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# ST2 and left ventricular remodeling after ST-segment elevation myocardial infarction: A cardiac magnetic resonance study☆

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ABSTRACT

*Background:* The association of soluble interleukin-1 receptor-like 1 (ST2) with left ventricular (LV) remodeling is unclear in patients with a first ST-segment elevation myocardial infarction (STEMI). The objective of this work was to assess the relationship between ST2, a marker of inflammation, and cardiac magnetic resonance (CMR) imaging-derived LV remodeling after a first STEMI.

*Methods:* We prospectively evaluated 109 patients with a first STEMI treated with primary percutaneous coronary intervention who had ST2 assessed 24 h post-reperfusion. All patients underwent CMR imaging 1 week and 6 months after STEMI. The independent associations between ST2, LV diastolic and systolic volume indices, and LV ejection fraction (LVEF) were evaluated by linear mixed models.

*Results:* The mean age of the sample was 59 ± 12 years, 85 patients (78%) were male, and 13 (11.9%) had a LVEF ≤40%. The median (IQR) of ST2 was 55.3 (38.7–94.1) pg/mL. At 1-week CMR higher ST2 was related to more infarct size and less myocardial salvage index ($p < 0.01$). Overall, after comprehensive multivariable adjustment, higher baseline ST2 was associated with progressive LV volume indices dilation and LVEF deterioration ($p < 0.05$). This effect was stronger in patients with severe 1-week structural damage, namely those with large infarct size, extensive microvascular obstruction or LVEF ≤40%.

*Conclusions:* In patients with a first STEMI treated with primary percutaneous coronary intervention, soluble ST2 predicts dynamic changes in CMR-derived LV volumes and LVEF. Future studies must assess whether targeting interleukin-1 leads to lower ST2 levels and less LV remodeling.



## 1. Introduction

Left ventricular (LV) remodeling after ST-segment elevation myocardial infarction (STEMI) is related with an increased risk of adverse events [1–3]. Cardiac magnetic resonance (CMR) constitutes the state-of-the-art noninvasive imaging technique for its assessment and prediction [4–6]. In fact, CMR-derived infarct size and the extent of microvascular obstruction (MVO) at 1 week have emerged as the most important determinants of LV remodeling in patients with a first STEMI undergoing primary percutaneous coronary intervention [4].

Soluble interleukin-1 receptor-like 1 (also known as ST2) has a prominent role in cardiovascular disease as a marker of inflammation, tissue fibrosis, matrix remodeling, and myocyte strain [7–15]. There is consistently a robust association between ST2 and adverse events in

*Abbreviations:* CMR, cardiac magnetic resonance; hsTnT, high-sensitivity troponin T; LVEDVI, left ventricle end-diastolic volume index; LVEF, left ventricle ejection fraction; LVESVI, left ventricle end-systolic volume index; MSI, myocardial salvage index; MVO, microvascular obstruction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; STEMI, ST-segment elevation myocardial infarction; ST2, also known as interleukin 1 receptor like 1 (IL1RL1).

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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patients with heart failure, and it has been proposed as the new gold standard biomarker for heart failure prognostication [16]. However, its role is less clear in the setting of acute myocardial infarction. Pre-clinical experimental studies reported post-infarct ST2 up-regulation and suggested that it was related with an increased risk of adverse LV remodeling [17, 18]. At the clinical level, ST2 was examined in a post hoc analysis of the EPHESUS trial [11]. However, the value of ST2 in patients with a first STEMI treated with primary percutaneous coronary intervention is unknown.

The aim of this work was to assess the relationship between soluble ST2 determined 24 h after primary percutaneous coronary intervention and LV remodeling within the first six months after a first STEMI as derived from CMR.

## 2. Material and methods

### 2.1. Study population

This is a prospective observational study carried out from June 2009 to December 2010 that included 203 consecutive patients with a first STEMI [4, 19]. Eligibility criteria were: patients admitted for a first STEMI, defined according to current definitions [20], who were treated with primary percutaneous coronary intervention and underwent CMR imaging 1 week and 6 months after STEMI. Prior myocardial infarction was ruled-out based on the absence of suggestive electrocardiographic abnormalities and a previous history of admissions for cardiovascular events. A total of 94 patients were excluded from this study due to: in-hospital complications (n = 33) (death, reinfarction, and clinical instability), claustrophobia (n = 12), contraindications to CMR imaging (n = 14), incomplete CMR imaging studies (n = 20), insufficient image quality from CMR (n = 12), and refusal to participate (n = 3). The final sample included 109 patients. The baseline characteristics of the final sample and excluded patients are shown in Supplementary File 1. There were no differences between both groups except for a higher Grace score and diuretic use in patients excluded (Supplementary File 1).

The clinical, demographic, hemodynamic, angiographic, and electrocardiographic findings were prospectively registered in all cases upon admission. A specific STEMI unit managed patients during hospitalization and after discharge, and current recommendations were strictly followed [21, 22]. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

### 2.2. Biomarker assays

Routine blood tests were assessed on admission, including hemoglobin, white cell count, creatinine, and amino-terminal pro-brain natriuretic peptide (NT-proBNP) (Roche Diagnostics, Switzerland). High-sensitivity troponin T (hsTnT) (Elecsys hs-cTnT assay, Roche Diagnostics, Basel, Switzerland; myocardial infarction diagnosis cutoff >14 ng/mL) was measured on admission, at 3 h, and at 6- to 8-hour intervals for the first 24 h.

In order to select the best time to determine ST2 in these patients, their values were analyzed in 8 patients in 4 moments: previous to percutaneous coronary intervention, at 24 h, 96 h and 1 month. According with a previous study from Shimpo et al. [23], the highest values of ST2 were those corresponding to the determination at 24 h. ST2 was measured from stored frozen serum samples obtained 24 h after reperfusion using a high-sensitivity monoclonal sandwich immunoassay (Critical Diagnostic Presage ST2 assay). The antibodies used in the Presage assay were generated from a recombinant protein based on the human cDNA clone for the complete soluble sequence [24]. This platform offers improved accuracy in quantifying soluble ST2 levels, particularly at lower concentrations. The calibration and standardization of this assay were performed according to the manufacturer's protocol. Previous reports found intra- and inter-assay coefficients of variation of <2.5% and <4.0%, respectively [24]. Frozen serum samples of those patients who were finally excluded were not analyzed.

### 2.3. CMR imaging

Detailed information about CMR technique is described in Supplementary File 2. LVEF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), and LV mass were calculated using manual planimetry of endocardial and epicardial borders on short-axis cine images.

Initially, late gadolinium enhancement was regarded as signal intensity at least 5 standard deviations (SD) greater than that of a remote non-infarcted area in the same section. Subsequently, areas with late gadolinium enhancement were visually revised and quantified with manual planimetry. Infarct size was assessed as the percentage of LV mass with late gadolinium enhancement, and was considered extensive if >30% of LV mass [4]. The MVO was quantified with manual planimetry and defined as the percentage of LV mass with a lack of contrast material uptake in the core of tissues with late gadolinium enhancement [20, 25–27]. Extensive MVO was defined as >2.5% of the LV mass based on recent clinical validation [4].

Myocardial edema was regarded as areas of high signal intensity on T2-weighted images. A core of low signal intensity surrounded by an area with high signal intensity indicated myocardial hemorrhage (included in the area of myocardial edema). For all sections, only the T2-weighted sequence with the highest image quality was used to analyze edema and hemorrhage. All short axis sections were separately analyzed, and the presence of signal intensity at least 2 SD greater than that of a remote non-infarcted area in the same section indicated edema. Then, myocardial edema and myocardial hemorrhage were manually revised and expressed as the percentage of LV mass. The myocardial salvage index (MSI) was calculated by subtracting the mass of infarcted myocardium from myocardium showing edema and expressed as the percentage of LV mass with myocardial edema [26, 27].

Intra- and inter-observer variability for all CMR indices analyzed in the present study has been previously evaluated and reported by our group and is <5% [4].

### 2.4. Endpoints and follow-up

The primary endpoint was the relationship between ST2 measured at 24 h after primary percutaneous coronary intervention and the magnitude of dynamic changes in LVEDVI, LVESVI, and LVEF from 1-week to 6-month CMR.

The secondary end-points were the relationship between ST2 measured at 24 h after primary percutaneous coronary intervention across subgroups of surrogates of MI extension (LVEF >40% vs. ≤40%, extensive vs. non-extensive MVO, and extensive vs. non-extensive infarct size).

### 2.5. Statistical analysis

Continuous variables were expressed as the mean ± 1 SD or median (interquartile range [IQR]) when appropriate. Discrete variables were summarized as percentages. Baseline characteristics were compared among ST2 quartiles with ANOVA or the Kruskal–Wallis test for non-normally distributed variables. The association between soluble ST2 levels and changes in the 6-month LVEDVI, LVESVI, and LVEF were evaluated by linear mixed models. The same approach was used to evaluate the association between soluble ST2 levels and the state of LVEDVI, LVESVI, and LVEF at 6-month CMR. Multivariate logistic regression analysis was performed to assess the associations between ST2 and >10% decrease in LVESVI and >5% increase in LVEF. For the multivariate regression analyses, candidate covariates were chosen based on previous medical knowledge, independent of their p-value. Then, a

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