Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

Running title: Fontana et al.; Late Gadolinium Enhancement in Cardiac Amyloidosis

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Abstract

**Background**—The prognosis and treatment of the two main types of cardiac amyloidosis, immunoglobulin light chain (AL) and transthyretin (ATTR) amyloidosis are substantially influenced by cardiac involvement. Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) is a reference standard for the diagnosis of cardiac amyloidosis, but its potential for stratifying risk is unknown.

**Methods and Results**—250 prospectively recruited subjects underwent LGE CMR comprising 122 with ATTR amyloid, 9 asymptomatic mutation carriers, and 119 patients with AL amyloidosis. Subjects were followed up for a mean of 24±13 months. LGE was performed with phase sensitive inversion recovery (PSIR) and without (magnitude only, MAG-IR). These were compared with extracellular volume measured with T1 mapping (ECV). PSIR was superior to MAG-IR LGE since PSIR nulled always the tissue (blood or myocardium) with the longest T1 (least gadolinium). LGE was classified into 3 patterns: none, subendocardial and transmural, which were associated with increasing amyloid burden as defined by ECV (p<0.0001) with transitions from none to subendocardial LGE at an ECV of 0.40-0.43(AL), 0.39-0.40(ATTR); and to transmural at 0.48-0.55(AL), 0.47-0.59(ATTR). Sixty seven (27%) patients died. Transmural LGE predicted death (HR=5.4, 95%CI: 2.1-13.7, p<0.0001) and remained independent after adjusting for NT-proBNP, ejection fraction, stroke volume index, E/E’ and left ventricular mass index (HR=4.1, 95%CI: 1.3-13.1, p<0.05).

**Conclusions**—There is a continuum of cardiac involvement in systemic AL and ATTR amyloidosis. Transmural LGE is determined reliably by PSIR and represents advanced cardiac amyloidosis. The PSIR technique provides incremental information on outcome even after adjusting for known prognostic factors.

**Key words:** cardiac magnetic resonance imaging; amyloid; prognosis
Introduction

The prognosis of immunoglobulin light-chain (AL or primary systemic) and transthyretin (ATTR) amyloidosis is substantially influenced by the presence and severity of cardiac involvement which then governs therapeutic strategies.\(^1\)\(^-\)\(^2\) Although blood biomarkers are useful guides for risk stratification,\(^3\) they are not specific for cardiac involvement, and current strategies do not ascertain all patients at risk. Mortality, despite treatment progress, remains high.\(^4\)\(^-\)\(^7\) Over the last decade, new chemotherapy regimens and stem cell transplantation have been associated with improved survival in patients with AL amyloidosis, but the prognosis remains poor in those with cardiac involvement, which also contributes substantially to treatment related morbidity and mortality. There remains much unmet need for improved non-invasive criteria to stratify risk in selecting optimal therapy whilst avoiding serious toxicities.

Cardiac amyloid deposition represents a key process in amyloid pathophysiology.\(^8\)\(^,\)\(^9\) Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) identifies myocardial infiltration: after the administration of contrast, CMR shows a characteristic pattern of global subendocardial LGE coupled with abnormal myocardial and blood-pool gadolinium kinetics.\(^10\)\(^,\)\(^11\) However, despite excellent diagnostic accuracy for the presence of amyloid, conflicting results have been reported regarding the prognostic impact AL amyloidosis, and no studies have been published in ATTR amyloidosis.\(^12\)\(^-\)\(^19\) Newer techniques, particularly phase sensitive inversion recovery, an LGE image reconstruction technique that is less sensitive to operator choice of null point and renders signal intensity truly T1 weighted, may better reflect extent of cardiac involvement\(^20\) and thereby improve risk stratification.

We report here a prospective CMR study conducted in amyloidosis, in which we investigated the prognostic value of LGE in 250 consecutive CMR-eligible subjects.
The aims of the study were to assess: 1- patterns of LGE and the benefit of new more robust approaches (PSIR); 2- correlation with the cardiac amyloid burden; 3- the prognostic impact of LGE in both AL and ATTR cardiac amyloidosis.

Methods

Amyloidosis patients

Subjects were prospectively recruited at the National Amyloidosis Centre, Royal Free Hospital, London, United Kingdom, from 2010 to 2014 (Supplemental Figure 1). Outcome (dead/alive) was ascertained using death certificates. A total of 250 patients were categorized into 3 groups:

Subjects with AL amyloid

119 patients with biopsy proven systemic AL amyloid (77 male, 65%; age 62±10 years), with biopsies from the myocardium (n=7, 6%) or other tissues (n=112, 94%).

Subjects with ATTR amyloid

122 consecutive, consenting patients with ATTR amyloidosis (101 male, 83%; age 71±11 years) were recruited. 69 percent (n=84) had histological proof of ATTR amyloidosis by Congo red and immunohistochemical staining of myocardial (n=35, 29%) or other tissues (n=49, 40%). The presence of cardiac amyloid was defined by presence of ATTR amyloid in a myocardial biopsy or positive technetium-labelled bone scintigraphy using 3,3-diphosphono-1,2-propanodicarboxylicacid (DPD scintigraphy). All subjects underwent sequencing of exons 2, 3, and 4 of the TTR gene.

TTR gene mutation carriers

In addition, there were 9 subjects with amyloidogenic TTR gene mutations (3 male, 33%; age 47±6 years) defined as individuals with no evidence of clinical disease (no cardiac uptake on
DPD scintigraphy and normal echocardiography, CMR, N-terminal pro-brain natriuretic peptide [NT-proBNP] and Troponin T).

**Exclusion criteria**

We excluded all patients with contraindications to CMR: glomerular filtration rate <30 mL/min, CMR incompatible devices. All ethics were approved by the UCL/UCLH Joint Committees on the Ethics of Human Research Committee, and all participants provided written informed consent.

**CMR Image acquisition**

All subjects underwent standard CMR on a 1.5-T clinical scanner (Avanto, Siemens Healthcare, Erlangen, Germany). Within a standard clinical scan (pilots, transverse white and black blood images, cines images to assess volumes and mass) LGE imaging was acquired using magnitude (MAG-IR) and phase sensitive inversion recovery sequences (PSIR) reconstructions in 43% of patients.

T1 measurement was performed using the shortened modified look-locker inversion recovery sequence (ShMOLLI)\(^{21}\) with regions of interest drawn in the 4 chamber view at the level of the basal and mid inferoseptum (2 segments, large region of interest).\(^{22}\) After a bolus of Gadoterate meglumine (0.1 mmol/kg, gadolinium-DOTA, marketed as Dotarem © Guerbet S.A. France) and standard LGE imaging (standard FLASH-IR or bSSFP sequence with MAG-IR and PSIR reconstruction), the patient was removed from the scanner. The ECV measurement approach employed equilibrium CMR with a primed infusion: at 15-minute post bolus, an infusion at a rate of 0.0011 mmol/kg/min contrast (equivalent to 0.1 mmol/kg over 90 minutes) was given. Between 45 minutes and 80 minutes post bolus, the patient was returned to the scanner, with the infusion continuing, and the T1 measurement repeated using the same
parameters of the pre-contrast ShMOLLI sequence.

**CMR LGE interpretation**

During interpretation, prior to our adoption of PSIR for all amyloidosis patients, because myocardial nulling can be difficult in the presence of amyloid, any confusion with MAG-IR images was resolved by selecting the images that most matched the post contrast T1 maps – with “bright” LGE expected to correlate with areas with the lowest post contrast T1 (i.e. the highest gadolinium concentration, the highest interstitial expansion).

The LGE pattern was classified by 2 different observers (MF and SP) into 3 groups according to the degree of transmurality: 1-no LGE; 2-subendocardial LGE (when there was global subendocardial involvement but no transmural LGE); 3-transmural LGE (when the LGE was extending transmurally), (Figure 1). Thus a patient with basal transmural LGE but apical subendocardial LGE would be classified as “transmural LGE”.

**CMR PSIR versus MAG-IR**

A sample of 100 images (50 PSIR, 50 MAG-IR reconstruction) was analyzed for concordance or discordance with the post-contrast T1 maps which were use as the truth standard (Figure 2). We considered that nulled tissue should be the tissue with the least contrast (longest T1 on post contrast T1 map). This means that a normal subject should have nulled myocardium; a high infiltration amyloid patient bright myocardium (transmural) and nulled blood, and the possibility of intermediate blood and myocardium nulling concurrently (typically with “bright” endocardium). This is discussed further in the figure legends and discussion.

**Statistical analysis**

Statistical analysis was performed using IBM SPSS Statistics Version 19 (IBM, Somers, New York) and R programming language (available at http://www.r-project.org/). All continuous
variables were normally distributed (Shapiro-Wilk), other than NT-proBNP and Troponin T which were therefore ln transformed for bivariate testing; these are presented as mean ± standard deviation (SD) with non-transformed NT-proBNP presented as median and Q1-Q3. Comparisons between groups were performed by one-way analysis of variance with post-hoc Bonferroni correction. The chi-square test or Fisher exact test was used to compare discrete data as appropriate. Correlations between parameters were assessed using Pearson (r) or Spearman’s rho. To assess the agreement of the assignment of the LGE pattern by two different observes, Intraclass Correlation Coefficient (ICC) was calculated. Statistical significance was defined as p < 0.05.

Survival was evaluated using Cox proportional hazards regression analysis, providing estimated hazard ratios (HR) with 95% confidence intervals (CI) and Kaplan Meier curves. Variables selected a priori for the clinical relevance and first explored with univariate Cox regression were entered in the multivariable models. Multivariable models evaluated the independent predictive value of LGE above other clinically and statistically significant covariates. Harrell’s C statistic was calculated for the different models.

**Results**

**Study Population**

The details of the 250 subjects are shown in Table 1. At the time of scanning, the AL amyloidosis cohort had 46 new untreated (to date) patients; 21 patients undergoing second or third line therapy and 52 stable patients (complete or very good response 80%; stable partial response 20%). UK firstline therapy at the time of this study was typically Cyclophosphamide, Thalidomide and Dexamethasone (CTD) or Cyclophosphamide, Bortezomib and Dexamethasone.
(CVD). Relapse therapy was typically CVD or a Lenalidomide-containing regimen. The TTR mutations were: V122I \( [n = 23] \), T60A \( [n = 13] \), V30M \( [n = 10] \), E54G \( [n = 2] \), S77Y \( [n = 2] \), E89K \( [n = 2] \) and D38Y, G47V, E89K, I84S, I107F and L12P in one case each. Of the 9 asymptomatic individuals with TTR mutations, 5 had \( TTR \) V30M and 3 T60A and 1 S77Y.

**MAG-IR versus PSIR**

MAG-IR LGE and T1 maps were discordant in 57% (where the operator was selecting the inversion time according to his/her best judgment) meaning that operator TI selection was mainly incorrect. Ten patients with MAG-IR only had not one LGE images that matched the T1 mapping for classification (implying the operator systematically kept the TI incorrect for the whole scan). All patients with PSIR LGE had diagnostic images. PSIR LGE and T1 maps were never (0%) discordant, Figures 2 and 3. MAG-IR could be incorrect in three ways:

- Inappropriately nulling global LGE, Figure 2D, particularly the highest ECV cases; to get the incorrect distribution (especially making LGE apical rather than basal, Figure 2A and B; or creating transmural LGE where there should be global nulling (and the ECV was low), Figure 2C. With PSIR, the longest T1 tissue after windowing is always nulled.

**LGE pattern and correlation with ECV**

Three patterns of LGE are observed: no LGE; subendocardial LGE and transmural LGE, Figure 1. There was good agreement in the assignment of these patterns between two observers (ICC 0.97, 95%CI 0.97-0.98). All patterns were present in AL and ATTR cardiac amyloidosis (Figure 1) but to different extents, with subendocardial LGE being more prevalent in AL (39% in AL vs 24% in ATTR, \( p<0.05 \)) and transmural LGE more prevalent in ATTR (27% in AL vs 63%, \( p<0.0001 \)), Figure 4.

Increasing LGE (none, subendocardial, transmural) was associated with increasing ECV
transmural LGE was significantly associated with mortality (HR = 4.1, 65% in ATTR). The median survival in patients with transmural LGE was 17 months in AL and subendocardial LGE (81% in AL, 81% in ATTR) and 61% with transmural LGE (45% in AL, 65% in ATTR) compared to 81% for patients with no LGE (92% in AL, 94% in ATTR).

At follow up (mean 24±13 months), 67 (27%) of 250 patients had died. Transmural LGE was a significant predictor of mortality in the overall population (HR 5.4, 95% CI: 2.1-13.7, P<0.0001) (Figure 5).

The survival curves indicate that there is an approximately 92% chance of survival at 24 months in patients with no LGE (92% in AL, 94% in ATTR) compared to 81% for patients with subendocardial LGE (81% in AL, 81% in ATTR) and 61% with transmural LGE (45% in AL, 65% in ATTR). The median survival in patients with transmural LGE was 17 months in AL and 38 months in ATTR. Transmural LGE was significantly associated with mortality (HR = 4.1, 65% in ATTR). The median survival in patients with transmural LGE was 17 months in AL and 38 months in ATTR. Transmural LGE was significantly associated with mortality (HR = 4.1, 65% in ATTR). The median survival in patients with transmural LGE was 17 months in AL and 38 months in ATTR. Transmural LGE was significantly associated with mortality (HR = 4.1,
95% CI: 1.3-13.1, p<0.05) in multivariable Cox models that included NT-proBNP, ejection fraction, stroke volume indexed, E/E’, left ventricular mass indexed (Troponin results were not available in all patients). NT-ProBNP and stroke volume indexed also remained independently predictive (Table 3). Harrel C statistics for this model was 0.72.

The Harrel C statistics of a comparable preCMR-model including demographics, systolic and diastolic function parameters and biomarkers (Age, EF, EE, BNP, interventricular septal wall thickness) was 0.67.

Discussion

Cardiac infiltration is the chief driver of prognosis in systemic amyloidosis, and stratification of patients is essential for prognosis and optimal management, including selection of patients to receive aggressive higher risk therapies and to minimise cardiac toxicities. Echocardiography, once the gold standard cardiac investigation in amyloidosis, has limited sensitivity and specificity, and risk stratification is currently places great emphasis on blood biomarkers. However, these strategies do not identify all amyloidosis patients at risk, and the findings of studies on evaluation of cardiac involvement by CMR have been conflicting.4-7,19 Recently, considerable interest has emerged in using LGE to improve the risk stratification model,12-19 but studies in AL cardiac amyloidosis have been few, mostly small, retrospective and have employed non-standardized LGE approaches, and have produced inconsistent results10,12,13,15,16,19. No studies have been published in ATTR amyloidosis.

In the present study, the largest CMR study in amyloidosis to date, we showed that misleading results using the MAG-IR LGE technique was likely to account for the conflicting finding that have previously been published. By convention, LGE should display containing the most contrast (i.e. shortest T1 on T1 maps). For amyloidosis, myocardium can contain more...
gadolinium than blood – under those circumstances, myocardium should appear globally bright (transmural LGE). It is a property of MAG imaging that signal is highly dependent and non-linear with user defined choice of the TI (time to null), Figure 2, and images can be “inverted” with the wrong TI choice. When all of the myocardium is abnormal (frequent in cardiac amyloidosis), the abnormal myocardium could be wrongly nulled, as the MAG-IR relies on ‘nulling’ what is perceived to be normal myocardium. This limitation was quantified in our study by comparison with a true standard of post contrast T1. More importantly, this problem does not occur with the PSIR approach. PSIR substantially removes the issue of operator selected inversion time and completely removes the potential for a “mirror image”. On a PSIR reconstruction when windowed by the operator, the tissue with the longest T1 (least gadolinium - blood or myocardium), after windowing, is always nulled. The practical result is this: a) if myocardium is globally nulled by PSIR, the ECV is less than blood and <0.4-0.43: any amyloid present (detectable by an ECV>0.32), is not extensive. b) above this, LGE areas appear particularly in the subendocardium. PSIR LGE areas are the areas of most amyloid deposition in the heart; c) above an ECV of 0.47-0.59, blood has less gadolinium than myocardium and blood is nulled – myocardium appears uniformly bright – heterogeneity is present but it is swamped by all the myocardium becoming bright. Examples of MAG-IR errors are in Figure 2: mid myocardial rather than subendocardial (Figure 2 panel A); apical rather than basal (Figure 2 panel B), transmural LGE rather than normal (Figure 2 panel C) and normal rather than transmural (Figure 2 panel D).20, 23 Accordingly, we believe that PSIR should be universally adopted for amyloid LGE imaging – particularly as PSIR-LGE is easily available from all scanner manufacturers (whereas T1 mapping is not yet).

Using PSIR, three patterns were relatively easy to determine, and the previously
frequently described LGE pattern of “patchy” LGE was not evident using PSIR – many of these on PSIR appeared to have transmural LGE. A key insight is that amyloid cardiac involvement is not dichotomous, but a continuum from no LGE to subendocardial to transmural tracking increasing ECV (Figure 6). Transmural LGE appears to be the pattern that carries the most adverse prognosis – it is an important marker of all cause mortality, after adjustment for other relevant disease variables and regardless of treatment status (indeed irrespective of whether patients are presenting at diagnosis or years into the disease process). Indeed, in ATTR, the majority of the deaths are in patients with transmural LGE (no LGE, subendocardial LGE, transmural: 1, 6, 24 deaths respectively).

Within this spectrum, the degree of involvement is important, and with transmural LGE defining the high risk group. The prevalence of patients in the different stages of disease progression (Figure 6) is different in AL and ATTR. 39% of the no LGE patients had ECVs in the 0.32 to 0.4 range, particularly AL amyloidosis. It is expected that ATTR patient must pass through this phase, but it is not clinically recognised. Early cardiac involvement in AL is detected through cardiac screening of AL patients presenting with extracardiac disease. The majority of ATTR patients (wild type ATTR and mutant ATTR associated with the variant V122I) present with heart failure symptoms that appear only when advanced (LGE is invariably present, mostly transmural). This has potential treatment implications. Currently, patients with subendocardial LGE may be classified as “cardiac involvement” and denied therapies, which are known to improve long term survival – but which are contraindicated in “cardiac involvement” – such as stem cell transplants (AL), some chemotherapy regimens (AL) and liver transplants (ATTR). More data is needed and consideration of cardiac involvement as a continuum should provide the insights into the impact of different degrees of cardiac infiltration and possibly
changing the current therapeutic approach. Within the transmural pattern, the median survival is significantly different in the two amyloid types, 17 months for AL and 38 months for ATTR. These findings support the concept that cardiac amyloid is not a disease of solely infiltration but may have with superimposed toxicity (AL > ATTR) or that the rate of accumulation is myotoxic, a contributor to different prognosis between AL and ATTR despite ATTR higher degrees of LVH, cardiac dysfunction and amyloid burden. T1 mapping techniques provide new insights into this, being able to follow the disease at three different levels, i.e. infiltration (amyloid burden, ECV), edema (native T1) and myocyte response (intracellular volume) and providing new prognostic markers. These new biomarkers may aid diagnosis, risk stratifications and act as surrogate end points in clinical trials. However the current limited availability, the technical challenges related to sequence and vendor specific differences limit the role of T1 mapping in routine clinical practice. The common use of the LGE technique in all clinical CMR scans and the availability of PSIR reconstruction on all different vendor platforms make LGE a robust and reliable approach for routine risk stratification of patients with cardiac amyloidosis.

Limitations of the study are that patients are at different treatment stages, with treatment reflecting current UK practice. Cardiac biopsy is present only in a minority of patients, but this cohort of patients was fully characterized with all other clinical investigative techniques currently available including DPD scanning. This composite diagnostic pathway is known to provide high diagnostic accuracy. The causes of death are not known as patients die locally and the National Amyloidosis centre only receives notification of death rather than cause of death. Although this study highlights the prognostic role of transmural LGE for risk stratification of patients with cardiac amyloidosis, further studies are needed to assess the direct correlation between patterns of LGE and treatment related mortality.
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**Conflict of Interest Disclosures:** None.

**References:**


cardiac rhythm recorders in advanced cardiac amyloidosis. *Eur Heart J.* 2014; 36:1098-1105.


Table 1. Main Clinical Characteristics, echocardiographic and ECG findings in patients with AL and ATTR amyloidosis according to the LGE pattern.

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<thead>
<tr>
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<th>All Patients</th>
<th>AL patients</th>
<th>ATTR patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n=250</td>
<td>No LGE n=37</td>
<td>Subendocardial LGE n=42</td>
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<tr>
<td>Age, y</td>
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<td>63±10</td>
<td>61±11</td>
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<td>Diastolic BP, mmHg</td>
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<td>188±51</td>
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<td>QRS, ms</td>
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AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; MR, magnetic resonance; LV, left ventricular; LA area, left atrial area indexed; LVEF, left ventricular ejection fraction; SV, stroke volume indexed NT-proBNP, N-terminal pro-brain natriuretic peptide. p-values: * p<0.05, † p<0.01, ‡ p<0.001 for trend (one-way analysis of variance) in AL and ATTR patients across different pattern of LGE. All continuous variables are presented as mean and standard deviation with non-transformed NT-proBNP presented as median and Q1-Q3.
Table 2. CMR findings in patients with AL and ATTR amyloidosis according to the LGE pattern.

<table>
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<th>All patients</th>
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<th>ATTR patients</th>
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<td>n=250</td>
<td>No LGE n=37</td>
<td>Subendocardial LGE n=42</td>
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<td>203±77</td>
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<td>108±39</td>
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<td>RA area_i, cm²/m²</td>
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</tr>
<tr>
<td>ECV, %</td>
<td>0.50±0.12</td>
<td>0.31±0.04</td>
<td>0.47±0.06</td>
</tr>
</tbody>
</table>

*less 10 patients with non-diagnostic MAG-IR LGE images
AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; LV, left ventricular; IVS interventricular septum; EDV, end diastolic volume; EDV_i, end diastolic volume indexed; ESV, end systolic volume; ESV_i, end systolic volume indexed; LVEF, left ventricular ejection fraction; LA area left atrial area; LA area_i left atrial area indexed; RV, right ventricle; RA, right atrium; MAPSE: mitral anular plane systolic excursion; TAPSE: tricuspid anular plane systolic excursion; ECV, extracellular volume.
p-values: * p<0.05, † p<0.01, ‡ p<0.001 for trend (one-way analysis of variance) in AL and ATTR patients across different pattern of LGE.
All variables are presented as mean and standard deviation.
Table 3. Univariate and multivariate analysis of risk of death in the overall population.

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th></th>
<th></th>
<th>Multivariable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Transmural LGE</td>
<td>5.38 (2.11-13.72)</td>
<td>p&lt; 0.0001</td>
<td>4.13 (1.30-13.07)</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, each incremental 100 pmol/L</td>
<td>1.03 (1.02-1.05)</td>
<td>p&lt; 0.0001</td>
<td>1.04 (1.02-1.07)</td>
<td>p&lt;0.0001</td>
<td></td>
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<tr>
<td>SVi, each decrement 5 ml/m²</td>
<td>1.33 (1.19-1.51)</td>
<td>p&lt; 0.0001</td>
<td>1.21 (1.02-1.44)</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>LVEF, each increment 3%</td>
<td>0.91 (0.87-0.96)</td>
<td>p&lt; 0.0001</td>
<td>1.02 (0.94-1.11)</td>
<td>NS p=0.634</td>
<td></td>
</tr>
<tr>
<td>LV massi, each increment 10 g/m²</td>
<td>1.08 (1.02-1.14)</td>
<td>p&lt; 0.01</td>
<td>0.99 (0.90-1.01)</td>
<td>NS p=0.885</td>
<td></td>
</tr>
<tr>
<td>E/E’, each increment 1</td>
<td>1.07 (1.04-1.10)</td>
<td>p&lt; 0.0001</td>
<td>1.03 (0.99-1.08)</td>
<td>NS p=0.145</td>
<td></td>
</tr>
</tbody>
</table>
Figure Legends:

**Figure 1.** Characteristic PSIR LGE patterns in 3 AL and 3 ATTR patients. No gadolinium enhancement (LGE) (left panels); Subendocardial LGE (middle); transmural LGE (left panels).

**Figure 2.** Characteristic CMR scans. Late gadolinium enhancement (LGE) with magnitude reconstruction (left panels); LGE with phase sensitive inversion recovery reconstruction (PSIR) (middle) and post contrast ShMOLLI T1 maps (right panels). On PSIR, there is 100% concordance between myocardial T1 and LGE: firstly areas of low T1 (darkest blue) and focal areas of LGE; secondly where myocardial T1 is lower than blood T1, global LGE is demonstrated and thirdly, where myocardial T1 is higher than blood T1, no LGE is demonstrated. On MAG-IR images, discordance is present in all 4 of these cases: mid myocardial rather than subendocardial (Panel A); apical rather than basal (panel B), transmural LGE rather than normal (panel C) and normal rather than transmural (panel D).

**Figure 3.** Two patients (top and bottom) with MAG and PSIR LGE reconstruction images (left). In both patients, the MAG and PSIR are discordant with opposite LGE patterns. Only one can be correct. The tissue to null is the one with the slowest T1 recovery (i.e. the least gadolinium). On the right are the signal intensity curves as the TI varies for MAG and PSIR. How the operator sets the TI matters in MAG imaging – but not in PSIR. The operator set the TI for both patients at X, nulling the wrong tissue. Only had they set the TI greater than Y would the image have been correct. With PSIR, the TI could have been set anywhere and the tissue with the least gadolinium has lower signal and will be nulled after windowing.
Figure 4. LGE patterns correlation with amyloid burden. Histograms showing the prevalence of the different LGE patterns (upper panels) in AL and ATTR patients; correlation with the amyloid burden (lower panels), measured as extracellular volume (ECV) in AL and ATTR patients. Bonferroni-adjustment was applied.

Figure 5. Kaplan Meier curves. Kaplan Meier curves for late gadolinium enhancement patterns in all patients (upper panel), AL (left lower panel) and ATTR patients (right lower panel).

Figure 6. Hypothesized cardiac amyloid progression across time. When amyloid starts to accumulate 3 steps can be identified; 1-No evidence of LGE but increase in native T1 and extracellular volume (ECV); 2-Further increase in T1 and ECV and appearance of subendocardial LGE; 3-Further increase in native T1 and ECV and progression to transmural LGE.
Figure 5: Survival functions for LGE pattern in all patients, AL patients, andATTR patients.
Supplemental Figure 1. Consort diagram.

Patients with ATTR amyloidosis and mutation carriers (n=122 and n=9) → Patients with AL amyloidosis (n=119) → Prospectively recruited for CMR (n=250) → MAG-IR LGE and PSIR (n=108) → Patients analyzed (n=108) Excluded from the analysis (n=0) as with PSIR all images were felt to be diagnostic → Patients analyzed (n=132) Excluded from the analysis (n=10) as MAG-IR did not give diagnostic images
Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis


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