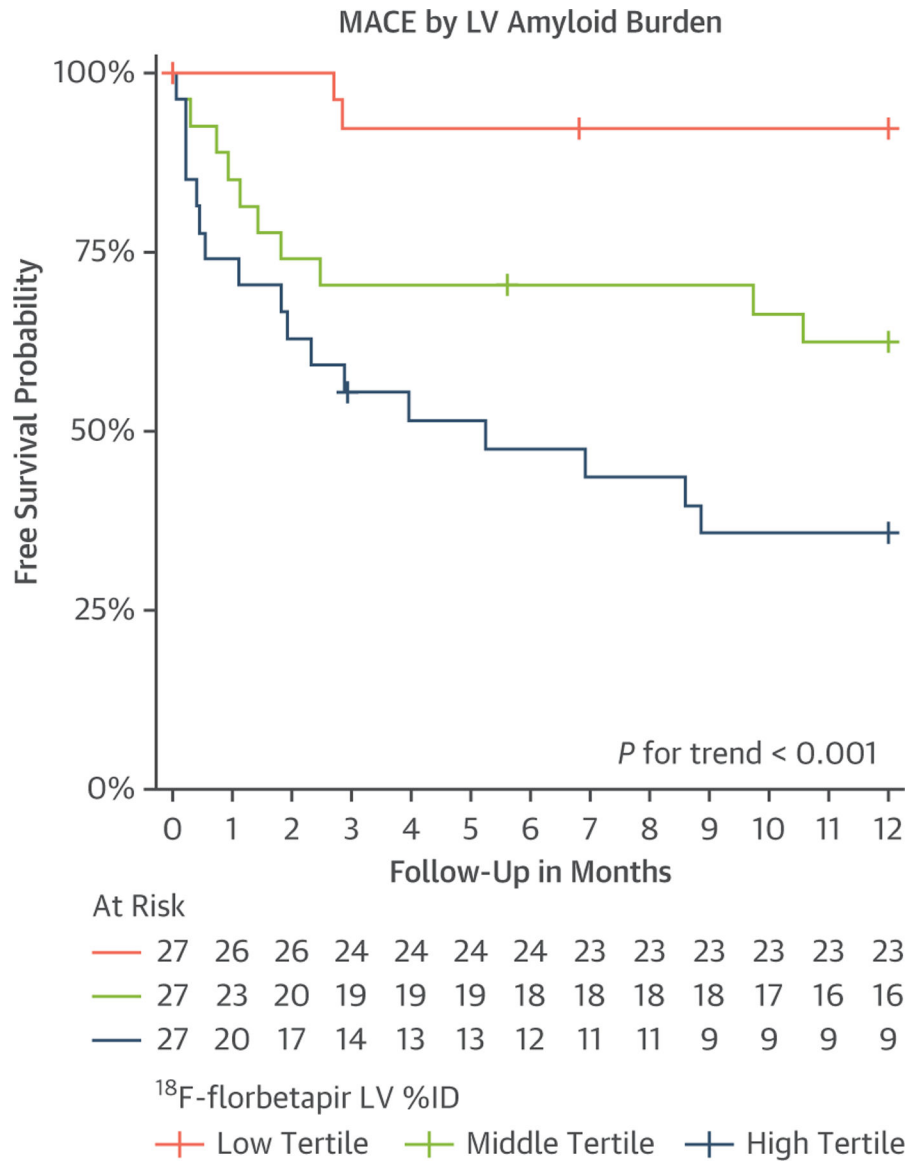

FIGURE 7. Prognostic Value of ^{18}F-Florbetapir PET/CT to Quantify Amyloid in the Heart and Predict Outcomes

Eighty-one participants with newly diagnosed systemic AL amyloidosis were prospectively enrolled and underwent ^{18}F-florbetapir PET/CT. This Kaplan-Meier analysis demonstrates a graded response to ^{18}F-florbetapir PET/CT % ID and outcomes in patients with AL amyloidosis. Patients with the lowest tertile showed the best outcomes and in the highest tertile showed the worst outcomes. Reproduced with permission from Clerc et al.[70] Abbreviations as in Figures 1, 5, and 6.

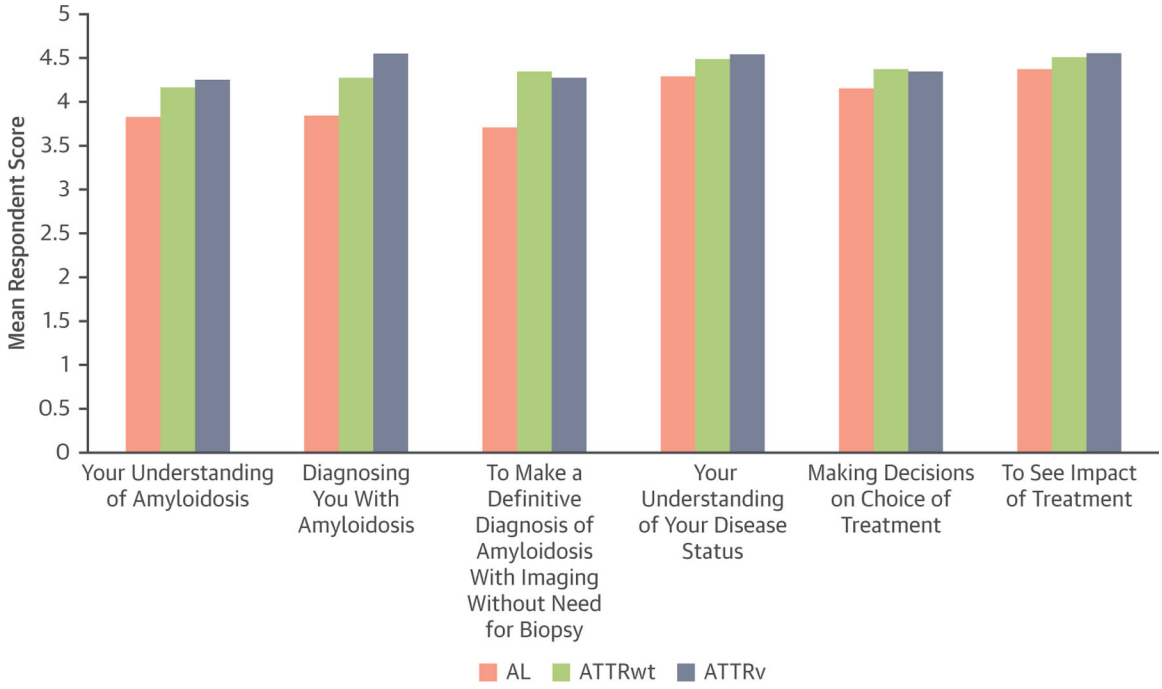

FIGURE 8. Patient Perspectives on the Value of Imaging: Survey Results

Results of informal online survey (N = 653 respondents) provide the patient perspective on the value of imaging in their management of amyloidosis. Mean score represents patient response on a 5-point progressive scale with 1 representing *"*not important*"* and 5 representing *"*very important.*"* AI = artificial intelligence; ATTR = transthyretin; ATTRv = variant; ATTRwt = wild type.

TABLE 1

Patient Imaging Survey Results

		Amyloidosis Type		
	All Respondents	**AL**	**ATTRwt**	**ATTRv**
Patient respondents	653 (100)	248 (38)	236 (36)	132 (20)
Imaging experience				
Diagnosis only	131 (20)	22 (9)	77 (33)	25 (19)
Monitoring only	144 (22)	85 (35)	11 (4.7)	41 (31)
Both diagnosis and monitoring	251 (39)	60 (24)	132 (57)	53 (40)
None	120 (19)	78 (32)	12 (5)	13(10)
Imaging type for diagnosis				
Echocardiography	258 (67)	64 (73)	143 (68)	45 (58)
SPECT	190 (49)	20 (23)	113 (54)	54 (69)
CMR	171 (44)	41 (47)	92 (44)	33 (42)
ECG	187 (48)	47 (53)	100 (48)	35 (45)
None/other/don’t know	45 (12)	22 (25)	18 (9)	4 (5)
Imaging type for monitoring				
Echocardiography	314 (78)	119 (82)	116 (79)	74 (78)
SPECT	70 (18)	12 (8)	19 (13)	38 (40)
CMR	87 (22)	28 (19)	28 (19)	29 (31)
ECG	212 (53)	72 (50)	75 (51)	57 (60)
None/other/don’t know	48 (12)	22 (15)	14 (10)	7 (4)

Values are n (%).

AL = immunoglobulin light chains; ATTR = transthyretin; ATTRv = variant; ATTRwt = wild-type; CMR = cardiac magnetic resonance; ECG = electrocardiogram; SPECT = single-photon emission computed tomography with bone-avid radiotracers