Left Atrial Strain in Acute Heart Failure: Clinical and Prognostic Insights

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Abstract

Aims: In acute heart failure (AHF), the consequences of impaired left atrial (LA) mechanics are not well understood. We aimed to define the clinical trajectory of LA mechanics by left atrial strain (LAS) analysis.

Methods and Results: 85 consecutive AHF patients with reduced, mildly reduced, and preserved left ventricular ejection fraction (LVEF) were enrolled in the LAS-AHF trial and underwent LA mechanics analysis by speckle tracking echocardiography. 77 patients were followed-up at 6 and 12- months. At hospital admission, discharge, 6 and 12-months post-discharge, LA reservoir function (LAS), LA pump strain, LAVi, LA stiffness, indicators of right ventricular (RV) and left ventricular (LV) function, congestion indexes (B lines, IVC, X-ray congestion score index) and biomarkers (NT-pro-BNP) were measured. The primary outcome was time to first event of re-hospitalization, worsening HF or cardiovascular death.

From admission to discharge, RV function significantly improved after decongestion, while no significant differences were observed in LA dynamics and LV function. In sinus rhythm patients with mild or no mitral regurgitation, decongestion was associated with a significant improvement of LAS and LA pump strain rate during hospitalization. At 12 months, 24 CV events occurred and of LAS impairment at 12 months follow-up emerged as the most powerful predictor followed by NT-pro-BNP. Kaplan-Meier Curves showed a better survival for LAS >16%, improvement of LAS>5% and a LAS/LAVi ratio >0.25 %/ml/m2 compared to lower cutoff values (log-rank: HR 3.5 CI 95% 1.8-7.3, p=0.004; log-rank: HR 3.6 CI 95% 2-7.9, p<0.01; log-rank: HR 3.27 CI 95% 1.4-7.7, p=0.007).

Conclusions: In AHF of any LVEF, LA dynamics is highly predictive of re-hospitalization and cardiovascular outcome and allows to ease risk-stratification, potentially becoming an early reference target for improving long-term outcome.

Key words: acute HF, left atrial mechanics, prognosis.

Introduction

The physiology of the left atrium (LA) is crucial to maintain cardiac performance through modulation of left ventricular (LV) filling and serving as a buffer to the bursts of elevated left atrial pressure impacting on pulmonary pulsatile loading, overall playing a central role to maintain cardiac output [1]. Heart failure (HF) of any left ventricular ejection fraction (EF) alters LA size and function making LA an active contributor to hemodynamic instability and symptoms deterioration [2]. The LA chamber acts as a watershed between the LV and the pulmonary circulation impacting on right ventricular (RV) afterload and as soon as its functional properties exhaust, pressure and volume overload trigger pulmonary venous congestion which impairs gas exchange and promotes vascular remodeling [3]. This is most significant in the setting of acute heart failure (AHF), whose direct implications of LA functional impairment yield to a stepwise increase in pulmonary capillary pressures impairing RV function [4,5].

Recently, LA dynamics has been studied by speckle tracking echocardiography (STE) with the evaluation of LA reservoir and pump strain and there is established evidence that LA strain and LV filling pressures correlate with exercise capacity [1,2]. Furthermore, an impaired LA mechanics, documented by a reduced LA strain (LAS), is an established independent predictor of HF worsening clinical status and hospitalization.

Nonetheless, the response and the dynamic changes of LA function to targeted decongestion therapy in patients hospitalized for AHF seems worth of implementing evidence.

We hypothesized that a thorough analysis of LA dynamics, especially its reservoir function by LAS, would offer incremental value for outcome prediction and may represent a powerful prognostic echocardiographic tool that may ease and add to risk stratification of AHF patients, identifying those at higher risk for early re-hospitalization.

Methods

Study design and population— **Figure 1** reports the study design of the *Left Atrial Strain (LAS)- Heart Failure (HF)* trial. Between March 2017 and January 2020, 85 consecutive patients (median age 78 IQR [68.5-84], 59% male) presenting at the Emergency Department (ED) with AHF, were prospectively enrolled within 24 hours from admission in the LAS-AHF trial. In the acute phase and at pre-discharge, all patients underwent chest X ray with assessment of congestion score index (CSI) [7], lung

ultrasonography (LUS), transthoracic echocardiography (TTE) (M-Mode, 2-D and Doppler), blood test analysis and NT-pro-BNP evaluation. The initial evaluation consisted of clinical examination, blood analysis, TTE and LUS which were performed close to the arrival in the emergency department. Specifically, in 70% of cases the echo recording in relation to IV diuretics timing was performed within 2 hours of admission and in 30% after 4 hours or more from admission.

All patients were re-contacted at 6 and 12 months for event collection with a phone interview. 77 patients out of the 85 initial subjects enrolled were re-evaluated in ambulatory care setting at 6- and 12-months follow-up and underwent chest X ray, blood analysis, LUS and TTE. Event collection was obtained at 12 months. A combined primary outcome of major adverse cardiovascular events (MACE) was defined as worsening HF, HF re-hospitalization, and cardiovascular death. Worsening HF was defined as the need for intravenous diuretic therapy in the emergency or outpatient setting.

Patients were eligible if presenting at the ED with acute heart failure (AHF) defined, according to current Guidelines,[8] by the clinical presentation of symptoms and signs of congestion and poor organ perfusion (e.g. breathlessness, paroxysmal nocturnal dyspnoea, elevated jugular venous pressure, pulmonary crepitations, peripheral oedema, tachycardia, confusion) due to HF requiring urgent intravenous therapy. Patients with either "De novo" or "acute on chronic HF" presentation were included. Their hemodynamic phenotype (e.g. wet, dry, warm, cold) was classified according to Forrest et al. criteria.[9] E*xclusion criteria* were a recent acute coronary syndrome (<1 month); admission to the Cardiology ward later than 24 hours from ED presentation; previous mitral valve replacement; patients with known history of severe pulmonary disease such as pulmonary fibrosis, pneumothorax, fibrothorax and lung cancer due to the limited reliability of B-lines at LUS. All patients signed an informed consent for the execution of laboratory analysis and sonographic tests and for the scientific use of clinical and instrumental data. The study protocol was approved by our local Ethical Committee.

Echocardiographic Evaluation--Transthoracic echocardiography was performed at rest using a Philips Echocardiograph EPIQ system equipped with a 2.5 MHz transducer. LV and LA dimensions, LVEF, and diastolic LV filling velocities, along with RV dimensions, RV systolic longitudinal function assessed with tricuspid annular plane systolic excursion (TAPSE), pulmonary arterial systolic pressure (PASP) and maximum inferior vena cava (IVC) diameter were measured according to current recommendations of

the European Association of Cardiovascular Imaging (EACVI) and of the American Society of Echocardiography (ASE).[10] Right atrial pressure was estimated from inferior vena cava diameter and collapsibility. LVEF was obtained by Simpson's rule method. LA volumes were measured using the Simpson's rule method, from the apical four and two chamber views and then indexed. LV stroke volume (SV) and SV indexed (SVi) by body surface area were estimated by the non-invasive Doppler method multiplying the left ventricular outflow tract (LVOT) cross-sectional area (CSA) and the velocity time integral (VTI) of the LVOT. Cardiac output (CO) and CO indexed (COi) was obtained as SV × heart rate (HR). Right heart longitudinal systolic function was assessed by tricuspid annular peak systolic excursion (TAPSE), estimated artery pulmonary systolic pressure (PASP) and their ratio as indicator of right ventricular (RV) to pulmonary circulation (Pc) coupling.[11] LA dimensions were assessed by volume index (LAVi) and LAS/LAVi ratio was used as a an index of function related to dimensions.

Left ventricular filling pressure and LV diastolic dysfunction were estimated according to the EACVI/ASE recommendation with a multiparametric approach that included the assessment E/e' ratio (≥14), septal e' velocity (<7 cm/sec) and lateral e' velocity (<10 cm/sec), maximal tricuspid regurgitation velocity (≥2.8 m/s) and LA volume index (≥34 ml/m^2).[11]

STE Analysis-- Two-dimensional STE was performed using the QLAB-9 Imaging system. The LA dynamic analysis was performed offline on apical four- and two-chamber views with a stable EKG recording. Special care was taken to avoid LA foreshortening and to prevent the visualization of the LA appendage, to minimize its effect on LAS measurements. All images used for STE analysis were obtained at a frame rate of 50 to 70 fps. The beginning of the QRS was used as the reference onset point based on the ASE and EACVI Guidelines. For technical information see the supplemental material.

LUS evaluation—B-lines analysis were obtained at the anterior and lateral chest on the right and left hemi-thoraxes to detect signs of interstitial and alveolar edema. For technical information see the supplemental material.

Statistical Analysis--Data are presented as number and frequencies for categorical and binary variables, respectively. Normality of variables was assessed by the Shapiro–Wilk test and normally continuous variables were described as means ± standard deviation (SD). For non-normally distributed continuous

variables median with interquartile range (IQR) was used. Comparisons among groups and between admission/discharge and admission/6 and 12 months follow-up were performed using 2-sided, independent-samples unpaired Student's t test for normally-distributed continuous variables and Mann–Whitney–Wilcoxon test for not-normally distributed continuous data. For qualitative variables, differences in the sample were investigated using the chi- square test or Fisher test, while the ANOVA test was used for multiple comparisons among groups. Confidence intervals (CIs) for the difference between the means and the medians were calculated for normally and non-normally distributed variables, respectively. As for qualitative variables, Newcombe (hybrid-score) confidence limits for the risk difference were constructed from the Wilson score confidence limits for each of the two individual proportions. Pearson's correlation coefficient was used to examine the relationship between LA dynamics and other non-invasive established prognostic indexes, such as LAVi, SVi, CI, GLS, NT-proBNP and TAPSE/PASP ratio. Univariable and multivariable Cox proportional hazards models were performed for initial exploratory analyses to estimate coefficients and hazard ratios and determine prognostic relevance of LAS, LA dimension, LA stiffness, LAS/LAVi ratio and NT-proBNP levels. Variables for inclusion in multivariate regression models were selected based on statistical and/or their appropriate clinical value in AHF setting. Kaplan-Meier Curve of event-free from MACE for LAS, ΔLAS and LAS/LAVi ratio were plotted and compared using the log-rank test. An optimal cut-off of 16% for LAS was chosen according to previous literature, and the receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off of 0.25 %/ml/m^2 for LAS/LAVi ratio and of ≥5% for the delta LAS admission/12 months follow-up (**Figure 1** ***supplement***). For all tests, a p-value <0.05 (2-sided) was considered significant. Data were analyzed by STATA (version: STATA 15.1, STATA Corp, College Station, Texas, USA) and SPSS version 26 (IBM, Armonk, New York).

Results

The *study flow chart* with the final population is depicted in **Figure 2** *supplement.* Of the original cohort 77 patients out of 85 were re-evaluated at 6 and 12 months.

Clinical Characteristics and Therapy Distribution (**Table 1**)—The median age of the population in study was 78 years with a slight predominance of males and a high prevalence of hypertensive disease (86%) and diabetes (42%). At hospital admission 51% were classified as HFrEF, 20% as HFmrEF and 29% as

HFpEF. 60% and 40% of patients presented with ischemic and idiopathic dilated cardiomyopathy, respectively. The wet and warm phenotype was the most common at presentation (84%), 10% were congested and hypoperfused (*wet and cold* phenotype), while 6% exhibited exclusively signs of hypoperfusion (*dry and cold*). Most patients presented at ED with AHF, with a progressive decompensation and congestion; in 14% of cases, AHF was caused by an infective disease (e.g. pneumonia, urinary tract infection) and in 25% AHF was due to non-adherence to therapy. The average hospitalization period was 8±3 days, with almost the entire cohort presenting with an "acute on chronic HF" phenotype (90%). During hospitalization, almost all patients received intravenous loop diuretics (85% treated initially with a maximal diuretics stimulus with intravenous continuous infusion), 5.9 % (N=5) subjects were treated with inotropic agent, while one subject required renal ultrafiltration.

Echocardiographic, Laboratory and Congestion Analysis (**Table 2**)— The average systolic blood pressure at baseline was 139 ± 24 mmHg, which significantly increased at pre-discharge (149 ± 35 mmHg; p=0.05). At hospital admission patients exhibited moderate LV dilation with an average LVEF of 40±16% and a moderate reduction in GLS. Despite symptoms' relief, decongestion therapy did not promote significant changes in E/e', SVi, and CI at discharge Conversely, significant improvements were observed in measures of RV function, RV coupling with pulmonary circulation and pulmonary hypertension, along with a significant decrease of NT-proBNP values. **Table 3** reports the admission to discharge LA dimensions and functional changes. Interestingly enough, no significant differences were observed in LAVi, LAS, LA pump strain and LAS/LAVi.

When evaluated with Pearson coefficient analysis, LA reservoir function directly correlated with LV longitudinal systolic function, showing that a worse GLS was associated with reduced LAS and both LV and LA mechanics did not respond to acute decongestion. Similarly, higher NT-proBNP values correlated with a lower LAS (**Figure 3** *Supplement*).

Patients characteristics according to LVEF subdivision— **Table 1** *supplement* summarizes patients characteristics based on LVEF distribution. Male gender was predominant n HFrEF with this group of patients significantly younger than HFpEF and HFmrEF. Irrespective of LVEF, patients exhibited a comparable degree of congestion, as documented by increased IVC max. diameter, incremented PASP and a rising number of B-lines on LUS. HFrEF presented with the highest levels of NT-proBNP values.

HFrEF patients presented also with higher LA dimensions and LAS impairment (lowest LAS/LAVi ratio) while HFmrEF patients showed the more favorable LA function to dimensional coupling compared to HFrEF and HFpEF (LAVi: HFpEF 50.7±16 ml/m^2 vs HFrEF 53.9±15 ml/m^2 vs HFmrEF 42.8±10.8 ml/m^2, p=0.05; LAS: HFpEF 17±9.1% vs HFrEF 10±4.85% vs HFmrEF 18.3±6.2%, p<0.001).

Characteristics of sinus rhythm (SR) patients— 66% of the patients enrolled were in sinus rhythm (SR); of these, 89% (n=50) had mild or trivial MR. The group free of significant MR exhibited some degree correlation between markers of pulmonary congestion with LAS, and LA pump strain at pre-discharge which persisted at 12 months follow-up. Table 2 reports the admission to discharge laboratory, hemodynamic and congestion data. GLS, the whole LA dimensional and functional variables, PASP, TAPSE/PASP, NT-pro-BNP and indexes of congestion significantly improved.

Hemodynamic, laboratory and congestion data analysis at 6- and 12- months follow-up (**Table 4**)— Of the initial cohort, 77 pts were re-evaluated at 6 and 12- months FU. LA dimensional and functional data at 12 months maintained a significant improvement compared to admission. A significant improvement in LVEF, GLS and E/e' was also observed at 12 months follow-up. The same pattern of improvement was observed for TAPSE, PASP, TAPSE/PASP and estimated RAP. No differences in serum creatinine and Hb were observed and a trend of increase in NT-pro-BNP levels was observed from 6 moths follow-up to 12 months. The indexes of congestion analysis showed a sustained improvement at either 6- and 12 months of observation.

Patients were then stratified into two groups according to the presence or the absence of a significant increment of LAS at 12 months (ΔLAS>5% increment was considered significant according to the ROC curve performance.

Outcome Analysis—At 1-year follow-up the primary endpoint occurred in 24 patients (28.2%), with 16 patients (16.5%) re-hospitalized for AHF; 7 deaths for CV reason (8.2%), 1 patient undergoing mitral valve replacement for severe chronic MR. Briefly, patients that developed CV events (Event +), despite exhibiting similar demographic and physical characteristics, showed higher levels of NT-proBNP values, a more dilated LA, a more deteriorated LA function and a higher rate of moderate to severe MR (**Table 3** *supplement*). Conversely, in patients that did not experience any MACE at 12-months FU (Event -),

smaller LAVi, higher LAS, LAS/LAVI and LA Stiffness index were found, along with significantly higher LVEF, GLS, SVi and CI and lower PASP and TAPSE/PASP ratio (**Figure 2**).

Figure 3 depicts a typical case of Event – (A) versus Event+ (B) subject according to the CSI score, NT-pro-BNP levels, B-lines and LAS analysis at admission, discharge, and 12 months follow-up.

Univariate and multivariate analysis are shown in **Table 5**. At multivariate analysis ΔLAS emerged as the most powerful predictors of MACE followed by NT-pro-BNP (**Table 5**). When evaluating Kaplan-Meier Curve of event-free survival, patients with a LAS >16%, a LAS/LAVi ratio >0.25 %/ml/m^2 and ΔLAS>5% exhibited a significantly higher survival free from MACE compared to subjects discharged with a LAS≤16%, LAS/LAVi≤0.25 %/ml/m^2 and ΔLAS≤5% (log-rank: HR 3.5 CI 95% 1.8-7.3; p=0.004; log-rank: HR 3.27 CI 95% 1.4-7.7; p=0.007 log-rank: HR 3.6 CI 95% 2-7.9, p<0.01) **Figure 4a, Figure 4b** and **4c**.

Discussion

The LAS-HF is the first prospective trial designed to address the long-term clinical trajectory of changes in LA dynamics in patients admitted for AHF. Trial findings point on a strong predictive value of LA mechanics assessed by STE approach in the acute settings which implements the phenotyping process of individual at higher risk for adverse cardiac related outcome. Specifically, the main study messages are: a) the in-hospital assessment of LA dynamics does not improve from admission to discharge; b) similar results are found for GLS, which strongly correlates with LAS; c) improvements in LAS over time fits with a better clinical evolution, free from congestion and rehospitalization during the follow-up period; d) subjects in SR and without hemodynamically significant mitral regurgitation are more prone to reverse LA functional performance.

LA Dynamics Insights in AHF—The pathophysiological contribution and prognostic impact of LA mechanics and its size are quite well characterized in chronic stable HF [2] but less is known in AHF. Two studies have so far approached the implications of LA dysfunction in the acute HF setting under its different hemodynamic presentations. In a previous study, Deferm et al.[4] studied the pattern of LA mechanics in 31 HFrEF patients with a combined invasive and echo STE-derived analysis. Enrolment criteria included a severe impairment in LV filling (diastolic restrictive pattern) and increased pulmonary pressure (PASP > 40 mmHg) and all patients presented with severe AHF and a "cold and

wet" phenotype. Decongestion induced an in-hospital LAS and LA pump strain with an increase in LAS correlating with a decrease in pulmonary capillary wedge pressure (PCWP) at 6 weeks of follow-up. A poor LAS response to decongestion therapy was associated with worse outcome. Conversely our findings were obtained in a larger cohort with longer follow-up and documented no improvement in either LAS and LA pump strain during the in-hospital decongestion phase, while some extent of improvement at 6 and 12 months for approximately half of patients. Our findings are basically strengthened by a comprehensive echo-derived study of geometrical and intrinsic physical properties of the LA chamber.

A second study by Park JH et al.[5] reports a retrospective analysis of the 3983 AHF patients enrolled in the TRATS-HF (STrain for Risk Assessment and Therapeutic Strategies in patients with Acute Heart Failure) registry documented a cardiovascular-event predictive role of LAS except for patients with atrial fibrillation. Present observations align also with the TRATS-AHF trial and extend on the prognostic definition of LAS analysis by identifying a LAS > 16% as specific prognostic cut-off. As anticipated, the group of patients presenting with SR with mild or trivial MR exhibited an average improvement in LA function and geometry over time suggesting that SR is a key background for successful reversibility.

Overall, this is the first long-term longitudinal analysis comparing LA functional data with established parameters of congestion, biomarkers and left and right heart hemodynamic indicators of clinical evolution and prognosis and thus, it offers the first clinical evidence that AHF phenotyping through the study of LA mechanics in HF results to be prognostic and eases the identification of higher risk patients.

The Interaction Between LA Mechanics and Congestion—The study of LA function is intense, having a central role in the pathophysiology and clinical evolution of patients with HF. Indeed, especially in AHF, the definition of the active role of the LA in impacting congestion state and response to targeted therapy is crucial and represents a central information in our study findings, where we performed both a baseline evaluation and a continuous monitoring over time of LA mechanics and congestion index. Interestingly, from admission to discharge, no recovery of LA function and geometry was observed, despite significant decongestion, i.e. resolution of B-lines, CSI, IVC dimensions and NT-pro-

BNP levels reduction and improvement in right heart function and RV to pulmonary circulation coupling.

Specifically, our findings suggest that acute decongestion may be well effective in unloading the pulmonary circulation and in modulating NT-pro-BNP levels, but does not impact on LV GLS and LAS. This surprising and challenging finding calls into question the reasons for this discrepancy. Intriguingly, the lack of improvement in LAS from admission to discharge can be explained by a lack of full resolution of subclinical tissue edema affecting LA load. Also, a reversal biological effect on atrial myocyte and fibrosis with targeted pharmacological therapy may require longer time considering also the role of main hemodynamic and ethiological factors at wors on the already preexistent atrial chamber dysfunction. Accordingly, a different behaviour was found when analysing only patients in SR and excluding those with hemodynamically significant MR. SR patients exhibited a stronger correlation between decongestion and improvement of LA mechanics (both reservoir and pump function), which was more evident at long-term follow-up.

Over time, both LA and LV hemodynamic significantly improved along with a further modulation in the right heart hemodynamic and the strongest determinant of prognosis emerged to be the LAS increase at 12 months follow-up. These findings suggest considering LAS and GLS as active target of therapeutic goals during the early in-hospital treatment phases, aiming at promoting LA reverse remodelling rather than a simple unloading effect.

LV Mechanics as a determinant of LAS— In HF, GLS is a sensitive index of LV pump failure with a pivotal prognostic value.[14] GLS is tightly linked to LA reservoir function,[15] and is primarily involved in determining the LA mechanics. Indeed, recent evidence by Mălăescu et al.[16] demonstrated a strong relationship between GLS and LA and LV volumes, showing how both LAS and GLS may be modulated by pathology that interferes with the blood volume sharing between the two cavities. This interaction and their relationship with LV and LA volumes are confirmed by our data. Patients in SR with reduced LA sizes and mild or trivial MR presented with the highest LAS and GLS values, that improved significantly after targeted decongestion therapy. The discrepancy between decongestion and LV and LA dynamics evaluated by strain analysis in hemodynamically significant MR and increased LV and LA dimensions, points on the importance to monitor these functional indicators together to definitively improve risk stratification and reduce early re-hospitalization. This has direct implications in

addressing the role of recent pharmacological therapies, especially sGLT2 inhibitors and ARNI, in reversing atrial remodelling and dysfunction.

Study Limitations—This is a single centre trial performed in a relatively limited number of patients. Nonetheless, information on congestion and hemodynamic were quite comprehensive. Some discrepancy detected between levels of NT-pro-BNP and LAS average values which may be explained by the fact that NT-pro-BNP clearance is highly dependent on renal clearance and its kinetics may dissociate from LA dynamics.

The analysis of LA mechanics by STE may be hampered in the acute destabilization of HF due to the difficult image quality to precisely track the thin wall of the LA. Even though the main outcomes are statistically significant, the data distribution is quite wide, which may question reproducibility of data pointing on larger confirmatory observations.

Our numbers do not allow to dissect the influence of MR on LA function and viceversa.

Conclusions— In AHF, irrespective of the underlying LVEF, a thorough analysis of LA dynamics through STE and especially LAS analysis is predictive of early re-hospitalization and Cv outcome over time and would allow to identify specific phenotypes at risk. In this setting, the functional LA pattern overcomes the outcome prediction ability of well-established right heart indicators of hemodynamic instability and associated risk.

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Legend for Figures

Figure 1. LAS-AHF Study Design. After 24 hours enrolment period, data collection was performed at hospital discharge 6- and 12- months follow-up with a phone call interview at 3 months. Event collection was performed at 12 months.

Figure 2. Box and Whisker plots of Event + versus Event- patients. Event + exhibited more enlarged and dysfunctional LA at pre-discharge, along with worse LV systolic functional dynamics.

Figure 3. Representative cases of Event – (A) versus Event+ (B) subjects according to the CSI score, NT-pro-BNP levels, B-lines and La-strain analysis at admission, discharge and 12 months follow-up.

Figure 4. Kaplan-Meier Curve of event-free survival according to LAS (A), LAS/LAVi ratio (B) at discharge (B) and increment of LAS at 12-months follow-up (C). Patients discharged with a LA-strain >16% and a LAS/LAVi ratio >0.25 %/ml/m^2 exhibited a significantly higher survival free from MACE compared to subjects discharged with a LAS≤16% and LAS/LAVi≤0.25 %/ml/m^2 (A: log-rank: HR 3.5 CI 95% 1.8-7.3; p=0.005; B: log-rank: HR 3.27 CI 95% 1.4-7.7; p=0.007). Panel C shows that patients that increased LAS after 12 months >5% exhibited a significantly greater free from MACE survival when compared with patients that did not improve LAS at follow-up (log-rank: HR 3.6 CI 95% 2-7.9, p<0.01).

Table 1. Baseline Characteristics and Therapy Distribution

Age, years	78 [68.5-84]
Male gender, %	59
Body mass index, kg/m^2	28.2 ± 6.6
Systolic BP, mmHg	139 ± 24
Heart rate, beats/min	69 ± 12
Sinus rhythm, %	66
Atrial Fibrillation, %	34
Permanent AF	30
Paroxysmal AF	2.5
Persistent AF	1.5
Cardiovascular Risk Factors, %	
Hypertension	86
Diabetes mellitus	42
Dyslipidemia	62
Current or ex-smoker	47
Obesity	39
Etiology and type of AHF, %	
Idiopathic,%	40
Ischemic, %	60
De novo, %	10
On CHF, %	90
Therapy, %	
Loop diuretics	92
β blockers	88
Aldosterone antagonists	67
ACE inhibitors or ARBs	66
ARNIs	12
CRT-D	9
LVAD	0

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; ARNIs = Angiotensin Receptor Neprilysin Inhibitors; CRT-D = Cardiac Resynchronization Therapy; LVAD = Left Ventricular Assist Device;

Table 2. Hemodynamic, Laboratory and Congestion Data at Admission and Discharge

	Admission	Discharge	*P* Value	CI 95%
SBP, mmHg	139 ± 24	149 ± 35	0.05*	3.3 to 16
LV Analysis				
LV EDVi, ml/m^2	77.3±31	77±30.7	0.95	-9.9 to 9.7
LV ESVi, ml/m^2	49.9±27.9	49.6±27.7	0.9	-9.7 to 7.6
LVEF, %	39 ±16	41.0±15	0.65	-3.4 to 5.7
GLS, %	-12.2±4.3	-11.95±4.15	0.4	-1.7 to 0.7
E/E',	17.16±6.6	16.05±6.7	0.29	-3.1 to 0.85
SVi, ml/m^2	27.3±9.3	28.3±9.6	0.5	-1.6 to 4.1
CI, l/min/m^2	2.1±0.8	2±0.8	0.38	-0.33 to 0.1
Moderate to severe MR, %	24	/	/	
Secondary MR, %	80	/	/	
Primary MR, %	20	/	/	
RV Analysis				
TAPSE, mm	16.5±3.95	17.5±3.97	0.08	-0.2 to 2.2
PASP, mmHg	39.6±12	31.6±10.7	<0.001*	-11 to -3.9
TAPSE/PASP, mm/mmHg	0.44±0.18	0.61±0.22	<0.001*	0.1 to 2.1
RAP, mmHg	9.01±5	7.2±4.1	0.01*	-3 to -0.3
Laboratory Variables				
Serum creatinine, mg/dl	1.39±1	1.55±1.1	0.46	-0,19 to 0,44
Hemoglobin, g/dl	12.3±1.96	12.36±2.03	0.84	-0.5 to 0.67
NT-pro-BNP, ng/l	8453±925	4111±645	<0.001*	-6875 to -2056
Congestion Analysis				
B-lines, N	22.2±17	6.5±5.0	<0.001	-19 to -11
IVC, mm	18.94±6.3	16.65±5.6	0.013*	-4 to -0.28
CSI	2.3±1.0	0.9±0.5	<0.001	-1.9 to -0.3

Values are mean ± SD. NT-proBNP = N-Terminal Brain Natriuretic Peptide; LVEF = Left Ventricular Ejection Fraction; GLS = Global Longitudinal Strain; DD = Diastolic Dysfunction; SVi = Stroke Volume indexed; CI = Cardiac Index; LV EDVi = Left Ventricular End-Diastolic Volume indexed; LV ESVi = Left Ventricular End-Systolic Volume indexed; TAPSE=Tricuspid Annular Plane Systolic Excursion; PASP= Pulmonary Arterial Systolic Pressure; IVC = Inferior Vena Cava – maximum diameter; RAP = Right Atrial Pressure; CSI= Congestion Score Index;
(*) p statistically significant

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Table 3. Echocardiographic Evaluation of Left Atrial Changes Admission to Discharge

	Admission	Discharge	*p* Value	95% CI
LAVi, ml/m^2	50.7±16	47±16	0.14	-8.5 to 1.2
LAS, %				
Apical 2- and 4- chamber views	13.9±7.6	14.6±8.5	0.56	-1.7 to 2.9
Apical 2- chamber view	13.3±7.7	14.1±8.6	0.55	-1.7 to 3.3
Apical 4- chamber view	14.1±8.4	14.5±8.5	0.79	-2.5 to 2.8
LA pump strain, per s				
Apical 2- and 4- chamber views	-1.53±0.68	-1.69±0.79	0.32	-0.2 to 0.45
Apical 2- chamber view	-1.57±0.82	-1.78±0.82	0.27	-1.18 to 0.6
Apical 4- chamber view	-1.46±0.67	-1.59±0.82	0.44	-0.2 to 0.4
LAS/LAVi, %/ml/m^2	0.35±0.31	0.39±0.34	0.44	-0.05 to 0.1

Values are mean ± SD. LAVi = Left Atrial Volume indexed; LAS = Left Atrial Strain; (*) p statistically significant

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Table 4. Hemodynamic, Echocardiographic and Laboratory Data at 6- and 12-Months Follow-up

	Admission (n=85)	FU 6 months (n=77)	FU 12 months (n=77)	*P* Value	CI 95%
LA analysis					
LAVi, ml/m^2	50.7±16	42.6±13.9	44.4±20.6	0.04*	-12.2 to -1.7
LAS, % Apical 2- and 4-chamber views	13.9±7.6	18±10	21.4±7.7	<0.001*	1.2 to 6.9
LA-sr, per s Apical 2- and 4- chamber views	-1.53±0.70	-1.87±1.3	-1.92±0.5	0.048*	-1 to -0.18
LAS/LAVi, ml/m^2	0.35±0.31	0.5±0.38	0.56±0.33	0.046*	-0.93 to -0.12
LA Stiffness index	1.63±1	1.52±1.16	1.2±0.55	0.05*	-0.9 to -0.12
LV analysis					
LVEF, %	39±16.0	46.4±14.1	46±15.3	0.018*	1.9 to 11.8
GLS, %	-12.2±4.3	-14.2±4.6	-16±5.2	0.01*	0.3 to 3.2
E/E',	17.16 ±6.6	14.4±5.6	13±4.8	0.011*	-4.7 to -0.2
SVi, ml/m^2	27±9.3	27.6±10	28.6±11.3	0.6	-1.1 to 4.8
CI, l/min/m^2	2.1±0.8	2±0.8	2.1±0.6	0.7	-0.37 to 0.16
RV analysis					
TAPSE, mm	16.5±3.95	18.5±4.1	18.6±5.2	0.009*	0.67 to 3.3
PASP, mmHg	39.6±12	35.8±12.45	31.7±9.3	0.08	-8 to 0.16
TAPSE/PASP, mm/mmHg	0.44±0.18	0.59±0.27	0.62±0.21	<0.001*	0.07 to 0.2
RAP, mmHg	9.01±5	7.2±4.3	6.3±4	0.03*	-3.5 to -0.09
Laboratory variables					
Serum creatinine, mg/dl	1.39±1	1.32±0.46	1.26±0.48	0.83	-0.2 to 0.4
Hemoglobin, g/dl	12.3±2	12.55±1.94	12.8±1.5	0.8	-0.8 to 0.6
NT-pro-BNP, ng/l	8453±925	2745±441	3310±531	<0.001*	-8494 to -2964
Congestion analysis					
B-lines, N	22.2±17	7.0±5.0	6.9±4.8	<0.001*	-20 to -8
IVC, mm	18.94±6.3	17±6.5	13.5±5.5	0.04*	-5 to -0.38
CSI, N	2.3±1.0	0.7±0.4	0.6±0.5	<0.001*	-1.8 to -0.16

Comparisons were made between values at admission and values at 12-months follow-up. Values are mean ± SD.
LAVi = Left Atrial Volume indexed; LAS = Left Atrial Strain; LA-sr = Left Atrial strain rate; NT-proBNP = N-Terminal Brain Natriuretic Peptide; LVEF = Left Ventricular Ejection Fraction; GLS = Global Longitudinal Strain; SVi = Stroke Volume indexed; CI = Cardiac Index; LV EDVi = Left Ventricular End-Diastolic Volume indexed; LV ESVi = Left Ventricular End-Systolic Volume indexed; TAPSE=Tricuspid Annular Plane Systolic Excursion; PASP= Pulmonary Arterial Systolic Pressure; IVC = Inferior Vena Cava – maximum diameter; RAP = Right Atrial Pressure; CSI= Congestion Score Index;
(*) p statistically significant

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Table 5. Univariate and Multivariate Analysis

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	**P value**	**Hazard Ratio (95% CI)**	***P* Value**
LV Analysis				
NT-proBNP, ng/l	1.3 (1-1.4)	<0.01*	1.3 (1-1.5)	0.01*
LAVi, ml/m^2	1.2 (1-1.4)	<0.01*	1.2 (1-1.3)	0.03*
LAS, % Apical 2- and 4- chamber views	0.85 (0.8-0.95)	<0.01*	//	//
ΔLAS,	0.8 (0.76-0.94)	<0.01*	0.80 (0.76-0.97)	<0.01*
GLS, %	0.87 (0.8-0.95)	<0.01*	0.88 (0.83-0.98)	0.05*

NT-proBNP = N-Terminal Brain Natriuretic Peptide; LAVi = Left Atrial Volume indexed; LAS = Left Atrial Strain; GLS = Global Longitudinal Strain;
(*) p statistically significant

Target of the analysis: prediction of MACE (re-hospitalization for AHF and death from CV causes)

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Figure 1

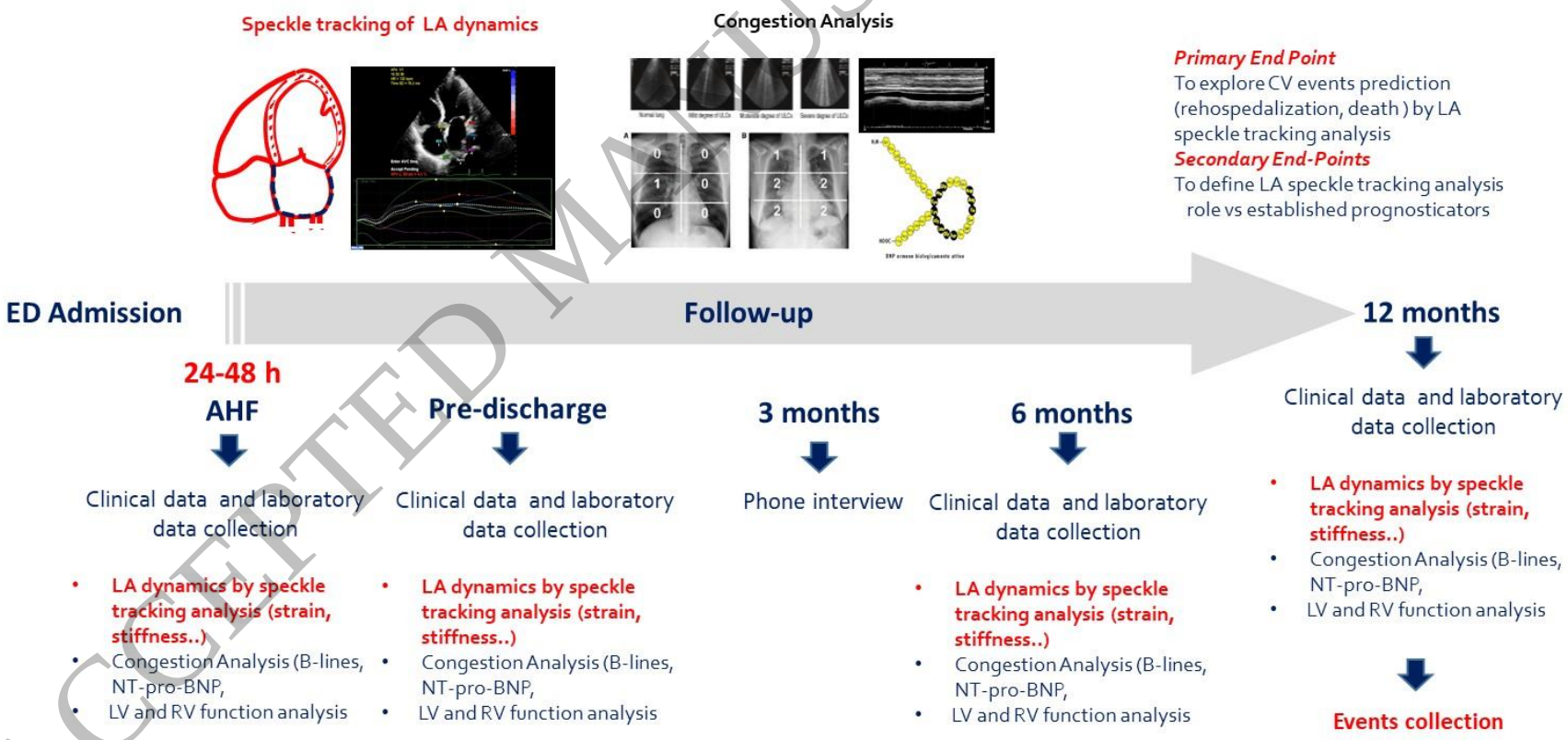

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Figure 2

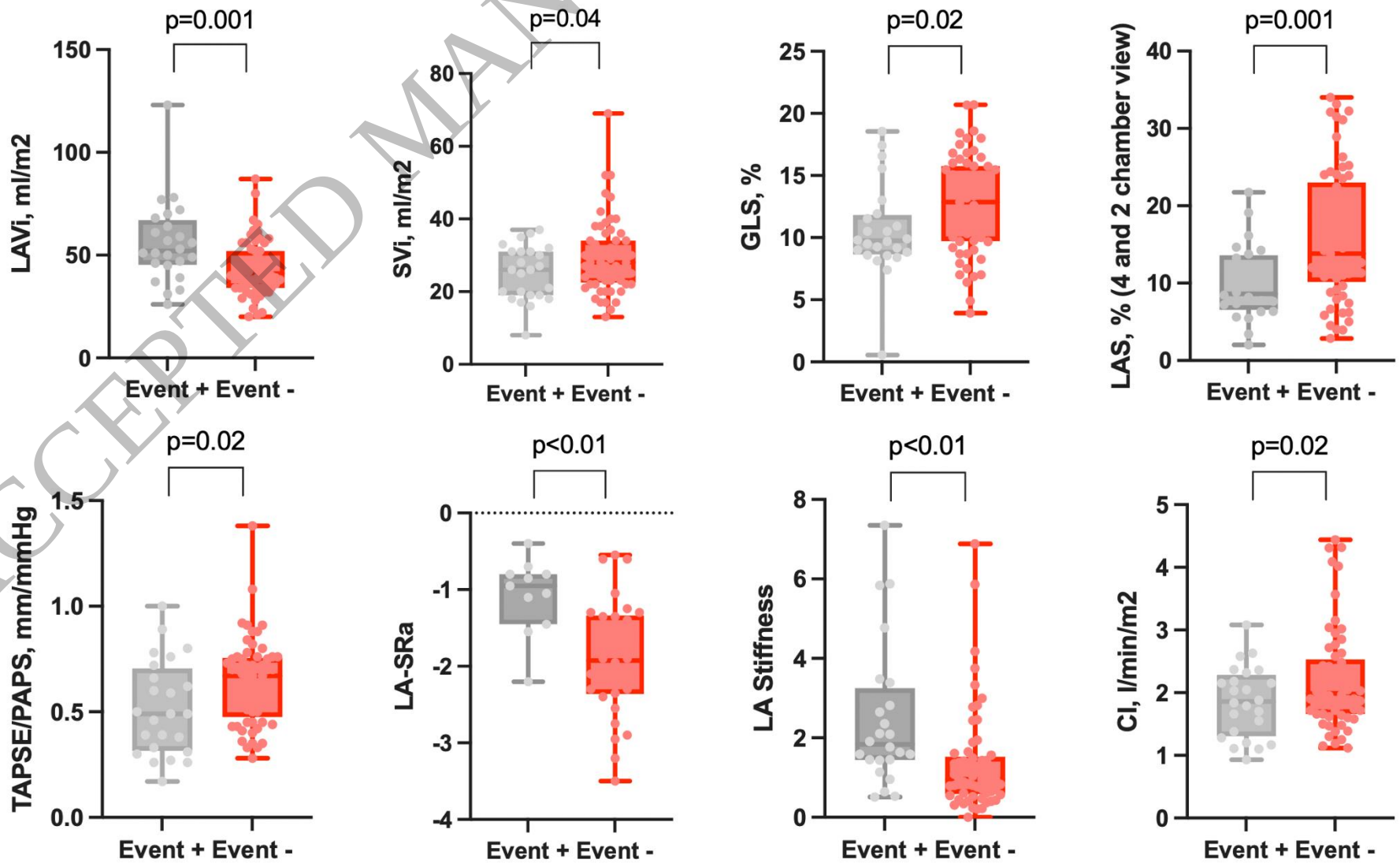


Figure 3

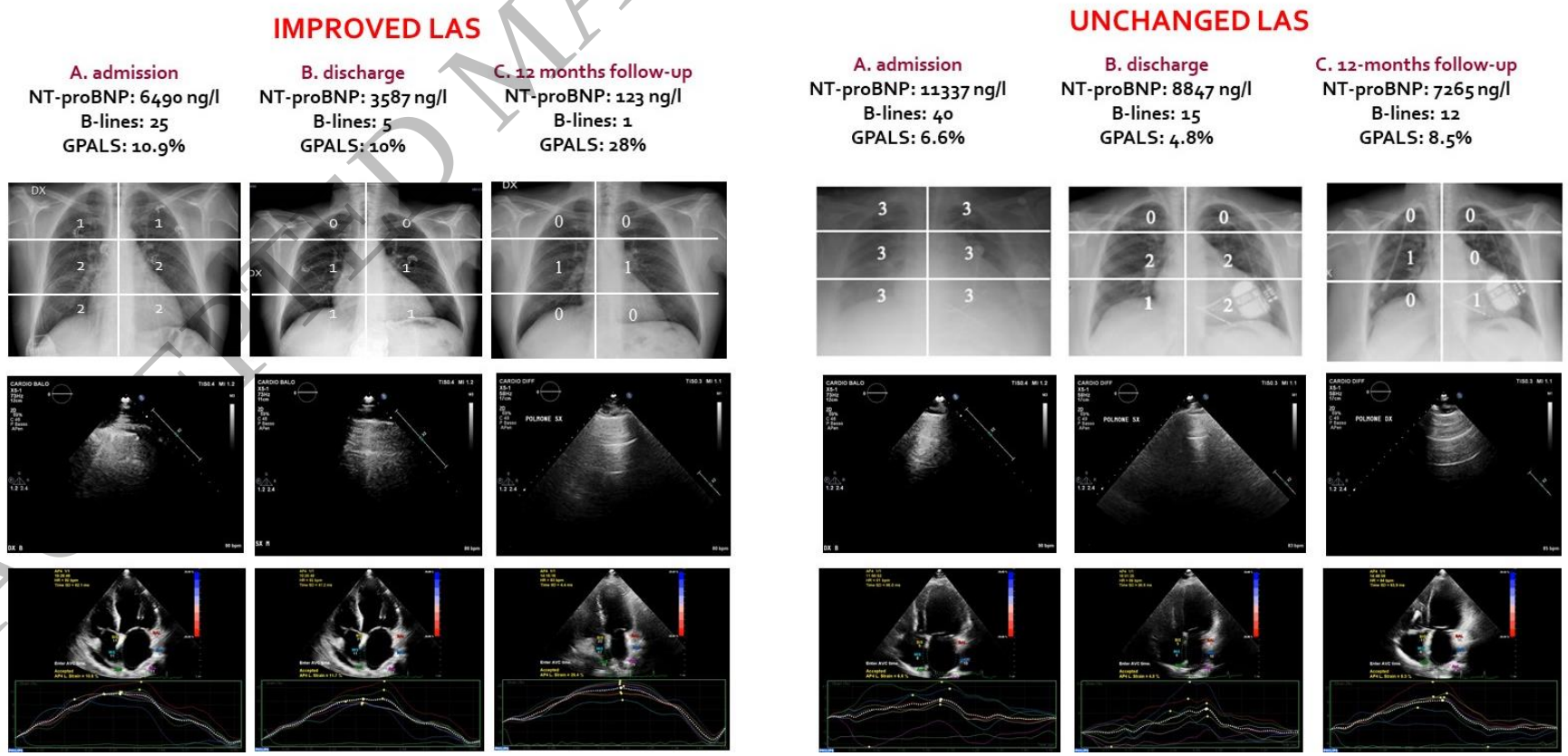
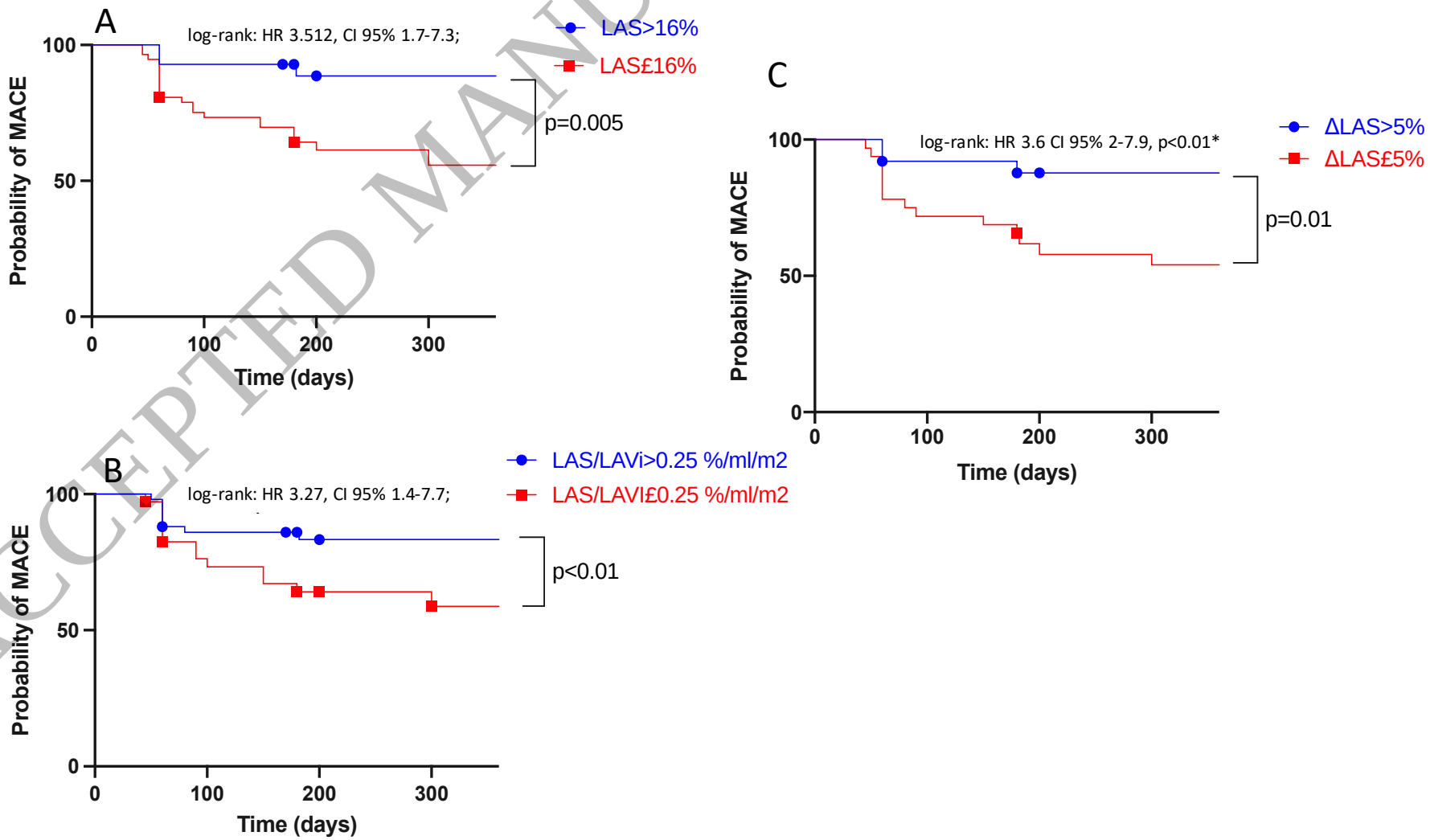
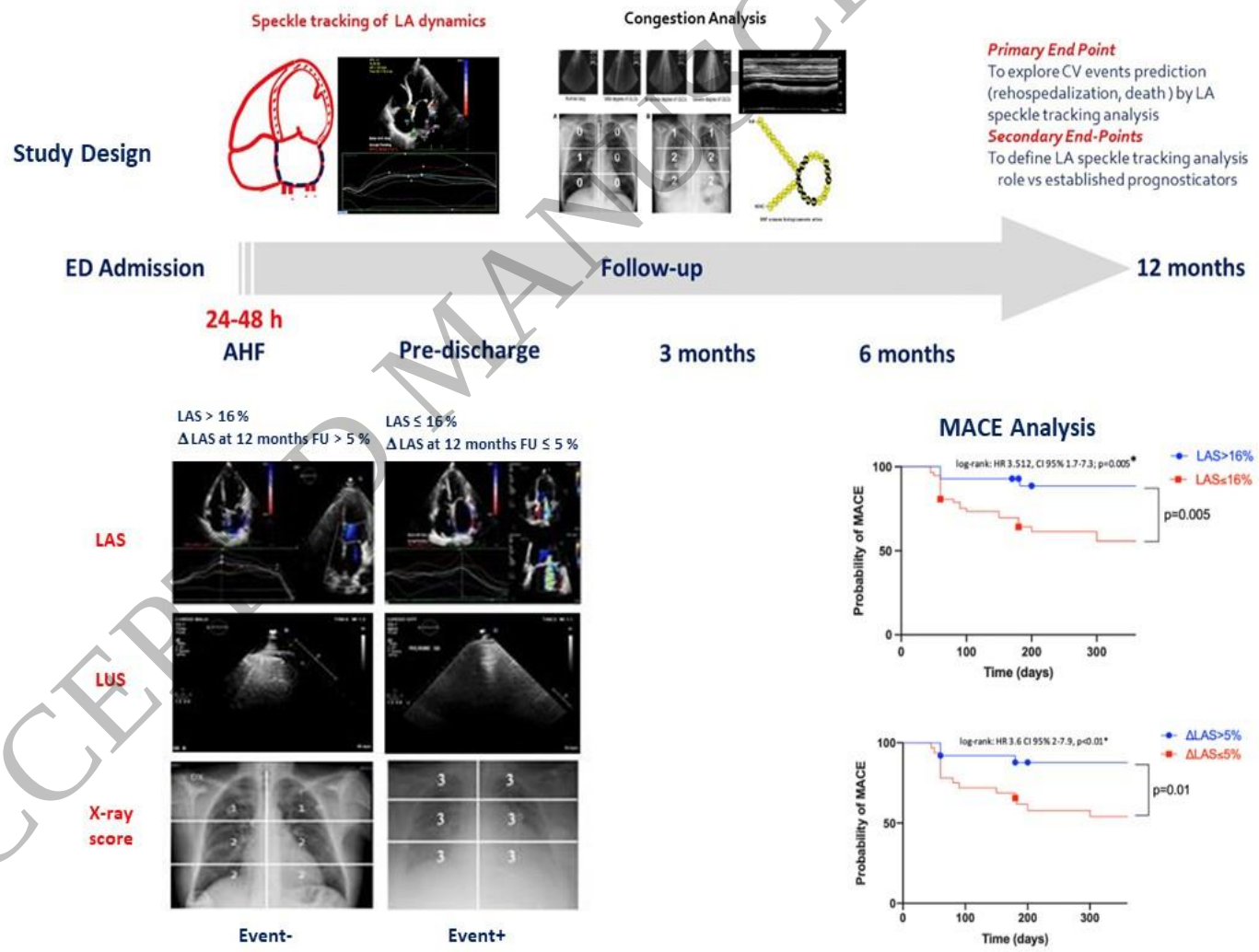


Figure 4





Graphical Abstract
170x96 mm (x DPI)