New ST-depression: an under-recognized high-risk category of 'complete' ST-resolution after reperfusion therapy

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Abstract

Aim: It is not known if there is an association between resolution of ST-elevation to ST-depression following fibrinolysis and 30-day mortality.

Methods: In an ECG substudy of HERO-2, which compared bivalirudin to unfractionated heparin following streptokinase in 12,556 patients with ST-elevation myocardial infarction ECGs were recorded at baseline and at 60 minutes after commencing fibrinolysis. The main outcome measure was 30-day mortality.

Results: Using summed ST-segment elevation and five categories of changes in the infarct leads, further ST-elevation, 0–30% ST-resolution, >30–70% (partial) ST-resolution, >70% (complete) ST-resolution, and new ST-depression occurred in 21.7, 24.9, 36.8, 14.8, and 1.8% of patients, with 30-day mortality of 12.3, 11.7, 8.0, 4.2, and 8.1%, respectively. For the comparison of new ST-depression with complete ST-resolution and no ST-depression, $p < 0.01$ with 24-hour mortality 4.5 vs. 1.3%, respectively ($p = 0.0003$). Patients with new ST-depression had similar peak cardiac enzyme elevations as patients with complete ST-resolution without ST-depression. On multivariate analysis including summed ST-elevation at baseline, age, sex, and infarct location, new ST-depression was a significant predictor of 30-day mortality (OR 1.82, 95% CI 1.42–4.29).

Conclusions: In patients with complete ST-resolution following fibrinolysis, new ST-depression at 60 minutes developed in 10.8% of patients. These patients had higher mortality than patients with complete ST-resolution without ST-depression and represent a high-risk group which could benefit from rapid triage to early angiography and revascularization as appropriate.

Keywords

Fibrinolysis, mortality, new ST-depression

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Introduction

After the administration of reperfusion therapies for ST-elevation myocardial infarction (STEMI), resolution of ST-segment elevation in the infarct leads helps risk stratification.^{1,2} Although the use of primary percutaneous coronary intervention (PCI) is dominant in Western countries, the use of fibrinolysis is widely used worldwide and the incidence of myocardial infarction (MI) is increasing in developing countries³ where many hospitals are non-PCI centres. In a recent meta-analysis, the prognostic meaning

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of early ST-resolution was found to be similar between fibrinolysis cohorts and primary PCI cohorts.⁴ The use of a similar single lead measurement for ST-resolution is as informative as using summed ST-changes in all infarct leads both after fibrinolysis^{5–7} and after primary PCI.⁸

In the group of patients with complete ST-resolution, there may be heterogeneity in prognosis between patients with resolution of ST-elevation to an isoelectric level and resolution to a negative level with new ST-depression. We therefore analysed in the large Hirulog Early Reperfusion Occlusion (HERO)-2 mortality trial, which compared bivalirudin and unfractionated heparin in patients with STEMI receiving streptokinase for the significance of ST-resolution with new ST-depression.

Methods

The HERO-2 study randomized 17,073 patients with STEMI within 6 hours of symptom onset to receive bivalirudin or heparin, in addition to streptokinase and aspirin.⁹ The randomized treatments had no effect on the primary endpoint of 30-day mortality.⁹ The sites reported maximal cardiac enzyme levels (creatinine kinase and creatine kinase MB) as multiples of the upper limit of normal in their sites; MIs were adjudicated by a blinded Clinical Events Committee (CEC). The protocol prespecified that a standard 12-lead ECG was to be performed at randomization and at 60 minutes after commencing streptokinase.^{10–17} All ECGs were sent to the core laboratory at Green Lane Hospital for analysis by eight ECG technicians who were unaware of treatment assignment and patient outcomes. The evaluation of the prognostic significance of ST-segment changes at 60 minutes was prespecified by protocol.

ECG analysis

To qualify for this study, the baseline ECG had to be obtained no more than 2 hours before or 8 minutes after commencing streptokinase and the 60-minute ECG from 45 to 75 minutes after commencing streptokinase. ECGs with conduction abnormalities, ventricular or paced rhythms, or technical problems were excluded. The amount of ST-segment change was measured to the nearest 0.5 mm at 60 milliseconds after the J point. Only patients who had normal intraventricular conduction at both time points and had sufficient amount of baseline ST-elevation by core lab measurements (≥ 2 mm ST-elevation in 2 contiguous leads V1–3 or ≥ 1 mm ST-elevation in any other 2 contiguous leads) were eligible for the current study.

ST-resolution analysis

As prespecified by protocol, we used two ST-resolution analysis methods:

1. summed ST-elevation in the AMI leads showing any elevation ≥ 0.5 mm. For anterior AMI, the leads

included I, aVL, and V1–V6. For inferior AMI, the leads included II, III, and aVF, and lateral leads V5, V6, I, and aVL

2. single lead ST-elevation using the lead with maximum elevation at baseline.

For analyses of changes in ST-elevation over 60 minutes in the infarct leads, five categories were defined:

1. further ST-elevation
2. no resolution of ST-elevation (0–30% resolution of baseline level)
3. partial resolution of ST-elevation of $>30\%$ –70% of baseline level
4. complete resolution of ST-elevation ($>70\%$ resolution of baseline level) but without developing ST-depression
5. new ST-segment depression ≥ 0.05 mm developing in the infarct-leads.

Analysis for new ST-depression in the infarct leads

The same ECG infarct leads were measured on the baseline ECG and the 60-minute ECGs. If the ST-segment level was below the isoelectric line at 60 minutes (i.e. new ST-segment depression), it was read as a negative ST-level in the calculation of summed ST-elevation. For single lead analyses, the lead with the greatest ST-elevation at baseline was chosen for the paired measurements. If two infarct leads happened to show the same magnitude of baseline ST-elevation, the lead with deeper ST-depression at 60 minutes was used for paired analysis.

Statistical analysis

Comparison of variables was done by Wilcoxon rank-sum test or χ^2 test wherever appropriate. Discrete variables were reported as number and percentage and continuous variables were reported as median and the 25th and 75th percentiles where appropriate. The Kruskal–Wallis test was used to compare continuous variables among the different groups of ST-segment change at 60 minutes; the χ^2 test was used to compare discrete variables.

The primary aim of this study was to evaluate the relationship of new ST-depression at 60 minutes with 30-day mortality. A multivariable logistic regression model including summed ST-elevation at baseline, age, sex, infarction location, and ST-resolution was created first. Then clinical factors, including age and sex, geographic region of the patient recruitment, systolic blood pressure, Killip class, heart rate, infarct location, history of previous MI, diabetes, hypertension, prior angina and time to randomization, plus the ST-segment changes on the baseline ECG were entered into a full multivariable logistic regression model.

Figure 1. Patient flow chart

The five categories of ST-changes were regarded as categorical variables in both analyses. Nagelkerke's R^2 was used to estimate the variability in the dependent variable explained by the model and Hosmer–Lemeshow's goodness-of-fit test was conducted to determine whether the model fit was adequate. A C-statistic was used to determine the association of predicted probabilities and observed responses.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA) and a significance level of $\alpha=0.05$ was used to determine statistical significance for all comparisons.

The authors are solely responsible for the design and conduct of this study, the drafting and editing of the paper and its final contents. Analyses were performed by the authors. All patients gave informed consent to participate.

Results

Of 17,073 patients randomized in HERO-2, 12,556 patients had paired ECGs that satisfied our prespecified criteria for analysing ST-resolution and formed the cohort for the current report (Figure 1). Table 1 reports baseline characteristics

of the 12,556 patients included in the ECG substudy and the 4517 patients excluded. The patients excluded were older, more likely had diabetes, presented later, and had higher mortality than the patients included in the ECG substudy. The 30-day mortality of the ECG cohort was 9.2% compared to 15.3% for the patients excluded. In the patients included in the substudy, the rate of angiography was 10.6%: 5.0% PCI and 0.6% coronary artery bypass grafting.

Figure 2a and 2b show the increasing mortality rates according to the amount of summed ST-elevation and depression. Table 2 reports the baseline characteristics of patients according to the five categories of summed ST-segment changes over 60 minutes (i.e. further ST-elevation, no ST-resolution, partial ST-resolution, complete ST-resolution, and new ST-depression). Respectively, these ST-changes occurred in 2678 (21.7%), 3070 (24.9%), 4535 (36.8%), 1829 (14.8%), and 221 (1.8%) patients.

Patients with new ST-depression were more likely to have a history of angina as compared with patients with complete ST-resolution ($p=0.03$). Multiples of the upper limit of normal (ULN) range for creatine kinase or creatine kinase MB were not different in patients with complete ST-resolution and no ST-depression vs. those with

Table 1. Baseline characteristics and outcomes.

	Patients included (n=12,556)	Patients excluded (n=4517)	p-value
Demographics			
Age (years)	61 (51–69)	63 (53–71)	<0.0001
≥75 years	1486 (11.8)	674 (14.9)	<0.0001
Female	3526 (28.1)	1317 (29.2)	0.1696
History of cardiovascular disease			
Angina	5909 (47.1)	2108 (46.7)	0.6499
Myocardial infarction	1798 (14.3)	788 (17.5)	<0.0001
Stroke	141 (1.1)	47 (1.0)	0.6488
PCI	130 (1)	59 (1.3)	0.0045
CABG	77 (0.6)	75 (1.7)	0.001
Smoking			
Never smoked	4820 (38.4)	1803 (39.9)	<0.0001
Past smoker	2047 (16.3)	895 (19.8)	
Current smoker	5689 (45.3)	1819 (40.3)	
Hypertension	6472 (51.6)	2354 (52.1)	0.5115
Diabetes	1649 (13.1)	746 (16.5)	<0.0001
Infarct location			
Anterior	6136 (48.9)	2340 (51.8)	0.0007
Inferior	6420 (51.1)	2177 (48.2)	
Randomization by region			
Russia	4790 (38.2)	1267 (28.1)	<0.0001
Eastern Europe	4601 (36.6)	1276 (28.3)	
Western countries	1445 (11.5)	1118 (24.8)	
Latin America	1175 (9.4)	645 (14.3)	
Asia	545 (4.3)	211 (4.7)	
Time from symptom onset to randomization (h)			
≤2	2629 (20.9)	981 (21.8)	<0.0001
>2–4	6446 (51.4)	2140 (47.5)	
>4	3479 (27.7)	1389 (30.8)	
Anthropometrics			
Weight (kg)	75 (68–85)	76 (68–85)	0.2167
Height (cm)	170 (164–175)	170 (164–175)	0.8478
Body mass index (kg/m ²)	26.3 (24.0–29.1)	26.4 (24.2–29.3)	0.1158
Haemodynamics			
Systolic blood pressure (mmHg)	135 (120–150)	130 (120–150)	<0.0001
Diastolic blood pressure (mmHg)	80 (72–90)	80 (70–90)	<0.0001
Heart rate (beats/min)	76 (65–88)	76 (65–90)	0.0205
Killip class			
I	10015 (79.8)	3421 (75.7)	<0.0001
II	2132 (17.0)	834 (18.5)	
III	275 (2.2)	152 (3.4)	
IV	134 (1.1)	110 (2.4)	
GUSTO risk score ³⁰	61 (50–70)	63 (51–74)	<0.0001
TIMI risk score ³¹	3 (2–5)	3 (2–5)	<0.0001
Randomized to bivalirudin	6263 (49.9)	2253 (49.9)	0.9979
Outcomes			
Death within 30 days	1160 (9.2)	690 (15.3)	<0.0001
Death within 24 hours	444 (3.5)	375 (8.3)	<0.0001
30-day death/non-fatal disabling stroke	1185 (9.4)	699 (15.5)	<0.0001
30-day death/reinfarction	1485 (11.8)	781 (17.3)	<0.0001

Values are median (interquartile range) or n (%). CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Figure 2. Relationship between summed ST-segment elevation on baseline ECG and 30-day mortality.

complete resolution and ST-depression (5.6 vs. 5.3 ULN, $p=0.108$).

Development of new ST-depression

Using summed ST-levels in the infarct leads, 2050 patients had >70% ST-resolution. The 221 patients who developed new ST-depression in the infarct leads represented (10.8%) of patients with complete >70% ST-resolution. The median and interquartile range of summed ST-depression at 60 minutes in the infarct leads was 1.0 (0.5–1.5) mm.

Relationship between ST-resolution and 30-day mortality

Table 3 shows outcomes in relation to the five ST-resolution categories. The 30-day mortality rates were 12.3% (ST-elevation), 11.7% (no resolution), 8.0% (partial resolution),

4.2% (>70% resolution), and 8.1% (>70% resolution with ST-depression) ($p<0.0001$). Death within 24 hours was 4.5% in those with new ST-depression vs. 1.3% in those with >70% ST-segment resolution without ST-depression ($p=0.0003$).

If the 221 patients with new ST-depression were classified into the traditional category of complete ST-resolution together with the 1829 patients with >70% ST-resolution, the 30-day mortality was 4.6%. For the patients with new ST-depression, mortality was higher in patients with anterior vs. inferior infarction (15.9 vs. 5.1%, $p=0.008$).

There was a trend for rates of reinfarction to be higher in patients with ST-depression compared to patients with >70% resolution and no ST-depression (6.3 vs. 3.9%, $p=0.09$; Table 3). Rates of combined death and reinfarction were higher in patients with new ST-depression compared with patients with >70% ST-resolution without ST-depression (14 vs. 7.7%, $p=0.0012$).

Table 2. Baseline characteristics in patients with the five different categories of ST-changes at 60 minutes.

	Further ST-elevation (n=2678)	Resolution			New ST- depression (n=221)	Overall χ^2 test p-value	p-value ^a
		0–30% (n=3070)	>30–70% (n=4535)	>70% (n=1829)			
Demographics							
Age (years)	61 (51–70)	61 (51–70)	61 (51–69)	60 (51–68)	60 (52–68)	0.0097	0.5641
≥75 years	346 (12.9%)	373 (12.2)	526 (11.6)	196 (10.7)	24 (10.9)	0.206	0.9481
Female	781 (29.2)	902 (29.4)	1222 (27.0)	505 (27.6)	56 (25.3)	0.0904	0.4744
History of cardiovascular disease							
Angina	1339 (50)	1488 (48.5)	2080 (45.9)	804 (44)	114 (51.6)	0.0001	0.0313
Myocardial infarction	440 (16.4)	443 (14.4)	623 (13.3)	243 (13.3)	36 (16.3)	0.0116	0.2187
Stroke	30 (1.1)	39 (1.3)	57 (1.3)	14 (0.8)	1 (0.5)	0.3781	0.7897
PCI	28 (1.1)	29 (0.9)	38 (0.8)	26 (1.4)	6 (2.7)	0.0292	0.1432
CABG	18 (0.7)	21 (0.7)	25 (0.6)	12 (0.7)	1 (0.5)	0.9382	0.7187
Smoking							
Never smoked	1088 (40.6)	1239 (40.4)	1699 (37.5)	651 (35.6)	74 (33.5)	0.0004	0.0603
Past smoker	424 (15.8)	510 (16.6)	734 (16.2)	291 (15.9)	49 (22.2)		
Current smoker	1166 (43.5)	1321 (43)	2102 (46.4)	887 (48.5)	98 (44.3)		
Hypertension	1485 (55.5)	1621 (52.8)	2327 (51.3)	838 (45.8)	105 (47.5)	<0.0001	0.6332
Diabetes	465 (17.4)	446 (14.5)	521 (11.5)	166 (9.1)	28 (12.7)	<0.0001	0.0847
Infarct location							
Anterior	1315 (49.1)	1785 (58.1)	2242 (49.4)	600 (32.8)	56 (25.3)	<0.0001	0.0246
Inferior	1363 (50.9)	1285 (41.9)	2293 (50.6)	1229 (67.2)	165 (74.7)		
Randomization by region							
Russia	1077 (40.2)	1245 (40.6)	1755 (38.7)	603 (33)	65 (29.4)	<0.0001	0.1902
Eastern Europe	984 (36.7)	1092 (35.6)	1599 (35.3)	719 (39.3)	105 (47.5)		
Western countries	286 (10.7)	331 (10.8)	519 (11.4)	262 (14.3)	24 (10.9)		
Latin America	230 (8.6)	288 (9.4)	446 (9.8)	155 (8.5)	16 (7.2)		
Asia	101 (3.8)	114 (3.7)	216 (4.8)	90 (4.9)	11 (5)		
Time from symptom onset to randomization (h)							
≤2	628 (23.5)	543 (17.7)	850 (18.7)	491 (26.9)	78 (35.3)	<0.0001	0.0289
>2–4	1346 (50.3)	1572 (51.2)	2387 (52.6)	927 (50.7)	101 (45.7)		
>4	704 (26.3)	954 (31.1)	1298 (28.6)	410 (22.4)	42 (19)		
Anthropometrics							
Weight (kg)	77 (68–86)	75 (68–85)	75 (68–85)	75 (66–84)	75 (68–85)	<0.0001	0.3375
Height (cm)	170 (164–175)	170 (163–175)	170 (164–175)	170 (163–175)	170 (164–175)	0.5977	0.7517
Body mass index (kg/m ²)	26.7 (24.2–29.7)	26.4 (24.1–29.1)	26.3 (24–29.1)	26 (23.8–28.8)	26.3 (23.8–29.6)	<0.0001	0.2422
Haemodynamics							
Systolic blood pressure (mmHg)	130 (120–150)	140 (120–150)	137 (120–150)	131 (120–150)	130 (110–140)	<0.0001	0.0021
Heart rate (beats/ min)	73 (62–85)	77 (66–90)	78 (68–88)	76 (65–88)	73 (62–87)	<0.0001	0.0486
Killip class							
I	2040 (76.2)	2395 (78)	3664 (80.8)	1545 (84.5)	173 (78.3)	<0.0001	<0.0001
II	527 (19.7)	566 (18.4)	741 (16.3)	239 (13.1)	35 (15.8)		
III	66 (2.5)	77 (2.5)	95 (2.1)	33 (1.8)	4 (1.8)		
IV	45 (1.7)	32 (1)	35 (0.8)	12 (0.7)	9 (4.1)		
GUSTO risk score ³⁰	61 (51–71)	61 (51–71)	60 (49–70)	57 (48–67)	60 (51–70)	<0.0001	0.1839
TIMI risk score ³¹	3 (2–5)	3 (2–5)	3 (2–5)	2 (1–4)	3 (1–5)	<0.0001	0.2709
Peak cardiac enzyme level ^b	9.1 (4.3–16.4)	8.0 (3.6–15.1)	7.6 (3.7–14.0)	5.6 (2.8–10.9)	5.3 (2.1–9.9)	<0.0001	0.108

Table 2. (Continued)

	Further ST-elevation (n=2678)	Resolution			New ST-depression (n=221)	Overall χ^2 test p-value	p-value ^a
		0–30% (n=3070)	>30–70% (n=4535)	>70% (n=1829)			
Randomized to bivalirudin	1317 (49.2)	1543 (50.3)	2232 (49.2)	953 (52.1)	109 (49.3)	0.2723	0.4340
Baseline summed ST-elevation							
2–5 mm	621 (23.2)	420 (13.7)	801 (17.7)	468 (25.6)	66 (29.9)	<0.0001	
5.5–10 mm	942 (35.2)	922 (30)	1409 (31.1)	573 (31.3)	93 (42.1)		
10.5–20 mm	793 (29.6)	1078 (35.1)	1461 (32.2)	529 (28.9)	51 (23.1)		
>20 mm	322 (12)	650 (21.2)	864 (19.1)	259 (14.2)	11 (5)		
Summed ST-elevation (mm)	9 (5.5–14)	11 (7–18.5)	10.5 (6.5–17.5)	9 (5–15)	7 (4.5–11.5)	>0.0001	0.0002
Baseline summed ST-depression in reciprocal leads							
0–0.5 mm	1088 (40.9)	1374 (45)	1702 (37.7)	540 (29.6)	61 (27.6)	<0.0001	0.3754
1–5 mm	1085 (40.8)	1138 (37.3)	1774 (39.3)	728 (40)	81 (36.7)		
5.5–10 mm	339 (12.7)	332 (10.9)	696 (15.4)	356 (19.5)	49 (22.2)		
10.5–20 mm	135 (5.1)	178 (5.8)	300 (6.6)	173 (9.5)	24 (10.9)		
>20 mm	15 (0.6)	29 (1)	43 (1)	25 (1.4)	6 (2.8)		
Summed ST-depression (mm)	1 (0–4)	1 (0–4)	2 (0–5)	3 (0–6)	3.5 (0–7.5)	<0.0001	0.1368

Values are median (interquartile range) or n (%). Total number of patients does not add up to 12,556 because 223 patients had missing or unsatisfactory tracing on 1 or more ECG leads. ^aComparing >70% resolution vs. new ST-depression. ^bPeak cardiac enzyme levels are expressed as multiple of the upper limit of normal. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Using the single lead with maximal baseline ST-elevation, mortality at 30-days was 9.1% in the 187 patients with new ST-depression and 4.8% in the 2240 patients with >70% ST-segment resolution without new ST-depression ($p=0.01$).

Figure 3a shows the relative extent of ST-resolution and 30-day mortality and Figure 3b shows the residual ST-level and 30-day mortality.

Multivariable predictors of 30-day mortality

In a multivariable analysis, including baseline summed ST-elevation, age, sex, and infarction location, new ST-depression was significantly associated with increased 30-day mortality when compared to ST-resolution >70% without ST-depression: (OR 1.82, 95% CI 1.42–4.29; Tables 4 and 5).

Tables 6 and 7 list the significant predictors for 30-day mortality when incorporating baseline variables, clinical factors, geographic region, and time to randomization in a multivariable model. For this model, the C index was 0.83. The location of the infarction, summed ST-elevation and summed ST-depression on the baseline ECG, and ST-segment changes at 60 minutes were all independent predictors. Compared to patients with >70% ST-resolution and no ST-depression, the 30-day mortality among those with new ST-depression was OR 1.77 (95% CI 0.97–3.24 compared to patients with ST-resolution 0–30% (no resolution; OR 0.67, 95% CI 0.38–1.19).

Discussion

The novel finding of this study is the prognostic significance of new ST-depression in the infarct leads following ST-resolution in patients receiving fibrinolytic therapy. A total of 221 patients (1.8% of the whole cohort and 10.8% of patients traditionally classified as having complete (>70%) ST-resolution) had ST-segment change from initial elevation to new depression in the infarct leads at 60 minutes after commencement of fibrinolytic therapy. This previously overlooked group of patients had an almost 2-fold higher 30-day mortality rate than those who achieved complete ST-resolution without new ST-depression. This finding remained significant following adjustment for baseline summed ST-elevation, age, sex, and infarct location. These are all factors that are readily available at the time of a 60-minute ECG. When a full multivariate analysis including all baseline factors, clinical factors, time to treatment, and geographic region was performed, the OR was 1.77 (95% CI 0.97–3.24).

The increased mortality was seen early within 24 hours with a trend to increased reinfarction rates and at 30 days. There was also an almost 2-fold increase in the 30-day rate of death and reinfarction. The resolution of ST-elevation suggests that epicardial and tissue reperfusion has occurred,¹⁸ consistent with our findings that infarct size, as judged by peak cardiac enzyme elevations, was similar in patients with ST-resolution and new ST-depression to those with complete ST-resolution and no new ST-depression.

Table 3. Outcomes in patients with the five different categories of ST-segment changes at 60 minutes.

	Further ST-elevation (n=2678)	Resolution			New ST-depression (n=221)	Overall χ^2 test p-value	p-value ^a
		0–30% (n=3070)	>30–70% (n=4535)	>70% (n=1829)			
Death within 30 days	330 (12.3)	358 (11.7)	361 (8.0)	77 (4.2)	18 (8.1)	<0.0001	0.0086
Death within 24 hours	138 (5.1)	135 (4.4)	134 (3)	23 (1.3)	10 (4.5)	<0.0001	0.0003
Reinfarction within 30 days	97 (3.6)	84 (2.7)	147 (3.2)	72 (3.9)	14 (6.3)	0.0149	0.0930
30-day death/reinfarction	400 (14.9)	418 (13.6)	476 (10.5)	140 (7.7)	31 (14)	<0.0001	0.0012

Values are n (%). ^aComparing >70% resolution vs. new ST-depression.

Figure 3. Bar graphs of 30-day mortality and death/reinfarction for the 2050 patients with complete ST-resolution ± new ST-depression according to ST-resolution (per 10%) (a) and residual ST-level (per 0.5 mm).

Table 4. Multivariable predictors of 30-day mortality including baseline summed ST-elevation, age, sex, infarct location, and ST-resolution.

	χ^2	df	p-value
Summed ST-elevation at baseline	74.0	3	<0.0001
Resolution of summed ST-elevation	93.5	4	<0.0001
Age	456.5	1	<0.0001
Female	62.7	1	<0.0001
Location of infarction	8.7	1	0.0032

Likelihood ratio $\chi^2=1063.7$, df=10, $p<0.0001$; C-statistics=0.77; $R^2=18\%$; Hosmer–Lemeshow goodness-of-fit $\chi^2=6.46$, df=8, $p=0.5965$. ST-resolution was analysed as five categorical levels for the whole cohort as shown in Table 5.

Table 5. Odds ratios for 30-day mortality with each independent ECG predictor including baseline summed ST-elevation, age, sex, infarct location, and ST-resolution.

	OR (95% CI)	p-value
Summed baseline ST-elevation		
2–5 mm	1.00	<0.0001
5.5–10 mm	1.10 (0.87–1.33)	
10.5–20 mm	1.55 (1.25–1.91)	
>20 mm	2.36 (1.85–3.00)	
ST-segment change by 60 minutes		<0.0001
I. Reference group >70% resolution		
Further ST-elevation	3.14 (2.41–4.10)	
0–30% resolution	2.60 (2.00–3.38)	
>30–70% resolution	1.82 (1.40–2.36)	
>70% resolution	1.00	
New ST-depression	1.82 (1.42–2.29)	
II. Reference group 0–30% resolution		
Further ST-elevation	1.21 (1.02–1.43)	
0–30% resolution	1.00	
>30–70% resolution	0.70 (0.60–0.82)	
>70% resolution	0.38 (0.30–0.50)	
New ST-depression	0.95 (0.57–1.59)	

The new ST-depression likely reflects ongoing ischaemia, such as from an infarct related artery lesion with a tight residual flow-limiting stenosis and/or clot micro-embolization plugging the microvasculature. Alternatively, ST-depression could have pre-existed before the AMI and with successful tissue reperfusion the ST-segments returned to the previous 'baseline' level. Both potential explanations for ongoing ischaemia are consistent with the increased 30-day incidence of combined death and reinfarction rates and the increased mortality within 24 hours as compared with patients with complete resolution without ST-depression.

The findings are very relevant as fibrinolysis is the most common form of reperfusion used worldwide, with increasing numbers of patients requiring treatment for MI in developing countries,³ particularly India where the prevalence of MI is increasing dramatically.¹⁹

This large-scale ST-segment resolution study confirms previous findings. On the baseline ECG, the total amount of ST-elevation and the total amount of reciprocal ST-depression both reflecting potential infarct size had independent prognostic value.²⁰ Also early ST-change at 60 minutes after commencing fibrinolytic therapy added to baseline ST-changes in predicting mortality⁴ by indicating the success or failure of reperfusion, both in the epicardial artery and at the tissue level.¹⁸ The angiographic HERO-1 study found with continuous ST-monitoring among those with documented patent infarct-arteries an association between earlier ST-resolution and better infarct-zone wall motion at 48 hours, probably reflecting the result of better tissue reperfusion.²¹

In the current analysis, up to five possible categories of ST-change (including further ST-elevation and new ST-depression) were used thereby incorporating the full spectrum of possible ST-changes, when assessing the

Table 6. Multivariable predictors of 30-day mortality, including baseline variables, clinical factors, geographic region, time to randomization, summed ST-elevation, age, sex, infarct location, and ST-resolution.

	χ^2	df	p-value
Summed ST-elevation at baseline	49.3	3	<0.0001
Change of summed ST-elevation	83.5	4	<0.0001
Age	67.5	1	<0.0001
Female	45.8	1	<0.0001
Heart rate	65.1	1	<0.0001
Systolic blood pressure	72.4	1	<0.0001
Killip class	50.1	3	<0.0001
Age/Killip class interaction	27.5	3	<0.0001
Region of recruitment	21.4	4	0.0003
Previous infarction	12.8	1	0.0003
Time to randomization	8.8	1	0.003
Previous angina	5.5	1	0.02
Diabetes	5.7	1	0.02
Location of infarction	8.6	1	0.003
Summed ST-depression at baseline	36.8	4	<0.0001

Likelihood ratio $\chi^2=1656.5$, $df=30$, $p<0.0001$; C-statistics=0.83; $R^2=27\%$; Hosmer–Lemeshow goodness-of-fit $\chi^2=12.86$, $df=8$, $p=0.1167$. The likelihood ratio χ^2 statistics was 1656 for the model containing all clinical and ECG predictors, and 1543 for the model containing only the clinical predictors. ST-resolution was analysed as five categorical levels for the whole cohort.

Table 7. Odds ratios for 30-day mortality with each independent ECG predictor, including baseline variables, clinical factors, geographic region, time to randomization, summed ST-elevation, age, sex, infarct location, and ST-resolution.

	OR (95% CI)	p-value
Summed baseline ST-elevation		<0.0001
2–5 mm	1.00	
5.5–10 mm	1.06 (0.85–1.33)	
10.5–20 mm	1.52 (1.21–1.91)	
>20 mm	2.14 (1.65–2.79)	
Summed baseline ST-depression		<0.0001
0–0.5	1.00	
1–5 mm	1.36 (1.16–1.59)	
5.5–10 mm	1.32 (1.05–1.67)	
10.5–20 mm	2.11 (1.58–2.82)	
>20 mm	3.24 (1.81–5.79)	
ST-segment change by 60 minutes		<0.0001
I. Reference group >70% resolution		
Further ST-elevation	3.08 (2.34–4.07)	
0–30% resolution	2.63 (2.00–3.46)	
>30–70% resolution	1.82 (1.39–2.38)	
>70% resolution	1.00	
New ST-depression	1.77 (0.97–3.24)	
II. Reference group 0–30% resolution		
Further ST-elevation	1.17 (0.98–1.40)	
0–30% resolution	1.00	
>30–70% resolution	0.69 (0.58–0.82)	
>70% resolution	0.38 (0.29–0.50)	
New ST-depression	0.67 (0.38–1.19)	

relationship to 30-day mortality, which was the primary end-point of the HERO-2 study. This is a more rigorous approach than using either three levels (with 30 and 70% ST-resolution cut-points) or two levels (with 50%

ST-resolution cut-point) of ST-changes. ST-elevation re-elevation occurred in a fifth of patients, and their 30-day mortality was numerically higher than those with no ST-resolution (OR 1.17, 95% CI 0.98–1.40).

Guideline recommendations for 'routine' angiography after successful fibrinolysis have been evolving. The 2007 update of the ACC/AHA guidelines recommend coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation <50% resolved after 90 minutes following initiation of fibrinolytic therapy in the lead showing the worst initial elevation) and there is a moderate or large area of myocardium at risk (anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression): Class IIa, level of evidence B.²²

The recent 2010 guideline from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery²³ recommends angiography within the first 24 hours following fibrinolytic therapy. However rapid transfer to a PCI centre for rescue angioplasty is recommended to be considered if ST-segment resolution is <50% based on studies showing the value of rescue angioplasty.^{24,25} Given that we found an increased 24-hour mortality risk among those with new ST-depression compared to those with otherwise complete ST-resolution, angiography and revascularization should also be considered among patients with new ST-depression even though resolution has occurred.

ST-segment depression at baseline in patients with STEMI undergoing primary PCI has attracted recent interest. The Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) investigators found resolution of ST-segment depression after primary PCI to be a good prognostic marker after primary PCI.²⁶ However, the APEX-AMI study did not address the development of new ST-depression after ST-segment resolution. ST-depression in patients with STEMI, particularly for patients with inferior MI, could be due to reciprocal changes from infero basal²⁷ or lateral involvement not fully captured by the standard 12-lead ECG,²⁸ thus explaining the favourable prognosis of ST resolution after primary PCI. The current report describes the new observation of infarct lead ST-segment levels changing from elevation to depression after fibrinolytic therapy and the relationship to increased mortality. It is unknown if this phenomenon is also seen after primary PCI.

Limitations

This study, which prospectively specified that ECGs be performed at baseline and at 60 minutes after beginning fibrinolytic therapy, was a post-hoc analysis in respect of analyses of new ST-depression. The study is limited by the fact that ECGs after 60 minutes were not collected. It is, thus, uncertain as to how new ST-depression might have evolved. Also we did not analyse the relationship between left ventricular hypertrophy and new ST-depression.

The study was in a cohort of patients receiving fibrinolysis with low rates of early angiography and angiographic

findings are unknown. Also funding for mechanistic angiographic substudies was not available. In addition, the frequency of post-infarction angina was not collected. The statistical analysis was not corrected for multiple comparisons.

Conclusion

New ST-depression following complete ST-resolution after reperfusion with fibrinolysis is a novel and important marker for identifying patients at high risk of 30-day mortality. There is a need for further studies to confirm the prognostic value of our findings.

New ST-depression, likely reflecting ongoing ischaemia, identifies patients at higher risk than patients with otherwise complete ST-resolution. This additional parameter should be used in analysing ST-segment changes after patients have received fibrinolytic therapy and may be useful in triaging patients at high risk to early angiography and revascularization.

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Conflict of interest

HDW has received research grants from Alexion, Sanofi-Aventis, Eli Lilly, Merck Sharpe & Dohme, The Medicines Company, NIH, Neuren, Glaxo Smith Kline, Pfizer, Roche, Fournier Janssen Cilag, Johnson & Johnson, Proctor & Gamble, and Schering Plough, honoraria from Sanofi Aventis and The Medicines Company, and consultancy fees from The Medicines Company, Neuren Pharma, Glaxo Smith Kline, CSL, Bayer, and Sanofi Aventis.

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The remaining authors have no conflict of interests to declare in connection with this work.

References

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients

- With Acute Myocardial Infarction). *Circulation* 2004; 110: 588–636.
2. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29: 2909–2945.
 3. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; 367: 1747–1757.
 4. Wong CK, de la Barra SL and Herbison P. Does ST resolution achieved via different reperfusion strategies (fibrinolysis vs percutaneous coronary intervention) have different prognostic meaning in ST-elevation myocardial infarction? A systematic review. *Am Heart J* 2010; 160: 842–848.
 5. French JK, Andrews J, Manda SOM, et al. Early ST-segment recovery, infarct artery blood flow, and long-term outcome after acute myocardial infarction. *Am Heart J* 2002; 143: 265–271.
 6. Schroder K, Wegscheider K, Zeymer U, et al. Extent of ST-segment deviation in a single electrocardiogram lead 90 min after thrombolysis as a predictor of medium-term mortality in acute myocardial infarction. *Lancet* 2001; 358: 1479–1486.
 7. Schroder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. *Circulation* 2004; 110: e506–e510.
 8. Buller CE, Fu Y, Mahaffey KW, 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.
 9. The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 2001; 358: 1855–1863.
 10. Wong CK, Stewart RAH, Gao W, et al. Prognostic differences between different types of bundle branch block during the early phase of acute myocardial infarction: insights from the Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial. *Eur Heart J* 2006; 27: 21–28.
 11. Wong CK, Gao W, Stewart RA, et al. The prognostic meaning of the full spectrum of aVR ST segment changes in acute myocardial infarction. *Eur Heart J* 2011; 33: 384–392.
 12. Wong CK, French JK, Aylward PE, et al. Patients with prolonged ischemic chest pain and presumed-new left bundle branch block have heterogeneous outcomes depending on the presence of ST-segment changes. *J Am Coll Cardiol* 2005; 46: 29–38.
 13. Wong CK, Gao W, Raffel OC, et al. Initial Q waves accompanying ST-segment elevation at presentation of acute myocardial infarction and 30-day mortality in patients given streptokinase therapy: an analysis from HERO-2. *Lancet* 2006; 367: 2061–2067.
 14. Wong CK, Gao W, Stewart RA, et al. Risk stratification of patients with acute anterior myocardial infarction and right bundle-branch block: importance of QRS duration and early ST-segment resolution after fibrinolytic therapy. *Circulation* 2006; 114: 783–789.
 15. Wong CK, Gao W, Stewart RAH, et al. Relationship of QRS duration at baseline and changes over 60 minutes after fibrinolysis to 30-day mortality with different locations of ST elevation myocardial infarction: results from the HERO-2 trial. *Heart* 2009; 95: 276–282.
 16. Wong CK, Gao W, Stewart RAH, et al. aVR ST elevation: an important but neglected sign in ST elevation acute myocardial infarction. *Eur Heart J* 2010; 31: 1845–1853.
 17. Wong CK, Gao W, Stewart RA, et al. Prognostic value of lead V1 ST elevation during acute inferior myocardial infarction. *Circulation* 2010; 122: 463–469.
 18. Angeja BG, Gunda M, Murphy SA, et al. TIMI myocardial perfusion grade and ST segment resolution: association with infarct size as assessed by single photon emission computed tomography imaging. *Circulation* 2002; 105: 282–285.
 19. Xavier D, Pais P, Devereaux PJ, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet* 2008; 371: 1435–1442.
 20. Willems JL, Willems RJ, Willems GM, et al. Significance of initial ST segment elevation and depression for the management of thrombolytic therapy in acute myocardial infarction. European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator. *Circulation* 1990; 82: 1147–1158.
 21. Andrews J, Straznicki IT, French JK, et al. ST-segment recovery adds to the assessment of TIMI 2 and 3 flow in predicting infarct wall motion after thrombolytic therapy. *Circulation* 2000; 101: 2138–2143.
 22. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008; 51: 210–247.
 23. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010; 31: 2501–2555.
 24. Gershlick AH, Stephens-Lloyd A, Hughes S, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005; 353: 2758–2768.
 25. Wijeyesundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2007; 49: 422–430.
 26. Tjandrawidjaja MC, Fu Y, Westerhout CM, et al. Resolution of ST-segment depression: a new prognostic marker in ST-segment elevation myocardial infarction. *Eur Heart J* 2010; 31: 573–581.
 27. Bayes de Luna A, Wagner G, Birnbaum Y, et al. A new terminology for left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging: a statement for healthcare professionals from a committee appointed by the International Society for Holter and Noninvasive Electrocardiography. *Circulation* 2006; 114: 1755–1760.
 28. Wong CK. Usefulness of leads V7, V8, and V9 ST elevation to diagnose isolated posterior myocardial infarction. *Int J Cardiol* 2011; 146: 467–469.