



Incidence and Significance of Spontaneous ST Segment Re-elevation After Reperfused Anterior Acute Myocardial Infarction – Relationship With Infarct Size, Adverse Remodeling, and Events at 1 Year–

Léo Cuenin, Sophie Lamoureux, Mathieu Schaaf, Thomas Bochaton, Pierre Monassier, Marc Claeys, Gilles Rioufol, Gérard Finet, David Garcia-Dorado, Denis Angoulvant, et al.

► To cite this version:

Léo Cuenin, Sophie Lamoureux, Mathieu Schaaf, Thomas Bochaton, Pierre Monassier, et al.. Incidence and Significance of Spontaneous ST Segment Re-elevation After Reperfused Anterior Acute Myocardial Infarction – Relationship With Infarct Size, Adverse Remodeling, and Events at 1 Year–. Circulation Journal, 2017, 82 (5), pp.1379-1386. 10.1253/circj.CJ-17-0671 . hal-01654821

HAL Id: hal-01654821

<https://hal.science/hal-01654821>

Submitted on 14 Mar 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Incidence and Significance of Spontaneous ST Segment Re-elevation After Reperfused Anterior Acute Myocardial Infarction

— Relationship With Infarct Size, Adverse Remodeling, and Events at 1 Year —

Léo Cuenin, MD; Sophie Lamoureux, MD; Mathieu Schaaf, MD; Thomas Bochaton, MD; Jean-Pierre Monassier, MD; Marc J. Claeys, MD; Gilles Rioufol, MD, PhD; Gérard Finet, MD, PhD; David Garcia-Dorado, MD, PhD; Denis Angoulvant, MD, PhD; Meyer Elbaz, MD, PhD; Nicolas Delarche, MD; Pierre Coste, MD, PhD; Marc Metge, MD; Thibault Perret, MD; Pascal Motreff, MD, PhD; Eric Bonnefoy-Cudraz, MD, PhD; Gérald Vanzetto, MD, PhD; Olivier Morel, MD, PhD; Inesse Boussaha; Michel Ovize, MD, PhD; Nathan Mewton, MD, PhD

Background: Up to 25% of patients with ST elevation myocardial infarction (STEMI) have ST segment re-elevation after initial regression post-reperfusion and there are few data regarding its prognostic significance.

Methods and Results: A standard 12-lead electrocardiogram (ECG) was recorded in 662 patients with anterior STEMI referred for primary percutaneous coronary intervention (PPCI). ECGs were recorded 60–90 min after PPCI and at discharge. ST segment re-elevation was defined as a ≥ 0.1 -mV increase in ST_{Max} between the post-PPCI and discharge ECGs. Infarct size (assessed as creatine kinase [CK] peak), echocardiography at baseline and follow-up, and all-cause death and heart failure events at 1 year were assessed. In all, 128 patients (19%) had ST segment re-elevation. There was no difference between patients with and without re-elevation in infarct size (CK peak [mean \pm SD] $4,231 \pm 2,656$ vs. $3,993 \pm 2,819$ IU/L; $P=0.402$), left ventricular (LV) ejection fraction ($50.7 \pm 11.6\%$ vs. $52.2 \pm 10.8\%$; $P=0.186$), LV adverse remodeling ($20.1 \pm 38.9\%$ vs. $18.3 \pm 30.9\%$; $P=0.631$), or all-cause mortality and heart failure events ($22 [19.8\%]$ vs. $106 [19.2\%]$; $P=0.887$) at 1 year.

Conclusions: Among anterior STEMI patients treated by PPCI, ST segment re-elevation was present in 19% and was not associated with increased infarct size or major adverse events at 1 year.

Key Words: Reperfusion syndrome; ST segment elevation myocardial infarction; ST segment re-elevation; ST segment regression

The electrocardiogram (ECG) is the first-line diagnostic tool in ST elevation myocardial infarction (STEMI). The ECG is a simple and easily reproducible test, with a non-ambiguous diagnostic ability.

ST segment resolution is commonly used as a marker of successful reperfusion. It is an independent prognostic parameter of subsequent adverse events in STEMI patients. In many studies, the absence of ST segment resolution has

Editorial p1249

been associated with the extent of myocardial damage, re-infarction, left ventricular (LV) remodeling, and mortality.^{1–5}

Regression of ST segment elevation has been used in several studies to assess the quality of reperfusion.^{6–9}

Received June 21, 2017; revised manuscript received July 27, 2017; accepted August 15, 2017; released online September 23, 2017
Time for primary review: 19 days

Hôpital Cardiovasculaire Louis Pradel, Hospices Civils de Lyon, Lyon (L.C., S.L., M.S., T.B., G.R., G.F., E.B.-C., I.B., M.O., N.M.); Centre Hospitalier de Mulhouse, Mulhouse (J.-P.M.); Hôpitaux Universitaires de Strasbourg, Strasbourg (M.J.C.), France; Hospital Universitari Vall d'Hebron, Barcelona (D.G.-D.), Spain; Centre Hospitalier Régional Universitaire de Tours, Tours (D.A.); Centre Hospitalier Universitaire de Rangueil, Toulouse (M.E.); Centre Hospitalier de Pau, Pau (N.D.); Hôpital Haut Lévêque, Bordeaux (P.C.); Hôpital Henri Duffau, Avignon (M.M.); Centre Hospitalier Saint-Joseph et Saint-Luc, Lyon (T.P.); Hôpital Gabriel Montpied, Clermont Ferrand (P.M.); Centre Hospitalier Universitaire de Grenoble, Grenoble (G.V.), France; and University Hospital Antwerp, Edegem (O.M.), Belgium

Mailing address: Nathan Mewton, MD, PhD, Hôpital Cardiovasculaire Louis Pradel, Cardiology Department, Clinical Investigation Center, 28 avenue Doyen Lépine, 69677 Lyon, France. E-mail: nathan.mewton@chu-lyon.fr

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Approximately one-quarter of patients with STEMI have ST segment re-elevation after initial regression following primary percutaneous coronary intervention (PPCI). There are few data regarding the significance of ST segment re-elevation after reperfusion, with most data coming from small clinical studies that were performed before the PPCI reperfusion era.^{10–14}

In these small studies, the results are discordant, suggesting either increased severity in myocardial injury,¹⁰ increased infarct size and poorer LV functional outcomes,^{11,12} subclinical pericarditis,¹³ or no significant effect on LV functional outcomes.¹⁴ Moreover, there have been no studies examining the relationship between ST segment re-elevation and clinical outcomes.

The primary aim of the study, a substudy of the CIRCUS (Cyclosporine to Improve Clinical Outcome in ST-elevation myocardial infarction patients) trial, was to assess the frequency of ST segment re-elevation and its association with infarct size, LV functional parameters, as evaluated by echocardiography, and all-cause death and heart failure events at 1 year in a patient population with anterior STEMI treated with PPCI.

Methods

CIRCUS Trial

The subjects in the present study were recruited from the CIRCUS trial database.⁹ Briefly, the CIRCUS trial was an international prospective multicenter randomized double-blind placebo-controlled clinical trial conducted between April 2011 and February 2014 that evaluated the efficacy of cyclosporine to prevent reperfusion injury in an anterior STEMI population. The CIRCUS trial did not show any significant effect of cyclosporine on clinical outcomes.⁹ Approval for the present study was obtained from ethics committees in the relevant countries and all patients provided written informed consent prior to inclusion in the CIRCUS trial.

To be eligible for enrollment in the present study, patients had to be ≥ 18 years of age, to have presented within 12 h after the onset of acute coronary syndrome symptoms, to have ST segment elevation ≥ 2 mm in at least 2 anterior leads, and referred for PPCI. The culprit coronary artery was the left anterior descending coronary artery, with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 or 1 at the time of coronary angiography. Complete inclusion and exclusion criteria, study design, and the primary results already been reported elsewhere.^{9,15}

Patients underwent percutaneous coronary intervention (PCI) according to standard guidelines. The use of thrombus aspiration, bare metal or drug-eluting stents, and glycoprotein IIb/IIIa inhibitor was left to the discretion of the treating physician.

Acquisition and Analysis of ECG Recordings

Standard 12-lead ECGs were recorded upon admission (ECG-1), 60–90 min after PCI (ECG-2), and at discharge from hospital (ECG-3). All ECGs were standardized (0.1 mV/mm, 25 mm/s) and performed carefully. All ECGs were recorded, anonymized, and sent to a core laboratory for centralized reading. All ECGs were read by 2 experienced observers, blinded to all other study characteristics and outcomes, and independently of previous ECG recordings. ST segment elevation was measured manually by each observer. ST segment elevation was measured as

“STmax”, whereby only the lead with the greatest ST segment elevation (from V1 to V4) on each ECG was considered.

In assessing the reproducibility of ST segment analysis, the intrareader correlation coefficient was found to be 0.9725, with a mean (\pm SD) difference of 0.05 ± 0.7 mm, and the inter-reader correlation coefficient was found to be 0.9659, with an average difference of 0.35 ± 0.81 mm. Patients were excluded from analysis there was at least 1 ECG missing or if there was a left branch bundle block or paced heart rhythm. Patients who died before discharge were also excluded from analyses. The “ST segment re-elevation” group (ReST+) was defined as those patients exhibiting an increase of ≥ 0.1 mV (≥ 1 mm) on ECG-3 compared with ECG-2. Patients with no re-elevation of the ST segment were classified as belonging to the “no ST segment re-elevation” group (ReST–).

Study Endpoints

Infarct size was estimated by peak creatine kinase (CK) release. CK concentrations were measured locally at admission, and then again 4, 12, and 24 h after reperfusion. The CK peak was defined as the highest concentration measured during the 24 h following PPCI.

All patients underwent echocardiography during the initial hospitalization and again after 1 year. The LV ejection fraction (EF) was estimated by the Simpson method, as were LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV). Absolute remodeling was defined as the relative increase in LVEDV between baseline and 1 year. Adverse LV remodeling was defined as a $\geq 15\%$ increase in LVEDV (i.e., $[LVEDV \text{ at 1 year} - \text{initial LVEDV}] / \text{initial LVEDV} > 15\%$).

Clinical outcomes were recorded prospectively at 1 year and were a composite of all-cause death and heart failure worsening during initial hospitalization or rehospitalization for heart failure. In addition, we assessed the incidence of pericarditis and stent thrombosis during the initial hospitalization. These are known adverse events possibly responsible for re-elevation of the ST segment. All clinical events were adjudicated by an events validation committee whose members were unaware of study group assignment.

Statistical Analysis

All statistical analyses were post hoc analyses and were not prespecified in the original CIRCUS statistical analysis plan. Continuous variables with a normal distribution are expressed as the mean \pm SD, whereas those that were not normally distributed are expressed as the median and interquartile range (IQR). Normality was tested using the Shapiro-Wilk test. Discrete variables are expressed as percentages.

Comparisons of baseline characteristics or outcomes were performed using the χ^2 test or Fischer's exact test, as appropriate, for categorical variables. Student's t-test or the Wilcoxon test were used for continuous variables according to variable distribution.

Unadjusted event-free survival was evaluated by Kaplan-Meier estimates and statistical significance was assessed by the log-rank test. Adjusted risk estimates were obtained using Cox proportional hazard models, including variables found to differ significantly between groups on univariate analysis or deemed to be clinically relevant.

The same analyses were performed after exclusion of all patients with pericarditis and/or stent thrombosis to assess

the effect of ST segment re-elevation from “unknown causes”.

For all comparisons, $P < 0.05$ was considered significant. All statistical analyses were conducted using STATA version SE 14.2 (StataCorp, College Station, TX, USA).

Results

ECG Characteristics

Complete ECG datasets were available for 662 patients from the CIRCUS trial and these patients were included in the present study. Of the original 969 patients enrolled in the CIRCUS trial, 307 were excluded from analyses because of left branch bundle block, paced heart rhythm, missing or non-analyzable ECG, or death before discharge (16 [1.7%] patients died before discharge).

Initial ST segment regression between ECG-1 and ECG-2 was compared and 3 groups were subsequently created: (1) complete ST segment regression ($>70\%$); (2) partial regression ($30\text{--}70\%$); and (3) no ST segment regression ($<30\%$). No regression, or even partial regression, was strongly correlated with 1-year all-cause mortality ($P=0.009$).

The median (IQR) time to recording of ECG-3 (at discharge) was 5 days (4, 7 days). In all, there were 128 patients (19%) in the ReST+ group. The median (IQR) change in ST segment elevation in the entire population between post-reperfusion and discharge was -1 mm (-2 , 0 mm). The distribution of ST segment changes is shown in Figure 1.

ST re-elevation occurred significantly more frequently in patients with complete initial ST regression (70 patients; 54.7% of the ReST+ group) than in patients with partial (44 patients; 34.4%) or absent (14 patients; 10.9%) ST regression ($P < 0.001$; Table 1).

Residual ST segment elevation was assessed on 1-year ECG recordings: 395 patients (59.7%) still had ST segment elevation of at least 1 mm, and 267 (40.3%) had complete ST segment resolution. In the ReST+ group, 89 patients (69.5%) still had ST segment elevation ≥ 1 mm at 1 year, whereas in the ReST- group 306 patients (57.3%) had ST segment elevation ≥ 1 mm at 1 year ($P=0.011$).

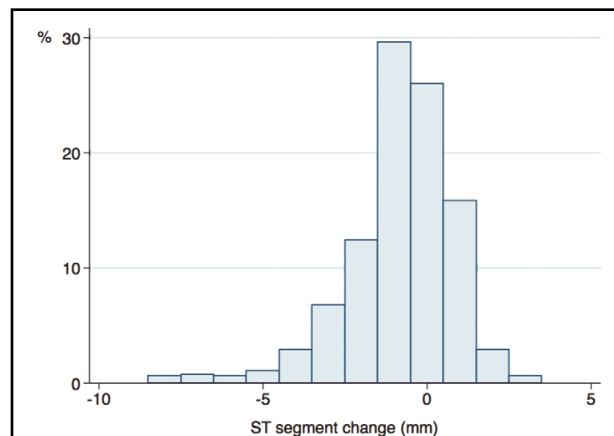


Figure 1. Changes in ST segment elevation from 90 min after primary percutaneous coronary intervention to discharge.

Procedural Characteristics and Hospital Course

Baseline characteristics for all patients are reported in Table 1. There was no difference in ST re-elevation between the cyclosporine-treated and control groups ($P=0.852$). There were no significant differences between the ReST+ and ReST- groups, with a similar proportion of patients in both groups having diabetes, hypertension, dyslipidemia, or current smoker status. In addition, there were no significant differences in the glycemia or creatinine clearance at admission. Although total ischemic time was the same in the 2 groups, the door-to-balloon time was significantly greater in the ReST+ group (141 ± 91 vs. 124 ± 81 min; $P=0.048$), with a mean difference of 17 min.

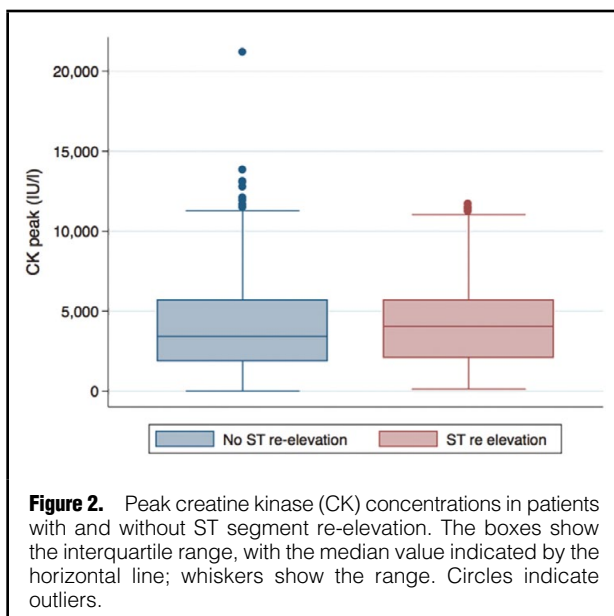
Procedural characteristics were similar between the ReST+ and ReST- groups, with the same initial and final coronary TIMI flow and proportion of multivessel disease and stenting (Table 2). There was no significant difference in medical prescriptions at discharge between the 2 groups.

	No ST re-elevation (n=534)	ST re-elevation (n=128)	P value
Male	445 (83.5)	103 (80.5)	0.441
Age (years)	59±13	60±13	0.189
BMI (kg/m ²)	27±4	26±4	0.227
Current smoker	245 (45.9)	47 (36.7)	0.061
Dyslipidemia	222 (41.6)	47 (36.7)	0.315
Hypertension	206 (38.6)	45 (35.2)	0.474
Diabetes mellitus	64 (12.0)	13 (10.2)	0.562
Previous MI	28 (5.2)	5 (3.9)	0.655
Peripheral ischemic disease	13 (2.4)	1 (0.8)	0.490
MDRD (mL/min)	92±26	89±22	0.365
Glycemia (mmol/L)	6.5±2.2	6.4±2.1	0.908
Initial ST segment resolution (%)			<0.001
<30	140 (26.2)	14 (10.9)	
30–70	276 (51.7)	44 (34.4)	
>70	118 (22.1)	70 (54.7)	

Data are given as the mean \pm SD or as n (%). BMI, body mass index; MDRD, creatinine clearance determined by the Modification of Diet in Renal Disease equation; MI, myocardial infarction.

	No ST re-elevation (n=534)	ST re-elevation (n=128)	P value
Procedural characteristics			
Ischemic time (min)	255±162	279±153	0.156
Door to balloon (min)	124±81	141±91	0.048
P2Y ₁₂ receptor inhibitor	482 (90.3)	109 (85.2)	0.094
Thrombolysis	21 (3.9)	7 (5.5)	0.438
Thrombus aspiration	404 (75.7)	104 (81.3)	0.178
Stenting	475 (89.0)	113 (88.3)	0.829
Angiographic no reflow	25 (4.7)	5 (3.9)	0.817
TIMI flow grade			
Initial			0.578
0	410 (80.6)	100 (80.7)	
1	61 (12.0)	17 (13.7)	
2	30 (5.9)	4 (3.2)	
3	8 (1.6)	3 (2.4)	
Final			0.328
0	5 (1.0)	3 (2.4)	
1	4 (0.8)	1 (0.8)	
2	26 (5.0)	10 (7.9)	
3	490 (93.3)	113 (89.0)	
Multivessel disease	211 (39.5)	41 (32.0)	0.117
Cyclosporine	217 (40.6)	51 (39.8)	0.852
Discharge treatment			
P2Y ₁₂ receptor inhibitor	509 (95.5)	123 (96.8)	0.497
Aspirin	528 (99.1)	128 (100)	0.273
ACE inhibitor	475 (89.1)	117 (92.1)	0.316
β-blocker	507 (95.1)	120 (94.5)	0.768
Statin	517 (97.0)	123 (96.9)	0.930
Aldosterone antagonist	140 (26.3)	27 (21.3)	0.244

Data are given as the mean±SD or as n (%). ACE, angiotensin-converting enzyme; TIMI, Thrombolysis in Myocardial Infarction.



Infarct Size and Echocardiography Endpoints

Infarct size did not differ between the ReST+ and ReST− groups, peak CK concentrations of 4,231±2,656 and 3,993±2,820 IU/L, respectively (P=0.402; **Figure 2**). In addition, LVEF, LVEDV, and LVESV were similar on initial echocardiography in both groups (**Table 3**). At 1 year, there was no difference in LVEF between the ReST− and ReST+ groups (52.2±10.8% vs. 50.7±11.6% respectively; P=0.186) and the proportion of patients exhibiting adverse LV remodeling at 1 year was similar in the 2 groups (317 [59.4%] vs. 75 [58.6%], respectively; P=0.874). Mean remodeling in the ReST− group was 18.3±30.9%, compared with 20.1±38.9% in the ReST+ group (P=0.631; **Figure 3**).

Adverse Events

There was no significant difference in the incidence of pericarditis and stent thrombosis between the ReST− and ReST+ groups. The incidence of in-hospital pericarditis was 47 (8.8%) in the ReST− group and 12 (9.4%) in the ReST+ group (P=0.863), whereas stent thrombosis occurred in 7 patients (1.3%) in the ReST− group and in 1 patient (0.8%) in the ReST+ group (P=1.0).

There was no significant difference in all-cause death between the 2 groups (19 [3.6%] vs. 3 [2.3%] in the ReST− and ReST+ groups, respectively; P=0.783). Similarly, there

	No ST re-elevation (n=534)	ST re-elevation (n=128)	P value
Infarct size			
Peak CK concentration (IU/L)	3,993±2,820	4,231±2,656	0.402
Echocardiographic outcomes			
At baseline			
LVEF (%)	47.4±10.1	47.7±10.0	0.745
LVEDV (mL/m ²)	55±15	54±11	0.521
LVESV (mL/m ²)	29±13	29±9	0.772
At 1 year			
LVEF (%)	52.2±10.8	50.7±11.6	0.186
LVEDV (mL/m ²)	63±20	65±21	0.516
LVESV (mL/m ²)	32±16	34±19	0.269
Adverse LV remodeling	317 (59.4)	75 (58.6)	0.874
% LV remodeling	18.3±30.9	20.1±38.9	0.631
In-hospital adverse events			
Pericarditis	47 (8.8)	12 (9.4)	0.863
Stent thrombosis	7 (1.3)	1 (0.8)	1.000
Clinical outcomes			
All-cause death/heart failure events	106 (19.2)	22 (19.8)	0.887
All-cause death	19 (3.6)	3 (2.3)	0.783
Heart failure	83 (15.5)	22 (19.8)	0.647

Data are given as the mean±SD or as n (%). CK, creatine kinase; LV, left ventricle; LVEDV, LV end diastolic volume; LVEF, LV ejection fraction (Simpson method); LVESV, LV end systolic volume.

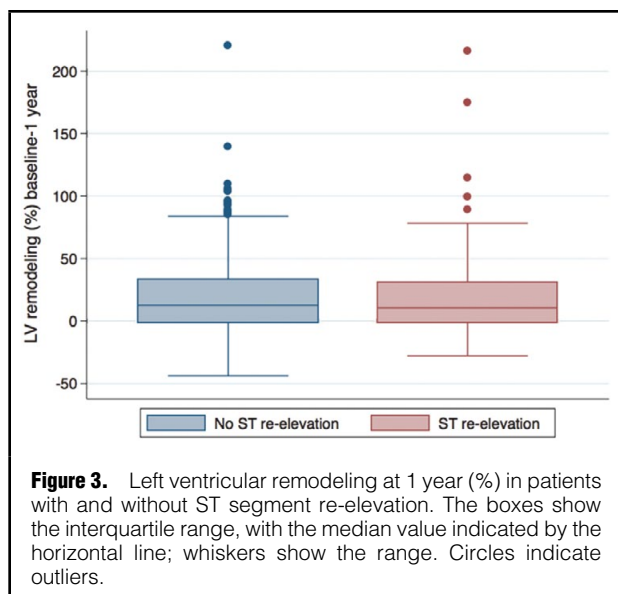


Figure 3. Left ventricular remodeling at 1 year (%) in patients with and without ST segment re-elevation. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Circles indicate outliers.

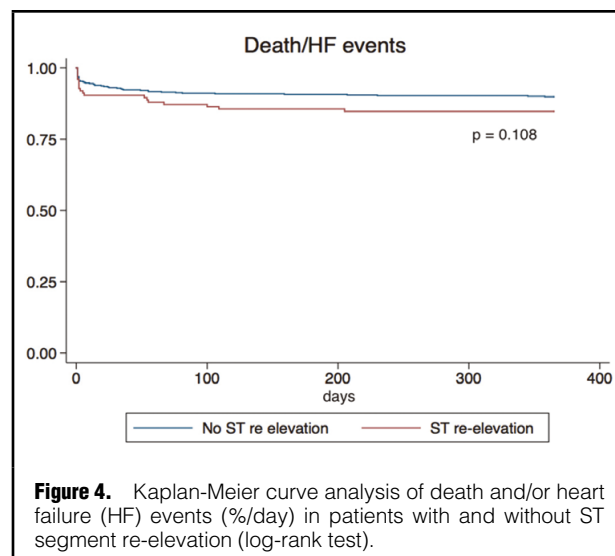


Figure 4. Kaplan-Meier curve analysis of death and/or heart failure (HF) events (%/day) in patients with and without ST segment re-elevation (log-rank test).

was no significant difference in the incidence of heart failure events between the ReST– and ReST+ groups (83 [15.5%] vs. 22 [19.8%], respectively; $P=0.647$).

There was no difference in the frequency of the composite outcome (all-cause death and heart failure) at 1 year, with 106 events (19.2%) in the ReST– group and 22 events (19.8%) in the ReST+ group ($P=0.887$). However, on the Kaplan-Meier survival curves, there was a non-significant trend towards an increased incidence of events in the ReST+ group ($P=0.108$; **Figure 4**).

Overall, the results were similar after exclusion of all

patients presenting with potential confounding clinical characteristics, such as pericarditis and stent thrombosis.

Discussion

In the present study we found that ST segment re-elevation after reperfusion is present in 19% of patients with anterior STEMI, but does not have any significant relationship with infarct size, LVEF, adverse remodeling, or the composite endpoint of all-cause mortality and heart failure at 1 year.

The present study is the first to analyze the relationship between ST segment re-elevation and several important endpoints in a large and homogeneous group of patients with anterior STEMI followed up for 1 year. The incidence of ST segment re-elevation in STEMI patients in the present study was similar to that reported in previous studies, which ranged between 23% and 29%.^{10,12,14} The absence of a significant relationship with any clinical endpoint is consistent with the findings of Matano et al.¹⁴ In that study on patients with anterior STEMI, the authors did not find any difference in LVEF or LVEDV between patients with or without ST-segment re-elevation, and the study did not have sufficient power to assess clinical outcomes. The present study in a larger (and more homogeneous) population of patients with anterior STEMI is more powerful, and takes the findings of Matano et al.¹⁴ further by showing the absence of any correlation between ST segment re-elevation and clinical outcomes.

In contrast, the results are not consistent with those reported by Okuda et al.,¹² who found ST segment re-elevation was associated with larger infarct size and poorer LVEF at 6 months. Okuda et al.¹² even showed that ST segment re-elevation (after initial ST resolution) was worse than the absence of initial ST segment resolution. However, the study population of patients with anterior STEMI in the study of Okuda et al.¹² differs significantly from the present study population because, in their study, 31% of patients underwent thrombolysis alone, and the proportion of patients undergoing PCI differed significantly between groups with and without ST segment re-elevation. Furthermore Okuda et al.¹² did not confirm their results in terms of clinical outcomes.

In a small observation cardiovascular magnetic resonance (CMR) study, Weaver et al.¹⁰ found a significant correlation between ST segment re-elevation and the extent and severity of myocardial injuries as assessed by contrast-enhanced CMR. The apparent discrepancy with the results of the present study could be explained by differences in study populations and the significantly smaller sample size in the study of Weaver et al.¹⁰ with potential selection bias limitations. The population in the present study was more homogeneous because we only enrolled patients with anterior STEMI. In addition, Weaver et al.¹⁰ compared sumST (i.e., the sum of ST elevation on all ECG leads affected by the infarction) using a very low border of 0.1 mV and mixing anterior and inferior STEMI, which may have affected their results.

Persistence of ST elevation after reperfusion has been evaluated in many studies. In most of these studies, it has been associated with echographic, biological, and clinically poor prognosis,^{2,16,17,20–28} even if some recent studies show only a weak or absent relationship.^{19,29–31} Patients with persistent ST elevation are older, have more diabetes, a longer ischemic time, and a predominance of anterior STEMI.^{2,16–22} Of note, there was no significant difference in these factors between the 2 groups in the present study population. Infarct size as assessed by peak CK or contrast-enhanced CMR is bigger if ST elevation persists,^{2,16,17,19,21,23–25} and is associated with degraded LV parameters on echography or angiography in both the short and long term after discharge.^{3,17,22,26} In most studies, persistent ST elevation was strongly associated with clinical outcomes, including 1-year mortality, heart failure, and major adverse cardiac events.^{2,3,16,17,20,21,23,27,28} However, some recent studies do not confirm the relationship between ST recovery and LV

functional parameters.^{29–31} Sejersten et al.¹⁹ showed a correlation between absence of ST recovery and long-term mortality only after thrombolysis, but not after PPCI.

ST segment resolution appears as an indication of epicardial reperfusion and is associated with a better final TIMI flow grade on the coronary angiogram.^{17,20} Despite a final TIMI flow of Grade 3, some patients still have ST segment elevation and a poorer prognosis. It has been suggested that ST segment elevation may also reflect microvascular obstruction (i.e., myocardial reperfusion). Indeed, ST segment recovery is associated with an improved myocardial blush grade³² on the coronary angiogram. Conversely, persistence of ST segment elevation is associated with no-reflow on myocardial contrast echocardiography³³ and microvascular obstruction on contrast-enhanced CMR.^{10,25,34} This was well established in the thrombolysis era,¹ and ST resolution is still used to assess the efficacy of thrombolysis.

Recent studies evaluating ST segment and tissue perfusion after PPCI show discordant results. For example, Galiuto et al.³¹ did not confirm a relationship between ST recovery and echocardiographic no-reflow.

In the present study, the absence of initial ST segment resolution was a strong predictor of poor prognosis. In addition, we found that initial ST resolution had a significant effect on the incidence of ST re-elevation: the greater the initial resolution, the higher the probability of re-elevation. Initial complete ST resolution in the present study remained a very powerful predictive factor of a positive outcome, but was associated with an increased risk of ST segment re-elevation at discharge. This interaction could explain, in part, the absence of an effect of ST segment re-elevation on clinical outcomes at 1 year.

Non-painful and spontaneous ST segment re-elevation is an incompletely understood phenomenon. Several clinical situations have been associated with ST segment re-elevation, including subclinical pericarditis,¹³ reinfarction or stent thrombosis, infarct expansion,³⁵ reperfusion injury, or an intense inflammatory response.¹² Zmyslinski et al.¹³ described ST segment re-elevation by ECG mapping in large groups of STEMI patients and found that its incidence was higher in case of pericarditis. The incidence of manifest pericarditis and stent thrombosis during the initial hospitalization did not differ between the 2 groups in the present study. So, we can suppose that these 2 adverse events, well known as being responsible for ST segment elevation, did not have any effect on the ST segment re-elevation we noted. This is backed up by the absence of any change in the results after these patients were excluded from the analyses.

Okuda et al.¹² reported that C-reactive protein concentrations at 3 days in STEMI patients were higher in cases of ST segment re-elevation. This suggests that a more intense inflammatory response could be associated not only with a larger infarct size, but also with the healing process of the infarct and the pathophysiology of secondary reperfusion injuries.³⁶ The dynamic changes to myocardial tissue after reperfusion have recently been emphasized in an experimental model of pig infarction, in which Fernández-Jiménez et al.³⁷ showed that there were 2 waves of edema seen on CMR after reperfusion. The 2nd wave and its intensity could play a role in the incidence of ST segment re-elevation.

In the present study, the door-to-balloon time was greater in the ReST+ group, although total ischemic time did not differ between the 2 groups. Even if we can assume that ST segment re-elevation is linked to a longer ischemic time,

the mean difference of 17 min between the 2 groups is low and its clinical significance seems weak. Somitsu et al³⁸ found that the history of angina predicted absence of ST segment re-elevation and they speculated that ischemic preconditioning and the development of good collaterals could be another explanation for this phenomenon.

Efficient reperfusion with PPCI has considerably improved the prognosis for patients with STEMI. With efficient reperfusion, ST segment dynamics have changed significantly. The clinical significance of ST segment modification (complete, partial, or absence of regression, and re-elevation) is probably different from prior reports in the era of absence of reperfusion or thrombolysis. However, ST segment regression is still currently used as a principal clinical endpoint in therapeutic studies on reperfusion.^{8,9} The present study shows significant modification in the ST segment in a large and homogeneous population of patients with anterior STEMI. We did not find any clinical significance of ST segment re-elevation, which occurs in approximately one-fifth of patients. Further studies reassessing the day-by-day dynamics of the ST segment are needed in broader groups of STEMI patients to better understand the pathophysiology of ST segment re-elevation following reperfusion.

Study Limitations

The principal limitation of the present study is the lack of a significant number of ECGs. The exclusion because of death before discharge could have been a bias, but it only concerned 16 patients. However, the power of the present study is much higher power than that of previously published studies.

The second limitation of the study is the time of ECG recording. ECG mapping studies^{13,35} show that ST levels fluctuate, especially during the first days after STEMI. The moment of ECG recording in the present study was variable, and depended on the time of hospital discharge; this may have affected the level of ST elevation recorded.

In all ECG studies, 100% reproducibility in ECG realization is impossible because of potential variation in the exact position of the electrodes (especially precordial leads). This could have affected the results of the present study, but is real-life practice and we have no technical way to control this variability. We tried to minimize this phenomenon by using the STmax method. ST segment elevation measurements using the STmax method are solid and reproducible. There are several methods for measuring ST segment elevation in the literature, but the STmax method is one of the most frequently used and the simplest.^{2,17,18,23,27} We did not study ST reciprocal deviation because this would have made the measures more complex and variable.

The 0.1 mV (1 mm) threshold was chosen because this is the minimum change that can be unequivocally detected visually by an expert reader. We did not choose a more elevated threshold because the proportion of patients with ST segment re-elevation would have been too small to enable any conclusions to be made (using a 0.2 mV [2 mm] threshold, the proportion of patients with ST segment re-elevation would have been 3%). The proportion of patients with ST segment re-elevation in the present was 19%, which is comparable with other published data.^{10,14}

Conclusions

In conclusion, in a group of patients with anterior STEMI,

ST segment re-elevation after revascularization by PPCI occurred in one-fifth of patients and was not predictive of increased infarct size, worse LV functional parameters, or major clinical adverse events. Further studies are needed to determine the significance of ST segment re-elevation.

References

- Schröder R, Wegscheider K, Schröder K, Dissmann R, Meyer-Sabellek W. Extent of early ST segment elevation resolution: A strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens: A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. *J Am Coll Cardiol* 1995; **26**: 1657–1664.
- van't Hof AW, Liem A, de Boer MJ, Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction: Zwolle Myocardial infarction Study Group. *Lancet* 1997; **350**: 615–619.
- Matetzky S, Novikov M, Gruberg L, Freimark D, Feinberg M, Elian D, et al. The significance of persistent ST elevation versus early resolution of ST segment elevation after primary PTCA. *J Am Coll Cardiol* 1999; **34**: 1932–1938.
- Monassier JP, Steg PG, Elkouby A, Hanssen M, Chalet Y, Gressin V. Evolution of the ST segment in myocardial reperfusion. *Arch Mal Coeur Vaiss* 1993; **86**: 79–84 (in French).
- Monassier JP. Reperfusion injury in acute myocardial infarction: From bench to cath lab. Part II: Clinical issues and therapeutic options. *Arch Cardiovasc Dis* 2008; **101**: 565–575.
- Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001–2015.
- Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**: 1045–1057.
- Hahn JY, Song YB, Kim EK, Yu CW, Bae JW, Chung WY, et al. Ischemic preconditioning during primary percutaneous coronary intervention: The effects of preconditioning on myocardial reperfusion in patients with ST-segment elevation myocardial infarction (POST) randomized trial. *Circulation* 2013; **128**: 1889–1896.
- Ovize M, Mewton N. Interventional cardiology: Ischaemic POSTconditioning—a long harvest for a little corn. *Nat Rev Cardiol* 2014; **11**: 8–10.
- Weaver JC, Ramsay DD, Rees D, Binnekamp MF, Prasan AM, McCrohon JA. Dynamic changes in ST segment resolution after myocardial infarction and the association with microvascular injury on cardiac magnetic resonance imaging. *Heart Lung Circ* 2011; **20**: 111–118.
- Shimizu M, Ishikawa K, Kanamasa K, Ogawa I, Koka H, Katori R. ST-segment re-elevation and left ventricular expansion soon after acute anterior myocardial infarction. *Jpn Circ J* 1992; **56**: 235–242.
- Okuda J, Kosuge M, Ebina T, Hibi K, Tsukahara K, Iwahashi N, et al. Clinical implications of serial changes in ST-segment elevation after reperfusion in patients with anterior acute myocardial infarction. *Circ J* 2008; **72**: 409–414.
- Zmislinski RW, Akiyama T, Biddle TL, Shah PM. Natural course of the S-T segment and QRS complex in patients with acute anterior myocardial infarction. *Am J Cardiol* 1979; **43**: 29–34.
- Matano S, Iwasaki K, Kusachi S, Murakami T, Kurazono S, Yamaji H, et al. ST-segment re-elevation unrelated to left ventricular ejection fraction or volume after anterior wall acute myocardial infarction treated with successful reperfusion. *J Electrocardiol* 2002; **35**: 87–93.
- Mewton N, Cung TT, Morel O, Cayla G, Bonnefoy-Cudraz E, Rioufol G, et al. Rationale and design of the Cyclosporine to ImpRove Clinical Outcome in ST-elevation myocardial infarction patients (the CIRCUS trial). *Am Heart J* 2015; **169**: 758–766.e6.
- Claeys MJ, Bosmans J, Veenstra L, Jorens P, De R, Vrints CJ. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction: Importance of microvascular reperfusion injury on clinical outcome. *Circulation* 1999; **99**: 1972–1977.
- Brodie BR, Stuckey TD, Hansen C, VerSteeg DS, Muncy DB, Moore S, et al. Relation between electrocardiographic ST-segment resolution and early and late outcomes after primary percutaneous coronary intervention for acute myocardial infarction. *Am J*

- Cardiol* 2005; **95**: 343–348.
18. Przyłuski J, Karcz M, Kalińczuk L, Kruk M, Pregowski J, Kaczmarska E, et al. Comparison of different methods of ST segment resolution analysis for prediction of 1-year mortality after primary angioplasty for acute myocardial infarction. *Ann Noninvasive Electrocardiol* 2007; **12**: 5–14.
 19. Sejersten M, Valeur N, Grande P, Nielsen TT, Clemmensen P; DANAMI-2 Investigators. Long-term prognostic value of ST-segment resolution in patients treated with fibrinolysis or primary percutaneous coronary intervention results from the DANAMI-2 (DANish trial in acute myocardial infarction-2). *J Am Coll Cardiol* 2009; **54**: 1763–1769.
 20. van der Zwaan HB, Stoel MG, Roos-Hesselink JW, Veen G, Boersma E, von Birgelen C. Early versus late ST-segment resolution and clinical outcomes after percutaneous coronary intervention for acute myocardial infarction. *Neth Heart J* 2010; **18**: 416–422.
 21. Tomaszuk-Kazberuk A, Kozuch M, Bachorzewska-Gajewska H, Malyszko J, Dobrzycki S, Musiał WJ. Does lack of ST-segment resolution still have prognostic value 6 years after an acute myocardial infarction treated with coronary intervention? *Can J Cardiol* 2011; **27**: 573–580.
 22. Ndrepepa G, Alger P, Kufner S, Mehili J, Schömig A, Kastrati A. ST-segment resolution after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. *Cardiol J* 2012; **19**: 61–69.
 23. Buller CE, Fu Y, Mahaffey KW, Todaro TG, Adams P, Westerhout CM, et al. ST-segment recovery and outcome after primary percutaneous coronary intervention for ST-elevation myocardial infarction: Insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. *Circulation* 2008; **118**: 1335–1346.
 24. Haecck JD, Verouden NJ, Kuijt WJ, Koch KT, Majidi M, Hirsch A, et al. Impact of early, late, and no ST-segment resolution measured by continuous ST Holter monitoring on left ventricular ejection fraction and infarct size as determined by cardiovascular magnetic resonance imaging. *J Electrocardiol* 2011; **44**: 36–41.
 25. Dizon JM, Brener SJ, Maehara A, Witzensbichler B, Biviano A, Godlewski J, et al. Relationship between ST-segment resolution and anterior infarct size after primary percutaneous coronary intervention: Analysis from the INFUSE-AMI trial. *Eur Heart J Acute Cardiovasc Care* 2014; **3**: 78–83.
 26. Poli A, Fétiveau R, Vandoni P, del Rosso G, D'Urbano M, Seveso G, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: Real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. *Circulation* 2002; **106**: 313–318.
 27. McLaughlin MG, Stone GW, Aymong E, Gardner G, Mehran R, Lansky AJ, et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *J Am Coll Cardiol* 2004; **44**: 1215–1223.
 28. Verouden NJ, Haecck JD, Kuijt WJ, van Geloven N, Koch KT, Henriques JP, et al. Prediction of 1-year mortality with different measures of ST-segment recovery in all-comers after primary percutaneous coronary intervention for acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 522–529.
 29. Bax M, de Winter RJ, Schotborgh CE, Koch KT, Meuwissen M, Voskuil M, et al. Short- and long-term recovery of left ventricular function predicted at the time of primary percutaneous coronary intervention in anterior myocardial infarction. *J Am Coll Cardiol* 2004; **43**: 534–541.
 30. Sciagrà R, Parodi G, Migliorini A, Valenti R, Antonucci D, Sotgia B, et al. ST-segment analysis to predict infarct size and functional outcome in acute myocardial infarction treated with primary coronary intervention and adjunctive abciximab therapy. *Am J Cardiol* 2006; **97**: 48–54.
 31. Galiuto L, Garramone B, Scarà A, Rebuzzi AG, Crea F, La Torre G, et al. The extent of microvascular damage during myocardial contrast echocardiography is superior to other known indexes of post-infarct reperfusion in predicting left ventricular remodeling: Results of the multicenter AMICI study. *J Am Coll Cardiol* 2008; **51**: 552–559.
 32. van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: Myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation* 1998; **97**: 2302–2306.
 33. Santoro GM, Valenti R, Buonamici P, Bolognese L, Cerisano G, Moschi G, et al. Relation between ST-segment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with direct angioplasty. *Am J Cardiol* 1998; **82**: 932–937.
 34. Husser O, Bodí V, Sanchis J, Núñez J, Mainar L, Rumiz E, et al. The sum of ST-segment elevation is the best predictor of microvascular obstruction in patients treated successfully by primary percutaneous coronary intervention: Cardiovascular magnetic resonance study. *Rev Esp Cardiol* 2010; **63**: 1145–1154.
 35. Reid PR, Taylor DR, Kelly DT, Weisfeldt ML, Humphries JO, Ross RS, et al. Myocardial-infarct extension detected by precordial ST-segment mapping. *N Engl J Med* 1974; **290**: 123–128.
 36. Anzai T, Yoshikawa T, Shiraki H, Asakura Y, Akaishi M, Mitamura H, et al. C-Reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. *Circulation* 1997; **96**: 778–784.
 37. Fernández-Jiménez R, Sánchez-González J, Agüero J, García-Prieto J, López-Martín GJ, García-Ruiz JM, et al. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: Imaging and histological tissue characterization. *J Am Coll Cardiol* 2015; **65**: 315–323.
 38. Somitsu Y, Nakamura M, Degawa T, Yamaguchi T. Prognostic value of slow resolution of ST-segment elevation following successful direct percutaneous transluminal coronary angioplasty for recovery of left ventricular function. *Am J Cardiol* 1997; **80**: 406–410.