Supplemental Material

Diagnosis and treatment of cardiac amyloidosis. A position statement of the ESC Working Group on Myocardial and Pericardial Disease.

Content:

Table 1S. Serum and Urine Tests to Rule Out AL Amyloidosis.

Tests*	What Does it Detect?	Most Sensitive Test for:	Normal Range
SPIE†	Clonal immunoglobulin and/or clonal light chain	Confirming clonal immunoglobulin production	No monoclonal protein present
UPIE†	Clonal immunoglobulin and/or clonal light chain	Confirming clonal light chain production	No monoclonal protein present
Serum free light chain assay	Ratio of serum kappa:lambda light chains	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1	Kappa:lambda ratio: 0.26–1.65‡

*If any of these tests are abnormal, bone scintigraphy should not be used to make the diagnosis of ATTR amyloidosis, and biopsy is recommended. †SPIE and UPIE are more sensitive than protein electrophoresis without immunofixation and should be ordered as the preferred tests. ‡In patients with kidney disease, mild elevations in the kappa:lambda ratio are frequently encountered. In the setting of a normal SPIE/UPIE, a kappa:lambda ratio up to 2.5 can typically be considered normal.

AL: light-chain amyloidosis; ATTR: transthyretin amyloidosis; SPIE: serum protein electrophoresis with immunofixation; UPIE: urine protein electrophoresis with immunofixation.

Prognosis in cardiac amyloidosis

Several univariate and multivariate survival analyses have identified independent predictors of outcome of these patients. The vast majority of data regarding outcome and prognostic stratification of cardiac amyloidosis derived from retrospective studies of patients with AL amyloidosis.

Amyloid subtype

AL is widely associated with more rapid progression of heart failure (HF) and worse prognosis with median of about six months compared to ATTR forms[1,2].

Classical studies reported unadjusted overall survival of 63% for AL at 2 years[1] and 74% for ATTRwt patients at 3 years[3]. Fortunately, the prognosis of AL amyloidosis has significantly improved with the introduction of very effective therapies capable of dramatically reducing the production of the cardiotoxic light chains[4].

The effect of cardiotoxic light chains present in the active stage of AL, a greater severity of hemodynamic impairment and disease burden in other organs, such as autonomic nervous system control of vasculature, plays a role in the poor prognosis of AL[5].

TTR variants

Genotype is an important source of heterogeneity in ATTR myocardial involvement. Prognosis depends on mutation and cardiac and/or neurologic phenotype, driven by the degree of cardiac involvement. Most series have reported a median survival in the range of 8 to 10 years for ATTRv with polyneuropathy compared to 2.5-3.5 years in those ones with HF.

In general, groups of ATTRv by non-p.Val50Met mutations tend to have a worse prognosis compared with p.Val50Met. P.Val50Met patients have the best four-year survival at 79%[6].

In contrast, subjects with cardiac mutations such as p.Val142Ile, p.Leu131Met, p.Thr80Ala or p.Ile88Leu, p.Glu109Gln presenting with cardiac or mixed phenotypes, have been associated with a lower survival rate than subjects with other genotype or neurologic phenotypes[7-10]. Despite their clinical overlap, data regarding survival in ATTRwt and p.Val142Ile ATTRh is controversial. Median survival of p.Val142Ile has been

reported around 26 months[11], with a median survival of 3.5 years in untreated ATTRwt, depending on the stage at diagnosis.

Data from The Transthyretin Amyloidosis Outcomes Survey (THAOS) registry comparing ATTRwt and Val142Ile did not support a significant difference in outcomes despite heart transplantation was performed more frequently in Val142Ile compared to ATTRwt, resulting in shorter time to combined outcome of death or cardiac transplant in Val142Ile[12]. Other groups have reported a significantly worse survival in Val142Ile than in ATTRwt though[13,14]. Reduced left ventricular ejection fraction (LVEF) at diagnosis has been shown to be more common in Val142Ile than in ATTRwt, which could reflect a more advanced stage and may support the reduced survival reported in this subgroup.

Clinical, functional and ECG factors

Severity of HF by New York Heart Association (NYHA) class has consistently been a strong predictor of survival in different studies of the main subtypes of cardiac amyloidosis[1]. Distance on the 6-minute walk test (6MWD) has been also associated with ATTR survival[14].

Assessing functional capacity objectively, reduced peak VO2 by cardiopulmonary exercise test (CPET) has been associated as an independent predictor of mortality with worse survival both in AL and ATTR (16). Additionally, in a study with 56 ATTRwt patients, higher VE/VCO2 (VE/VCO2 slope >40) identified patients with higher mortality risk[15] (Table 2S).

In ATTRv, age at disease onset has been identified as a predictor of survival in different studies by univariate and multivariate analysis[12,16]. Age has also been independently associated with survival in ATTRwt[14]. Lower arterial pressure along with age has also been observed as an independent predictor of survival[12].

Moreover, the modified body mass index (mBMI), a marker of nutritional status, has been shown to be prognostic and related to functional capacity, also in patients who have undergone liver transplantation[14,17].

Regarding ECG features, QRS amplitude $\leq$ 0.5m in all limb leads or Sololow $\leq$ 1.5mV, in both main subtypes of cardiac amyloidosis have been shown to be predict outcomes[18,19].

Finally, it has been shown quite recently that an earlier diagnosis in ATTR leads to better survival. This has been illustrated since the introduction of non-invasive diagnostic criteria on top of an increased awareness of the disease[14].

Echocardiography

Many morphological and functional parameters have demonstrated prognostic value when studied in isolation.

LV wall thickness, reduced LV systolic function by LVEF, shortened deceleration time and increased early-to-late diastolic filling ratio of transmitral flow have all been reported as predictors of death in cardiac amyloidosis in small series[1,20] (Table 2S).

In AL, increased wall thickness and transmitral restrictive filling pattern are the main two prognostic factors from an echocardiographic point of view. In ATTR, LV filling pattern, LV mass index and decreased longitudinal myocardial function by mitral annular plane systolic excursion (MAPSE) have been also proposed as predictive of survival.

Additionally, left ventricular longitudinal global strain (LGS) was found to be an independent predictor of overall survival[5] (Table 2S). Moreover, LGS has demonstrated superiority to clinical variables (age, Karnofsky index and NYHA), biomarkers and standard echo parameters, with additive prognostic value even when HF is present[21,22].

On top of LGS, Relative regional strain ratio, a measure of the relative apical sparing of longitudinal strain, showed to be an independent predictor of all-cause mortality or heart transplantation despite multivariable risk adjustment for other adversely prognostic factors in a both AL and ATTR[23].

Myocardial contraction Fraction (MCF), a ratio of stroke volume (SV) to myocardial wall volume, determined by linear dimensions, assuming a constant left ventricular density, did predict survival in a small cohort of AL patients, independent and superiorly to LVEF[24] (Table 2S). Later on, in a large cohort of AL patients, MCF and SV, defined by pulsed-wave Doppler of the LV outflow tract, and the derived cardiac index (SV multiplied by heart rate), demonstrated to be strong predictors of survival even after adjustment for biomarker stage although not manifestly superior to LGS. In this case, patients with a MCF <34% and SVI < 3L/min did exceptionally poorly, with a median survival of 6-12 months, while those ones with values above the threshold, survived between 4.4-6.8 years[25].

In a very recent work, incorporating classical and new imaging parameters, indexed SV (iSV) and CMR-derived tricuspid annular plane systolic excursion (TAPSE) emerged as the two independent predictors of survival, the latter being the most statistically significant independent marker of prognosis and the only one common to AL and ATTR, probably due to direct RV subendocardial infiltration (Table 2S). By subtypes, in ATTR, TAPSE was consistently significantly associated with mortality and indexed left atrial area, iSV and TAPSE in AL[26].

Cardiac magnetic resonance

So far, biomarkers, ECG and cardiac morphology and functional parameters rely on measuring surrogates rather than direct markers of interstitial expansion. Tissue characterization has emerged as a very useful tool, being able to estimate amyloid load which has been histologically associated with AL prognosis[27].

Results of early studies regarding the role of late gadolinium enhancement (LGE) in prognosis, defined as present or absent, showed negative results, but findings supported that abnormal myocardial contrast accumulation was associated with decreased survival[28].

Despite initial conflicting results from different studies, the two largest cohorts demonstrated in 2015 and 2016 that absence of LGE was associated with an improved prognosis while transmural LGE was associated with a poorer prognosis compared to other patterns of LGE in AL and ATTR, even after adjustment for NYHA, biomarkers and conventional echo prognostic factors[29] (Table 2S). In the second one, median survival was significantly different in the 2 amyloid types within the transmural pattern: 17 months for AL and 38 for ATTR. However, and interestingly, in a more recent study, focused on 263 ATTR patients, transmural LGE was not associated with a worse prognosis than subendocardial LGE[30].

Moreover, in AL, extracellular volume fraction (ECV), regardless of treatment status or time of presentation, has been shown to be the best predictor of survival. ECV > 0.45 was associated with a 3-to-4-fold increased likelihood of death- roughly a 35-40% chance of death at 23 months compared with lower ECV patients despite therapy[31,32].

For pre-contrast or native myocardial T1 (avoiding the use of gadolinium contrast), a cut-point of 1044 ms has been proposed as predictor of survival, providing very similar

prognostic information as ECV, although it has not been consistent in all studies. Post-contrast T1 did not show to predict survival though[32].

In the largest cohort of ATTR patients undergoing CMR, ECV demonstrated to be able to predict death in the overall population and separately in ATTRwt and ATTRv. ECV also correlated with amyloid burden, being an independent prognostic factor for survival, even after adjustment for known prognostic factors and regardless of the moment of presentation. The better prognostic power of ECV compared with LGE might reflect the ability of ECV to measure the continuum of amyloid infiltration rather than a binary categorization by LGE[30].

A similar cut-off of >1077 ms by native T1 has been associated with worse prognosis for ATTR, but not particularly prognostic when separated by hereditary and wild-type. However, ECV was more robust than native T1 probably due to the inability of native T1 to track increasing amyloid burden with ECV >0.40[33].

In the last few years, the role of myocardial edema has been investigated in cardiac amyloidosis. In keeping with results from histological studies[34], myocardial edema measured by T2 has recently been proven as a predictor of prognosis in AL. T2 predicted death in AL and remained significant after adjusting for known prognostic factors such as ECV and NTproBNP. A T2 <55 ms was associated with 88% chance of survival at 18 months while a T2 > 55ms was associated with 67%. On the contrary, no relationship between T2 and prognosis was found in ATTR (Table 2S)[35].

Scintigraphy

Scintigraphy using ^{99m}Tc-Pyrophosphate (PYP) demonstrated an association between PYP uptake and increased mortality and poor outcomes in ATTR[36]. Moreover, an apical sparing ratio (ASR) of myocardial uptake, has also recently shown to better predict survival than LGS with an ASR >2.75 being associated with better prognosis in ATTR[37]. Nonetheless, evidence is still conflicting as in this study, in which heart-to-contralateral lung (H/CL ratio) and indexed LV uptake indexed were not associated with prognosis.

Scare and unicentric data exist regarding HMDP. In 121 French patients with suspected cardiac amyloidosis, increased uptake by HMDP in 55 ATTR and 14 AL, was associated with increased risk of acute HF and/or death. This was the first evidence that HMDP

allows the identification of high-risk patients with ATTR, with a significantly positive correlation between heart-to-skull retention (HR/SR) ratio and NYHA class[38].

The prognostic role of ^{99m}Tc-DPD in ATTR is conflicting. Although a small series with a relatively low number of events did show that DPD myocardial uptake is a prognostic determinant of cardiac outcome[39], this was not confirmed by the use of Perugini grading in ATTR[40].

Table 2S. Techniques to Assess Cardiac Progression and Available Data.

Domains / Methods	ATTR Cardiac Amyloidosis	AL Cardiac Amyloidosis
Functional capacity		
- NYHA class	- Progressive worsening without treatment.	- Rapidly worsening without treatment.
- Six-minute hall walk distance(6MWD)	- Declines of ~25 meters every 6 months[11,41] or 100 meters every 2 years[14] with greater declines in hATTR compared to wtATTR in some[41] but not all studies[14]. - Declines of 0.35 m/sec over 18 months[42]. - Worse survival with lower peak VO2[43] and higher Ve/VCO2[15]. Longitudinal data not yet delineated.	- 6MWD associated with NYHA class, biomarkers and overall survival in AL[57], significant improvement in patients with cardiac response to chemotherapy[58].
- Gait speed		- Unknown.
- CPET*		- Worse survival with lower peak VO2[43]. Longitudinal data not yet delineated.
Quality of Life		
- KCCQ	- Declines of ~10 points in KCCQ-OS each year which is depend on NYHA class[41], with greater declines in hATTR compared to wtATTR[14,44].	- Data with KCCQ not reported in this population.
- Norfolk QOL	- Increases of ~10 points in Norfolk-DM QOL in placebo arm of silencer trials[42,45] in hATTR, with slower progression in ATTR cardiomyopathy patients[45].	- Not employed in this population.
- SF12/SF-36	- SF36 Physical component summary demonstrates decline of 3-5 points over 15 -24 months[45,46].	- Patients with cardiac amyloidosis reported more anxiety and role limitation due to emotional problems[59]. Longitudinal data not available.
Biomarkers / Lab results		
- NTproBNP/ BNP	-Progressively increase over time, staging systems[47,48] use NTproBNP level of 3,000 pg/ml to delineate stages. An increase of ~4,000 pg/ml was observed over 30 months[41] . A higher increase over time is observed in Val142Ile compared to wtATTR or non-Val142Ile subjects[14].	- Staging systems[60,61] employ natriuretic peptides, with extremely high levels >8,500 pg/ml, predictive of short term outcomes. NTproBNP has been validated and is used to determine a cardiac response defined as a decrease in NT-proBNP >30% and 300 pg/ml[62] as well as cardiac progression defined as increase in NT-proBNP >30% and 300 pg/ml

- Troponin T/I	- Troponin T > 0.05 ng/ml are used in a staging system[47], tend to increase over time and exponentially increase in advance disease.	- Troponin T is part of staging systems[60] and hs-Troponin alone can be used to stage disease[62,63]. Levels decline with anti-plasma cell therapy and are a marker of a cardiac response.
- eGFR	- Declines in eGF of ~5-10 ml/min/m2 every year[14].	- In cardiorenal AL amyloidosis outcomes are dictated by NT-proBNP and eGFR at diagnosis rather than proteinuria, and thus changes in NT-proBNP concentration are most predictive[64].
- Prealbumin/TTR levels	- TTR levels are prognostic[49], decline with knockdown therapy[42,45] and increase after stabilizer therapy[50].	- Mainly used as a negative acute phase reactant to identify poor nutrition.
Echocardiographic measures		
- LVEF	- Declines in LVEF of ~3% every 6 months[11] and ~5% over 2.5 years[41].	- Significant reductions in LVEF occurs in advanced disease and is a marker of poor outcomes, longitudinal changes over time not delineated.
- MCF*	- Associated with adverse outcomes independent of EF[25,51]. Longitudinal data not available.	- Reduced in cardiac amyloidosis[65] and is a predictor of survival[24]. Longitudinal data not available.
- Strain	- Declines by 2% over 2.5 years[41].	- Independent prognostic variable beyond biomarker staging[21,22]. Longitudinal changes not described.
- Stroke volume	- Declines in SV of 11-12 ml over 2.5 years[41].	- SV index is an independent predictor of survival similar to strain[25]. Longitudinal data not available.
CMR Imaging*		
- Delayed enhancement (LGE)	- Progressive enhancement from absent to subendocardial, to transmural occurs with increasing amyloid burden[29].	- Progressive enhancement from absent to subendocardial, to transmural occurs with increasing amyloid burden and transmural LGE predicted death[29]. - Independent prognostic value[30]. Longitudinal data not available. Myocardial edema is prognostic in AL amyloidosis[35].

- Extracellular Volume (ECV)	- Independent prognostic value[30]. Longitudinal data not available.	
Positron Emission Tomography*	- Can identify cardiac involvement[52-56] in both forms of amyloidosis including early involvement and may be able to track disease progression over time, though longitudinal data not available.	
Hospitalizations - CV and Non-CV causes	- CV hospitalizations at a rate of 0.7 `and all cause at 0.77 per year among subject surviving 2.5 years, median of 2 hospitalizations in initial year after diagnosis[14].	- Hospitalization data not published.
- Days alive out of hospital	- 344±61 days (94%) in 12 months, dependent on stage of disease.	- 262 ± 130 days (72%) in 12 months, dependent on stage of disease.
- Home days	- Data not available.	- Data not available

*Indicates data that is cross section but not longitudinal precluding definitive characterization about role in assessing progression of disease.

Hematologic therapy of AL amyloidosis

Newly diagnosed patients

The aim of therapy is the rapid elimination of the amyloid precursor that is usually followed by amelioration of cardiac function that translates into improved patients' quality of life and survival[66]. The suppression of amyloid light chain synthesis is effectively achieved using chemotherapy and, more recently, with immunotherapy targeting the B cell clone. The choice of therapy is based on risk assessment.

Patients at low risk should be considered for high-dose intravenous melphalan conditioning followed by autologous peripheral blood stem cell transplantation (HDM–SCT). The risk of major complications, including death, within 100 days from starting the procedure has been decreasing during the last decade but it can be still substantial, ranging from 5 to 15%, according to the experience of the transplanting center[67]. Lower doses of melphalan could reduce treatment-related toxicity but also lower hematological responses[68]. Appropriate patient selection is key to reducing morbidity and mortality[69]. Eligibility criteria for HDM–SCT vary between centers but broadly require the preserved function of vital organs (with the exception of patients in dialysis who are transplanted by some centers) with good performance status. Approximately 20% of patients are eligible for HDM-SCT.

HDM-SCT improves organ function and extends survival[70]. A report from an international registry showed an excellent 5-year survival of 77% in the period from 2007 to 2012[67]. In 421 patients treated with HDM–SCT at Boston University, those achieving a complete response (approximately 40%) had an impressive organ response of 78% with a median event-free survival of 8.3 years and a median overall survival of 13.2 years[71]. An expanded series of 629 patients from the same center reported a median overall survival of 7.6 years. The median overall survival has not been reached for patients achieving a hematologic complete response[72]. Conditioning with bortezomib-based regimens improves the outcome of HDM-SCT[73] and consolidation increases the response rate[74].

Patients at intermediate risk should receive upfront a bortezomib-based regimen that produces a rapid and profound reduction of the amyloid light chains with improvement of heart and kidney function[75]. Recently, a notable cardiac response rate of 61% has

been reported in patients treated upfront with bortezomib-based regimens who achieved a deep reduction of the involved FLC (dFLC<10 mg/L)[76]. These regimens, in general, do not harm hematopoietic stem cells and should be used in patients with potentially reversible contraindications to ASCT. In patients with neuropathy or fibrotic lung disease, the combination of melphalan and dexamethasone should be considered. This regimen is very well tolerated, with very good partial response or complete response in 60% of cases when full-dose dexamethasone can be given[77]. In an international phase III study, bortezomib plus melphalan and dexamethasone demonstrated a higher hematological response rate than melphalan and dexamethasone alone (81% versus 57%, P = 0.005)[78]. Combinations including IMiDs upfront showed good response rates but were associated with higher myelotoxicity[66], and these agents should be reserved for relapsing/refractory patients. Daratumumab, a CD38 monoclonal antibody has been recently reported to achieve good hematologic responses in relapsed/refractory AL amyloidosis and is expected to move to frontline therapy soon[79].

High-risk patients with advanced cardiac stage (IIIb) dysfunction or severe heart failure (NYHA class III or class IV) represent ~20% of all individuals with AL amyloidosis. So far, no treatment regimen can substantially alter the course of the disease in these patients who should be considered for heart transplantation[80]. The few patients (~20%) who survive long enough (1–3 months) to take advantage of the response to bortezomib-based chemotherapy can enjoy prolonged survival[81]. Much attention is now focused on this unmet need, and trials exploring the benefit of doxycycline[82] or immunotherapy targeting the amyloid deposits[83] are ongoing.

Treatment of relapsing/refractory patients

The majority of newly AL patients treated with front-line therapies achieve a hematologic response, few are resistant, however, most patients will relapse. Hematologic progression is defined by the reappearance of a detectable monoclonal protein or abnormal serum free light-chain ratio after having achieved a hematologic complete response or a 50% increase in serum M protein or urine M protein to >0.5 g/dL or >200 mg/day, respectively, or a free light-chain increase of 50% to >100 mg/L in those with stable disease or partial response[84]. The optimal timing for initiating additional

therapy after hematologic relapse is still a matter of debate but there is a tendency towards starting retreatment as soon as there is evidence of hematologic progression, since waiting until appearance of signs of organ progression is associated with reduced survival[85]. Treatment choice should be made by a multidisciplinary team, including a cardiologist, with consideration of the patient's functional status, previous therapy, duration of response and potential treatment toxicities. If the patient relapses after more than 2 years, a rechallenge with front-line therapy (if not HDM-SCT) should be considered. If the patient was not previously exposed to proteasome inhibitors, a bortezomib-based regimen is usually preferred[86]. Carfilzomib is also effective but is associated with significant toxicity. Ixazomib, the first-in-class oral proteasome inhibitor, is active in relapsed patients with a good toxicity profile[87]. If a patient has already been exposed to proteasome inhibitors then immunomodulatory agents are the most commonly chosen treatment. Lenalidomide is frequently used, and pomalidomide produces rapid and profound activity and fewer side effects[66]. If a patient has not been exposed to melphalan and is not eligible for HDM-SCT, then the regimen melphalan-dexamethasone should be considered, particularly in the presence of contraindications to bortezomib-based therapy[86]. Considering the high response rate obtained with daratumumab in relapsing patients, and its tolerability, this agent is now more and more used in this setting.

Table 3S. Survival and organ response probabilities based on the hematological response criteria.

Hematological response criteria	Definition	Overall survival	Overall organ response rate[88].	Cardiac response rate[88].
Complete response (CR)	Negative serum and urine immunofixation and normal FLC ratio	Median: 7.6 years 5-year rate: 73%	84%	81%
Very good partial response (VGPR)	dFLC < 40 mg/L	Median: 5.4 years 5-year rate: 54%	60%	51%
Partial response (PR)	dFLC decrease > 50%	Median: 2.6 years 5-year rate: 26%	20%	24%
No response (NR)	dFLC decrease ≤ 50%	Median: 1.2 years 5-year rate: 14%	3%	1%

Supplementary material references:

1. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation. 2009;120(13):1203-12.
2. Pellikka PA, Holmes DR, Jr., Edwards WD, Nishimura RA, Tajik AJ, Kyle RA. Endomyocardial biopsy in 30 patients with primary amyloidosis and suspected cardiac involvement. Arch Intern Med. 1988;148(3):662-6.
3. Gonzalez-Lopez E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. Eur Heart J. 2017;38(24):1895-904.
4. Madan S, Kumar SK, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. Blood. 2012;119(5):1117-22.
5. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation. 2014;129(18):1840-9.
6. Arruda-Olson AM, Zeldenrust SR, Dispenzieri A, Gertz MA, Miller FA, Bielinski SJ, et al. Genotype, echocardiography, and survival in familial transthyretin amyloidosis. Amyloid. 2013;20(4):263-8.
7. Damy T, Kristen AV, Suhr OB, Maurer MS, Plante-Bordeneuve V, Yu CR, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). Eur Heart J. 2019. 2019. doi: 10.1093/eurheartj/ehz173. Ahead of print.
8. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, et al. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. J Am Coll Cardiol. 2015;66(21):2451-66.
9. Rapezzi C, Perugini E, Salvi F, Grigioni F, Riva L, Cooke RM, et al. Phenotypic and genotypic heterogeneity in transthyretin-related cardiac amyloidosis: towards tailoring of therapeutic strategies? Amyloid. 2006;13(3):143-53.
10. Sattianayagam PT, Hahn AF, Whelan CJ, Gibbs SD, Pinney JH, Stangou AJ, et al. Cardiac phenotype and clinical outcome of familial amyloid

polyneuropathy associated with transthyretin alanine 60 variant. Eur Heart J. 2012;33(9):1120-7.

11. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J. 2012;164(2):222-8 e1.
12. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol. 2016;68(2):161-72.
13. Singh A, Geller HI, Falk RH. Val122Ile mt-ATTR Has a Worse Survival Than wt-ATTR Cardiac Amyloidosis. J Am Coll Cardiol. 2017;69(6):757-8.
14. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. Circulation. 2019;140(1):16-26.
15. Yunis A, Doros G, Luptak I, Connors LH, Sam F. Use of Ventilatory Efficiency Slope as a Marker for Increased Mortality in Wild-Type Transthyretin Cardiac Amyloidosis. Am J Cardiol. 2019;124(1):122-30.
16. Kristen AV, Maurer MS, Rapezzi C, Mundayat R, Suhr OB, Damy T, et al. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - Report from the Transthyretin Amyloidosis Outcome Survey (THAOS). PLoS One. 2017;12(4):e0173086.
17. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. J Intern Med. 1994;235(5):479-85.
18. Perlini S, Salinaro F, Cappelli F, Perfetto F, Bergesio F, Alogna A, et al. Prognostic value of fragmented QRS in cardiac AL amyloidosis. Int J Cardiol. 2013;167(5):2156-61.
19. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. Am J Cardiol. 2014;114(7):1089-93.

20. Koyama J, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging. 2010;3(4):333-42.
21. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, et al. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. J Am Coll Cardiol. 2012;60(12):1067-76.
22. Barros-Gomes S, Williams B, Nhola LF, Grogan M, Maalouf JF, Dispenzieri A, et al. Prognosis of Light Chain Amyloidosis With Preserved LVEF: Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System. JACC Cardiovasc Imaging. 2017;10(4):398-407.
23. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Stork S, et al. Impact of regional left ventricular function on outcome for patients with AL amyloidosis. PLoS One. 2013;8(3):e56923.
24. Tendler A, Helmke S, Teruya S, Alvarez J, Maurer MS. The myocardial contraction fraction is superior to ejection fraction in predicting survival in patients with AL cardiac amyloidosis. Amyloid. 2015;22(1):61-6.
25. Milani P, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R, et al. Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis. Circ Cardiovasc Imaging. 2018;11(5):e006588.
26. Knight DS, Zumbo G, Barcella W, Steeden JA, Muthurangu V, Martinez-Naharro A, et al. Cardiac Structural and Functional Consequences of Amyloid Deposition by Cardiac Magnetic Resonance and Echocardiography and Their Prognostic Roles. JACC Cardiovasc Imaging. 2019;12(5):823-33.
27. Kristen AV, Brokbals E, Aus dem Siepen F, Bauer R, Hein S, Aurich M, et al. Cardiac Amyloid Load: A Prognostic and Predictive Biomarker in Patients With Light-Chain Amyloidosis. J Am Coll Cardiol. 2016;68(1):13-24.
28. Ruberg FL, Appelbaum E, Davidoff R, Ozonoff A, Kissinger KV, Harrigan C, et al. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. Am J Cardiol. 2009;103(4):544-9.

29. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation. 2015;132(16):1570-9.
30. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017;70(4):466-77.
31. Lin L, Li X, Feng J, Shen KN, Tian Z, Sun J, et al. The prognostic value of T1 mapping and late gadolinium enhancement cardiovascular magnetic resonance imaging in patients with light chain amyloidosis. J Cardiovasc Magn Reson. 2018;20(1):2.
32. Banypersad SM, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A, et al. T1 mapping and survival in systemic light-chain amyloidosis. Eur Heart J. 2015;36(4):244-51.
33. Martinez-Naharro A, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, et al. Native T1 and Extracellular Volume in Transthyretin Amyloidosis. JACC Cardiovasc Imaging. 2019;12(5):810-9.
34. Siegismund CS, Escher F, Lassner D, Kuhl U, Gross U, Fruhwald F, et al. Intramyocardial inflammation predicts adverse outcome in patients with cardiac AL amyloidosis. Eur J Heart Fail. 2018;20(4):751-7.
35. Kotecha T, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, et al. Myocardial Edema and Prognosis in Amyloidosis. J Am Coll Cardiol. 2018;71(25):2919-31.
36. Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, et al. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. JAMA Cardiol. 2016;1(8):880-9.
37. Sperry BW, Vranian MN, Tower-Rader A, Hachamovitch R, Hanna M, Brunken R, et al. Regional Variation in Technetium Pyrophosphate Uptake in Transthyretin Cardiac Amyloidosis and Impact on Mortality. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):234-42.

38. Galat A, Rosso J, Guellich A, Van Der Gucht A, Rappeneau S, Bodez D, et al. Usefulness of (99m)Tc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. Amyloid. 2015;22(4):210-20.

39. Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. JACC Cardiovasc Imaging. 2011;4(6):659-70.

40. Hutt DF, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, et al. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. Eur Heart J Cardiovasc Imaging. 2017;18(12):1344-50.

41. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16.

42. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):11-21.

43. Hein S, Aus Dem Siepen F, Bauer R, Katus HA, Kristen AV. Peak V'O2 is an independent predictor of survival in patients with cardiac amyloidosis. Amyloid. 2018;25(3):167-73.

44. Maurer MS, Sultan MB, Rapezzi C. Tafamidis for Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2019;380(2):196-7.

45. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31.

46. Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA. 2013;310(24):2658-67.

47. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol. 2016;68(10):1014-20.

48. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018;39(30):2799-806.
49. Hanson JLS, Arvanitis M, Koch CM, Berk JL, Ruberg FL, Prokaeva T, et al. Use of Serum Transthyretin as a Prognostic Indicator and Predictor of Outcome in Cardiac Amyloid Disease Associated With Wild-Type Transthyretin. Circ Heart Fail. 2018;11(2):e004000.
50. Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, et al. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2019;74(3):285-95.
51. Rubin J, Steidley DE, Carlsson M, Ong ML, Maurer MS. Myocardial Contraction Fraction by M-Mode Echocardiography Is Superior to Ejection Fraction in Predicting Mortality in Transthyretin Amyloidosis. J Card Fail. 2018;24(8):504-11.
52. Manwani R, Page J, Lane T, Burniston M, Skillen A, Lachmann HJ, et al. A pilot study demonstrating cardiac uptake with 18F-florbetapir PET in AL amyloidosis patients with cardiac involvement. Amyloid. 2018;25(4):247-52.
53. Kim YJ, Ha S, Kim YI. Cardiac amyloidosis imaging with amyloid positron emission tomography: A systematic review and meta-analysis. J Nucl Cardiol. 2020;27(1):123-32.
54. Trivieri MG, Dweck MR, Abgral R, Robson PM, Karakatsanis NA, Lala A, et al. (18)F-Sodium Fluoride PET/MR for the Assessment of Cardiac Amyloidosis. J Am Coll Cardiol. 2016;68(24):2712-4.
55. Pilebro B, Arvidsson S, Lindqvist P, Sundstrom T, Westermark P, Antoni G, et al. Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR). J Nucl Cardiol. 2018;25(1):240-8.
56. Park MA, Padera RF, Belanger A, Dubey S, Hwang DH, Veeranna V, et al. 18F-Florbetapir Binds Specifically to Myocardial Light Chain and Transthyretin Amyloid Deposits: Autoradiography Study. Circ Cardiovasc Imaging. 2015;8(8).

57. Pulido V, Doros G, Berk JL, Sanchorawala V. The six-minute walk test in patients with AL amyloidosis: a single centre case series. Br J Haematol. 2017;177(3):388-94.
58. Decker I, Goodman SA, Phillips SE, Lenihan DJ, Cornell RF. The six-minute walk test is a valuable measure of functional change following chemotherapy for AL (light-chain) cardiac amyloidosis. Br J Haematol. 2017;177(3):481-3.
59. Shu J, Lo S, Phillips M, Sun F, Seldin DC, Berenbaum I, et al. Depression and anxiety in patients with AL amyloidosis as assessed by the SF-36 questionnaire: experience in 1226 patients. Amyloid. 2016;23(3):188-93.
60. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30(9):989-95.
61. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013;121(17):3420-7.
62. Palladini G, Barassi A, Klersy C, Pacciolla R, Milani P, Sarais G, et al. The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-proBNP) after chemotherapy best predicts survival in AL amyloidosis. Blood. 2010;116(18):3426-30.
63. Dispenzieri A, Gertz MA, Kumar SK, Lacy MQ, Kyle RA, Saenger AK, et al. High sensitivity cardiac troponin T in patients with immunoglobulin light chain amyloidosis. Heart. 2014;100(5):383-8.
64. Rezk T, Lachmann HJ, Fontana M, Naharro AM, Sachchithanantham S, Mahmood S, et al. Cardiorenal AL amyloidosis: risk stratification and outcomes based upon cardiac and renal biomarkers. Br J Haematol. 2019;186(3):460-70.
65. Arenja N, Fritz T, Andre F, Riffel JH, Aus dem Siepen F, Ochs M, et al. Myocardial contraction fraction derived from cardiovascular magnetic resonance cine images-reference values and performance in patients with

heart failure and left ventricular hypertrophy. Eur Heart J Cardiovasc Imaging. 2017;18(12):1414-22.

66. Merlini G, Dispenzieri A, Sanchorawala V, Schonland SO, Palladini G, Hawkins PN, et al. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers. 2018;4(1):38.

67. D'Souza A, Dispenzieri A, Wirk B, Zhang MJ, Huang J, Gertz MA, et al. Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study. J Clin Oncol. 2015;33(32):3741-9.

68. Tandon N, Muchtar E, Sidana S, Dispenzieri A, Lacy MQ, Dingli D, et al. Revisiting conditioning dose in newly diagnosed light chain amyloidosis undergoing frontline autologous stem cell transplant: impact on response and survival. Bone Marrow Transplant. 2017;52(8):1126-32.

69. Gertz MA, Lacy MQ, Dispenzieri A, Kumar SK, Dingli D, Leung N, et al. Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. Bone Marrow Transplant. 2013;48(4):557-61.

70. Sidiqi MH, Aljama MA, Buadi FK, Warsame RM, Lacy MQ, Dispenzieri A, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. J Clin Oncol. 2018;36(13):1323-9.

71. Cibeira MT, Sanchorawala V, Seldin DC, Quillen K, Berk JL, Dember LM, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. 2011;118(16):4346-52.

72. Sanchorawala V, Sun F, Quillen K, Sloan JM, Berk JL, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. Blood. 2015;126(20):2345-7.

73. Hwa YL, Kumar SK, Gertz MA, et al. Induction therapy pre-autologous stem cell transplantation in immunoglobulin light chain amyloidosis: a retrospective evaluation. Am J Hematol. 2016;91(10):984-988.

74. Landau H, Smith M, Landry C, Chou JF, Devlin SM, Hassoun H, et al. Long-term event-free and overall survival after risk-adapted melphalan and SCT for systemic light chain amyloidosis. Leukemia. 2017;31(1):136-42.
75. Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015;126(5):612-5.
76. Manwani R, Cohen O, Sharpley F, Mahmood S, Sachchithanantham S, Foard D, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019;134(25):2271-80.
77. Palladini G, Milani P, Foli A, Obici L, Lavatelli F, Nuvolone M, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Haematologica. 2014;99(4):743-50.
78. Kastritis E, Leleu X, Arnulf B, et al. A Randomized Phase III Trial of Melphalan and Dexamethasone (MDex) Versus Bortezomib, Melphalan and Dexamethasone (BMDex) for Untreated Patients with AL Amyloidosis. Blood. 2016;128(22).
79. Kaufman GP, Schrier SL, Lafayette RA, Arai S, Witteles RM, Liedtke M. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood. 2017;130(7):900-2.
80. Kristen AV, Kreusser MM, Blum P, Schonland SO, Frankenstein L, Dosch AO, et al. Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era. J Heart Lung Transplant. 2018;37(5):611-8.
81. Manwani R, Foard D, Mahmood S, Sachchithanantham S, Lane T, Quarta C, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica. 2018;103(4):e165-e8.
82. Wechalekar A, Whelan C, Lachmann H, et al. Oral Doxycycline Improves Outcomes of Stage III AL Amyloidosis - a Matched Case Control Study. Blood. 2015;126:732.

83. Edwards CV, Gould J, Langer AL, et al. Final Analysis of the Phase 1a/b Study of Chimeric Fibril-Reactive Monoclonal Antibody 11-1F4 in Patients with Relapsed or Refractory AL Amyloidosis (Abstract 509). Blood (ASH 59th Annual Meeting and Exposition, Atlanta, GA, December 9-12). 2017;130.
84. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. 2005;79(4):319-28.
85. Palladini G, Merlini G. When should treatment of AL amyloidosis start at relapse? Early, to prevent organ progression. Blood Adv. 2019;3(2):212-5.
86. Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood. 2016;128(2):159-68.
87. Sanchorawala V, Palladini G, Kukreti V, Zonder JA, Cohen AD, Seldin DC, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood. 2017;130(5):597-605.
88. Muchtar E, Lin G, Grogan M. The Challenges in Chemotherapy and Stem Cell Transplantation for Light-Chain Amyloidosis. Can J Cardiol. 2020;36(3):384-95.