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A strategy of using enoxaparin as adjunctive antithrombin therapy reduces death and recurrent myocardial infarction in patients who achieve early ST-segment resolution after fibrinolytic therapy: the ExTRACT-TIMI 25 ECG study

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Aims To determine the relationship between a strategy of enoxaparin (ENOX), early ST-segment resolution (STRes), and clinical outcomes on patients with ST-segment elevation myocardial infarction (STEMI) after fibrinolysis.

Methods and results Baseline and 180 min ECGs were analysed in 3208 of the 20 479 patients in the ExTRACT-TIMI 25 trial, which randomifzed patients with STEMI to ENOX vs. unfractionated heparin (UFH) as adjunctive therapy. STRes was defined as complete (70%), partial (30–70%), or none (<30%). There was no evidence for a difference in STRes between the groups assigned to the ENOX or UFH (median 69.4 vs. 67.2%; $P = 0.13$). Among patients with complete STRes ($n = 1100$), ENOX significantly reduced death or non-fatal recurrent MI at 30 days when compared with UFH (4.4 vs. 9.9%; OR_{adj} 0.39; $P < 0.001$), whereas there was no difference in patients with only partial or no STRes [14.2 vs. 12.5%; OR_{adj} 1.0; $P = 0.98$ ($n = 368$) and 16.2 vs. 15.9%; OR_{adj} 1.0; $P = 0.97$ ($n = 830$), P for interaction = 0.008].

Conclusion When compared with UFH, a strategy of ENOX significantly reduces death or non-fatal recurrent MI in patients who achieved complete STRes, but not in patients with less STRes. These data suggest that a strategy of ENOX improves outcomes by preventing re-occlusion in patients achieving initial successful reperfusion after fibrinolytic therapy rather than by facilitating initial reperfusion.

Introduction

Treatment of patients presenting with ST-segment elevation myocardial infarction (STEMI) centers on achieving early coronary reperfusion and maintaining arterial patency.[1] The resolution of ST-segment elevation (STRes) on serial ECGs is a simple non-invasive surrogate for epicardial and myocardial reperfusion.[2–6] Patients who achieve complete STRes have an improved short- and long-term prognosis.[3,7–10] Fibrinolysis, the most frequently utilized reperfusion strategy world-wide, achieves reperfusion as detected by angiography and complete STRes on ECG in more than half of the patients.[11–13] Re-occlusion of the infarct artery after initial successful reperfusion, leading to a recurrent myocardial infarction (MI), is associated with an almost three-fold increase in mortality.[14–17] Therefore, maintaining patency of the infarct-related artery after fibrinolysis may be expected to reduce adverse clinical outcomes, in particular, among patients who achieved early patency.

In the ExTRACT-TIMI 25 trial, patients with STEMI were treated with fibrinolysis. An antithrombin strategy of enoxaparin (ENOX) administered for the duration of hospitalization resulted in an improved net clinical benefit (death, non-fatal recurrent MI, or major bleeding) when compared with the standard strategy of unfractionated heparin (UFH) administered for 48 h.[18] This benefit may have been mediated by two potential mechanisms. First, as suggested by smaller studies,[19] the combined anti-Xa and anti-IIa activity of ENOX may facilitate fibrinolysis and improve the

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rate of early reperfusion. Alternatively, a strategy of ENOX may not improve initial fibrinolysis, but over the ensuing days may maintain patency in arteries that were initially reperfused. The ExTRACT-TIMI 25 ECG study was carried out in order to explore the mechanisms using early STRes as a marker of reperfusion after fibrinolysis and examining the clinical outcomes of enhanced antithrombotic treatment according to reperfusion status.

Methods

Patient selection and procedures

In the intention-to-treat cohort of the ExTRACT-TIMI 25 Trial, 20 479 patients who presented within 6 h before randomization, had ST-segment elevation of at least 0.1 mV in two limb leads or of 0.2 mV in at least two contiguous precordial leads or had left bundle-branch block, and received an approved fibrinolytic drug were randomly assigned in a 1:1 ratio to a strategy of ENOX given for the duration of hospitalization or weight-based UFH given for at least 48 h in a double-blind, double-dummy fashion. The dosing regimen has been previously described.[18,20] As part of a pre-specified substudy, ECGs were obtained in 3238 patients at baseline at the onset of fibrinolytic therapy and again at 180 min after the administration of fibrinolysis in consecutive patients at selected centers.

Outcomes

Each ECG was analysed by two investigators at the TIMI ECG Core Laboratory, who were blinded to study treatment and outcomes, using a hand-held electronic caliper (Fowler Inc., Newton, USA). The ST-segment deviation was measured 20 ms after the J point in all leads. For anterior MI, the sum of ST-elevations in leads V1 to V6, I, and aVL, was added to the sum of ST-depressions in leads II, III, and aVF. For inferior MI, the sum of ST-elevations in leads II, III, aVF (and I, aVL, V5, and V6, if present) was added to the sum of ST-depressions in leads V1–V4. Reciprocal ST-depression was used only in leads with $\geq$0.1 mV of ST-depression at baseline.[7,11] The percent resolution of ST-segment deviation from baseline to 180 min was calculated, and categorized according to a previously described three-component definition: complete ($\geq$70%) STRes, partial (30–70%) STRes, and no ($<$30%) STRes.[7] To meet the criteria for a recurrent MI, the MI must be a clinical event distinct from the index event. The criteria for recurrent MI in ExTRACT-TIMI 25 are adapted from the American College of Cardiology/American Heart Association guidelines for management of patients with STEMI.[1,20] Patients were followed for 30 days for clinical outcomes.

Statistical analysis

For the comparison of baseline characteristics between treatment groups, a χ^2 test was performed for categorical variables and a Wilcoxon rank-sum test for continuous variables. Differences were considered significant if the two-sided *P*-value was $<$0.05. To examine the relationship between assignment to treatment strategy and outcomes according to the presence of reperfusion at 180 min, patients were stratified according to STRes category. All comparisons between treatment groups were performed with a logistic-regression model that included terms for the treatment strategy group, TIMI risk score (TRS) for STEMI, the type of fibrinolytic agent used (fibrin-specific vs. non-fibrin-specific), time from symptom onset to fibrinolysis, and the anatomical location of the infarct. The TRS for STEMI is a weighted integer score based on eight clinical risk indicators that can be easily ascertained at presentation. It has been validated in several large patient populations.[21,22] Patients received three points for age $\geq$75 years, systolic BP$<$100 mmHg, two points for age 64–74, heart rate $>$100/min, Killip Class II–IV, and one point for a history of diabetes, hypertension, or angina, weight $<$67 kg, anterior MI or LBBB, or $>$4 h delay from symptom onset to reperfusion therapy. The interactions between treatment strategy, STRes category, and outcomes were analysed using the multivariable model described above with the addition of an interaction term of treatment strategy $\times$ STRes category. Statistical tests for significance of interactions were performed by comparing the likelihood ratios between the logistic regression models with and without the interaction terms. There was $>$90% power to detect a 10% relative difference in STRes as a continuous variable between treatment groups and $>$90% power to detect a 15% difference in the rate of achieving complete STRes at 180 min with an α level of 0.05. There were no corrections for multiple comparisons.

Results

Baseline characteristics and clinical outcomes of both patients who participated in the ExTRACT-TIMI 25 ECG substudy ($n = 3208$) when compared with the remainder of the ExTRACT-TIMI 25 patient population ($n = 17\,241$) and those patients in the ECG Substudy with baseline and 180 min ECGs valid for STRes calculation ($n = 2298$) when compared with patients having invalid ECGs ($n = 910$) are presented in *Tables 1* and *3*. Patients were excluded from analysis if: the baseline ECG was more than 10 min after fibrinolysis or the 180 min ECG was more than 20 min from the pre-specified 180 min time-point ($n = 503$); there was insufficient ST-deviation on baseline ECG ($n = 217$); a left bundle-branch block, accelerated idioventricular rhythm, or paced rhythm was present ($n = 74$), or if either ECG was not performed or not interpretable ($n = 116$). There were no important differences in baseline characteristics and initial therapy between the two treatment groups in patients with ECGs valid for STRes calculation (*Table 2*).

ST-segment resolution and outcomes

The degree of STRes was strongly associated with 30-day mortality (*Figure 1A*; *Table 3*). In contrast, there was no clear relationship between recurrent non-fatal MI and STRes. Patients with partial STRes experienced the highest, though not a statistically different, rate of non-fatal recurrent MI (*Figure 1B*).

Effect of enoxaparin on ST-segment resolution at 180 min

The median STRes at 180 min was 69.1% in the ENOX strategy group and 67.1% in the UFH strategy group ($P = 0.32$). The distribution of STRes category achieved at 180 min after fibrinolysis was also similar in the ENOX and UFH groups (complete STRes–48.6 vs. 46.0%, partial STRes–34.8 vs. 35.6%, and no STRes–16.8 vs. 18.4%).

Treatment effect of enoxaparin according to ST-segment resolution category

Among patients with complete STRes at 180 min ($n = 1100$), treatment with ENOX was associated with a significant reduction in death or non-fatal recurrent MI at 30 days when compared with UFH (4.4 vs. 9.9%, OR_{adj} 0.39, 95% CI 0.24, 0.65, $P < 0.001$). However, the rate of death or non-fatal recurrent MI was similar in the ENOX and UFH groups

Table 1 Baseline characteristics and initial treatment in the ECG and non-ECG cohort of ExTRACT-TIMI 25 and among patients in the ECG cohort with and without ECG valid for calculating ST-resolution at 180 min

	Entire ExTRACT-TIMI 25 cohort ($n = 20\,449$)		ECG cohort ($n = 3208$)	
	Non-ECG Cohort $n = 17\,241$	ECG cohort $n = 3208$	Invalid ECGs for STRes $n = 910$	Valid ECGs for STRes $n = 2298$
Baseline characteristics				
Age (years), median (IQR)	60 (51, 69)	57 (50, 68)*	58 (51, 70)	57 (49, 67)*
>75-years-old	2194 (12.7)	338 (10.5)*	121 (13.3)	217 (9.4)*
Male, no. (%)	13 191 (76.4)	2505 (78.1)*	705 (77.5)	1800 (78.3)
White race, no. (%)	14 817 (85.8)	3038 (94.7)*	833 (91.5)	2205 (96.0)*
Weight (kg), median (IQR)	76 (68, 85)	77 (70, 86)*	78 (70, 89)	77 (70, 85)
Hypertension, no. (%)	7608 (44.6)	1298 (40.9)*	335 (37.2)	963 (42.4)*
Hyperlipidaemia, no. (%)	2529 (18.6)	388 (16.6)*	166 (22.8)	222 (13.8)*
Current smoker, no. (%)	8038 (46.6)	1654 (51.6)*	408 (44.9)	1246 (54.2)*
Diabetes, no. (%)	2702 (15.8)	358 (11.3)*	120 (13.4)	238 (10.4)*
Prior myocardial infarction, no. (%)	2219 (12.9)	440 (13.8)	132 (14.6)	308 (13.5)
Prior angina, no. (%)	4745 (27.7)	970 (30.5)*	242 (26.8)	728 (31.9)
Prior percutaneous coronary intervention, no. (%)	549 (3.2)	111 (3.5)	37 (4.1)	74 (3.2)
Index presentation and treatment				
Anterior infarct location, no. (%)	7476 (43.6)	1457 (45.8)*	309 (34.8)	1148 (50.0)*
Long-term treatment with aspirin, no. (%)	2334 (13.5)	418 (13.1)	141 (15.6)	277 (12.1)*
Creatinine clearance (mL/min), median (IQR)	81.7 (63.0, 104.3)	83.6 (65.1, 105.0)*	84.0 (64.5, 104.6)	83.5 (65.5, 105.0)
Killip Class ≥2, no. (%)	1994 (11.6)	298 (9.3)	103 (11.3)	195 (8.5)
TIMI risk score >3, no. (%)	6195 (36.2)	1028 (32.3)*	289 (32.4)	739 (32.3)
Time for symptom onset to start of fibrinolytic therapy (h), median (IQR)	3.2 (2.2, 4.3)	3.1 (2.2, 4.2)*	3.1 (2.1, 4.2)	3.1 (2.2, 4.2)
Fibrinolytic therapy, no. (%)				
Tenecteplase	3737 (21.7)	249 (7.8)	124 (13.6)	125 (5.4)
Alteplase	8892 (51.7)	2283 (71.2)	457 (50.3)	1826 (79.5)
Reteplase	912 (5.3)	210 (6.6)	117 (12.9)	93 (4.1)
Streptokinase	3674 (21.3)	465 (14.5)	211 (23.2)	254 (11.1)
Time from fibrinolytic therapy to study drug administration				
Study drug given before lytic	64 (0.4)	4 (0.1)*	3 (0.3)	1 (0.1)*
0–15 min	1980 (11.6)	376 (11.8)	77 (8.6)	299 (13.0)*
15–30 min	14 599 (85.3)	2682 (85.1)	721 (80.7)	1961 (85.5)*
>30 min	472 (2.8)	124 (3.9)	92 (10.3)	32 (1.4)*
Cardiac medications during hospitalization, no. (%)				
Aspirin	16 380 (94.8)	3096 (96.5)*	862 (94.7)	2234 (97.2)*
Clopidogrel	4924 (28.4)	801 (25.0)*	280 (30.8)	521 (22.7)*
Beta-blockers	14 642 (84.8)	2914 (90.8)*	797 (87.6)	2117 (92.1)*
ACE-inhibitors or angiotensin-receptor blockers	13 415 (78.8)	2702 (84.2)*	722 (79.3)	1980 (86.2)*
Statins	12 101 (70.0)	2126 (66.3)*	658 (72.3)	1468 (36.9)*
PCI during index hospitalization, no. (%)	3348 (32.2)	569 (17.7)*	208 (22.9)	361 (15.7)*

*$P = 0.05$.

in the cohorts of patients with only partial STRes ($n = 830$) or no STRes ($n = 368$) at 180 min (14.2 vs. 12.5%, OR_{adj} 1.0, 95% CI 0.66, 1.5, $P = 0.98$ for partial STRes and 16.2 vs. 15.9%, OR_{adj} 1.0, 95% CI 0.57, 1.8, $P = 0.97$ for no STRes, P for interaction of STRes and outcome = 0.008) (*Figure 2*). A similar pattern of reduction in death and non-fatal recurrent MI in patients with complete STRes was seen by Day 8 after fibrinolytic therapy (*Figure 3*) and when comparing death or recurrent non-fatal MI separately (*Figures 2* and *3*).

The cumulative incidence of non-fatal recurrent MI among subjects who achieved complete STRes is shown in *Figure 4*. The rate of non-fatal recurrent MI increased substantially after Day 2 in patients of the UFH group but demonstrates a more gradual increase in the ENOX group.

Discussion

In this study, we provide several important insights into the mechanism by which a strategy of ENOX, given with fibrinolytic therapy in patients with STEMI and administered for the duration of hospitalization, reduces death or non-fatal recurrent MI. We observed that in comparison with a strategy of UFH, ENOX did not augment ST-segment resolution at 180 min after fibrinolysis. However, this strategy of ENOX administration was associated with a substantially lower incidence of death or recurrent MI in patients who exhibited 'complete' ST-segment resolution at 180 min after fibrinolysis. These findings suggest that ENOX does not facilitate reperfusion as assessed by STRes at 180 min but does significantly reduce the rate of death

Table 2 Baseline characteristics and initial treatment in patients with ECGs valid for ST resolution calculation

	Unfractionated heparin ($n = 1134$)	Enoxaparin ($n = 1164$)
Baseline characteristics		
Age (years), median (IQR)	57 (49, 67)	57 (50, 67)
>75-years-old	118 (10.4)	99 (8.5)
Male, no. (%)	876 (77.3)	924 (79.4)
White race, no. (%)	1093 (96.4)	110 (95.5)
Weight (kg), median (IQR)	77 (70, 85)	77 (69, 86)
Hypertension, no. (%)	466 (41.4)	497 (43.4)
Hyperlipidaemia, no. (%)	106 (13.3)	116 (14.3)
Current smoker, no. (%)	623 (54.9)	623 (53.5)
Diabetes, no. (%)	122 (10.8)	116 (10.0)
Prior myocardial infarction, no. (%)	147 (13.1)	161 (13.9)
Prior angina-no. (%)	361 (32.0)	367 (31.9)
Prior percutaneous coronary intervention, no. (%)	40 (3.5)	34 (2.9)
Index presentation and treatment		
Anterior infarct location, no. (%)	561 (49.5)	587 (50.5)
Long-term treatment with aspirin, no. (%)	139 (12.3)	138 (11.9)
Creatinine clearance (mL/min), median (IQR)	83.5 (65.2, 103.4)	83.6 (65.8, 106.2)
Killip Class ≥2, no. (%)	84 (7.4)	111 (9.5)
TIMI Risk Score >3, no. (%)	350 (31.0)	389 (33.5)
Time from symptom onset to start of fibrinolytic therapy (h), median (IQR)	3.1 (2.3, 4.2)	3.0 (2.2, 4.2)
Fibrinolytic therapy, no. (%)		
Tenecteplase	58 (5.1)	67 (5.8)
Alteplase	906 (79.9)	920 (79.0)
Reteplase	49 (4.3)	44 (3.8)
Streptokinase	121 (10.7)	133 (11.4)
Time from fibrinolytic therapy to study drug administration		
Study drug given before lytic	1 (0.1)	0 (0)
0–15 min	145 (12.8)	154 (13.3)
15–30 min	967 (85.5)	994 (85.5)
>30 min	18 (1.6)	14 (1.2)
Cardiac medications during hospitalization, no. (%)		
Aspirin	1103 (97.3)	1131 (97.2)
Clopidogrel	255 (22.5)	266 (22.9)
Beta-blockers	1043 (92.0)	1074 (92.3)
ACE-inhibitors or angiotensin-receptor blockers	970 (85.5)	1010 (86.8)
Statins	735 (64.8)	733 (63.0)
PCI during index hospitalization, no. (%)	163 (14.4)	198 (17.0)

P-values for all comparisons are >0.05.

and non-fatal recurrent MI when compared with UFH only among those subjects who do achieve early STRes with fibrinolysis. Thus, our data are consistent with the hypothesis that when compared with a strategy of UFH, a strategy of ENOX given for the duration of hospitalization improves clinical outcomes by preventing re-occlusion rather than by facilitating reperfusion as detected by ECG at 180 min.

The clinical benefit observed in this study supports the known pharmacological actions of ENOX, a potent antithrombin with anti-Xa and anti-IIa activity that provides stable levels of anticoagulation but does not have intrinsic fibrinolytic activity. The absence of a difference between ENOX and UFH in the rates of reperfusion as detected by STRes at 180 min after fibrinolysis is therefore not unexpected and consistent with previous trials that compared STRes in patients with ENOX and UFH.[23,24] One trial that compared ENOX vs. placebo in patients receiving streptokinase, did show improved early STRes with ENOX, which suggests that antithrombins may at least potentiate non-fibrin-specific fibrinolysis when compared with no adjunctive anticoagulation.[19] However, our results do not suggest that there is a relative advantage of ENOX over UFH in facilitating reperfusion as detected by STRes at 180 min among patients treated with fibrinolysis.

The significant and early reduction in death or recurrent MI observed with the ENOX strategy in ExTRACT-TIMI 25 among patients who achieved early STRes may have been the result of the longer duration of treatment with ENOX as well as from the more potent antithrombin activity of ENOX compared with UFH. In the ExTRACT-TIMI 25 trial, ENOX was by design administered until hospital discharge or Day 8, while UFH was given for the guideline recommended 48 h.[1] In the ECG study of ExTRACT-TIMI 25, there is a striking increase in the rate of recurrent MI after Day 2 after UFH was stopped, among patients who achieved complete STRes after fibrinolysis (*Figure 4*). This increase in recurrent MI in the UFH group may be the consequence of 'heparin-rebound' which prompted acute re-occlusion of arteries that were initially reperfused with fibrinolytic therapy and maintained patent while on UFH.

However, the termination of ENOX was not associated with a similar rebound. This may be due to the enhanced anti-Xa activity of ENOX preventing thrombin generation, the slow clearance of anti-Xa activity when compared with anti-IIa activity, or because the longer duration of therapy may have permitted the culprit lesion to passivate and become less thrombogenic. The reliable and prolonged antithrombotic therapy of ENOX in the days after fibrinolysis, when the risk of recurrent thrombosis is greatest, appears to be how ENOX exerts important clinical benefit. Importantly, in the main ExTRACT-TIMI 25 trial, ENOX also reduced death or non-fatal recurrent MI within the first 48 h after fibrinolysis when the great majority of the 20 479 patients were receiving either ENOX or UFH.[18] The cohort of patients in the ECG study of ExTRACT-TIMI 25 is likely too small have detected a similar benefit of ENOX within the first 48 h.

The relatively low rate of recurrent ischaemic events observed in patients with successful early re-perfusion after fibrinolysis treated with a strategy of ENOX supports the potential role for a pharmaco-invasive approach in patients with STEMI where patients can be treated very early with fibrinolytic therapy. If there is successful reperfusion as detected by STRes, they can undergo a subsequent, non-urgent catheterization with potent antithrombotic and antiplatelet pre-treatment.[25]

Limitations

There are several limitations to this study. Patients did not undergo immediate angiography to confirm successful or

Table 3 Clinical outcomes

Outcome at 30 days	Entire ExTRACT-TIMI 25 cohort ($n = 20\,449$)		ECG cohort ($n = 3208$)		ECG cohort in whom ST-segment resolution could be calculated ($n = 2298$)		
	Non-ECG cohort ($n = 17\,241$)	ECG cohort ($n = 3208$)	Invalid ECGs for ST-segment resolution ($n = 910$)	Valid ECGs for ST-segment resolution ($n = 2298$)	No ST-segment resolution ($n = 368$)	Partial ST-segment resolution ($n = 830$)	Complete ST-segment resolution ($n = 1100$)
Death	1266 (7.3)	207 (6.5)	69 (7.6)	138 (6.0)	44 (12.0)	63 (7.6)	31 (2.8)**
Non-fatal recurrent MI	618 (3.6)	149 (4.6)*	40 (4.4)	109 (4.7)	15 (4.1)	48 (5.8)	46 (4.2)
Death/non-fatal recurrent MI	1884 (10.9)	356 (11.1)	109 (12.1)	247 (10.7)	59 (16.0)	111 (13.4)	77 (7.0)**
TIMI bleeds							
Major	292 (1.7)	57 (1.8)	16 (1.8)	41 (1.8)	8 (2.2)	18 (2.2)	15 (1.4)
Minor	364 (2.1)	80 (2.5)	26 (2.9)	54 (2.4)	6 (1.6)	22 (2.7)	26 (2.4)
Major/Minor	645 (3.8)	134 (4.2)	40 (4.5)	94 (4.1)	14 (3.8)	40 (4.8)	40 (3.6)

All other comparisons are non-significant.
*$P = 0.003$.
**$P < 0.001$.

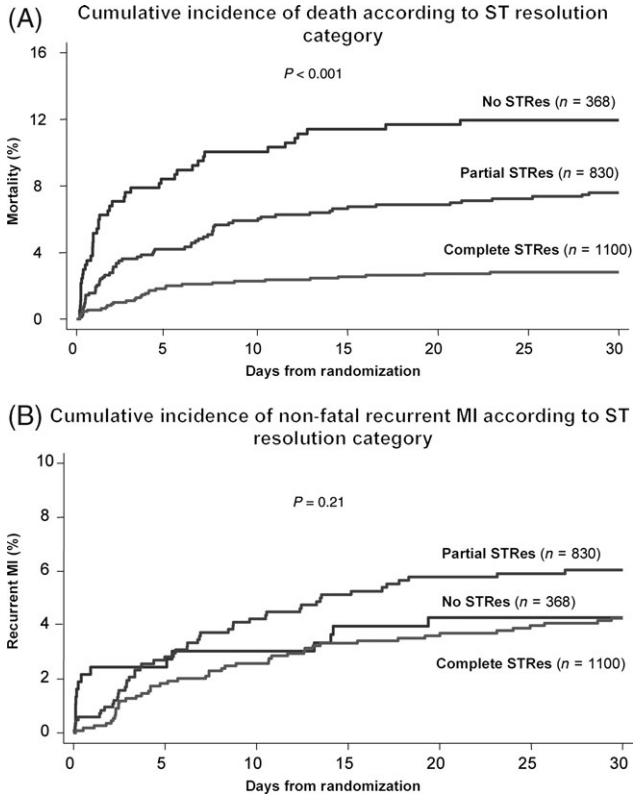

Figure 1 Cumulative incidence of death (*A*) and non-fatal recurrent myocardial infarction (MI) (*B*) according to ST-segment resolution (STRes) at 180 min.

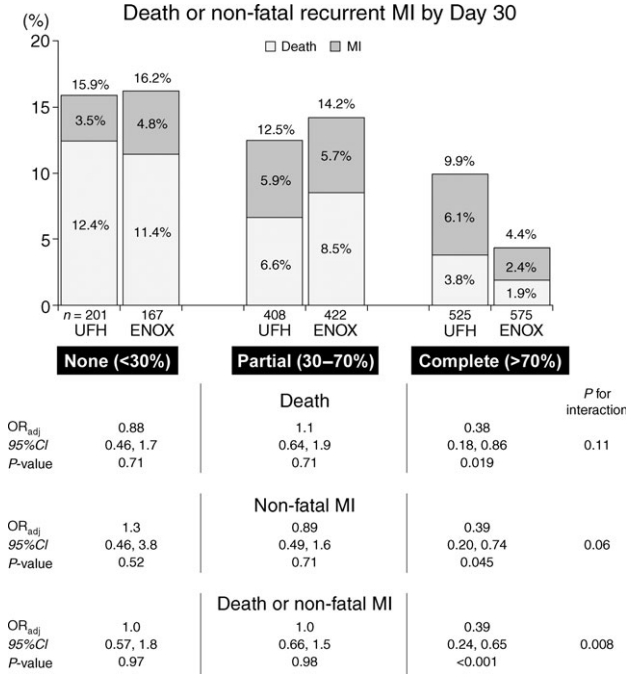

Figure 2 The rates of the primary endpoint, death, or non-fatal recurrent MI at Day 30, according to both STRes at 180 min and treatment strategy. OR_{adj}, odds ratio adjusted for treatment group; the type of fibrinolytic agent used (fibrin-specific vs. non-fibrin-specific); time from symptom onset to fibrinolysis and the location of the infarct; UFH, unfractionated heparin; ENOX, enoxaparin; MI, myocardial infarction.

failed epicardial reperfusion. STRes, however, has been shown in many trials with a variety of fibrinolytic and adjunctive agents to closely correlate not only with infarct-related patency, but perhaps even more importantly with myocardial perfusion and subsequent clinical outcomes. Nor was there direct angiographic evidence of re-occlusion as the mechanism for recurrent MI. We believe that recurrent thrombosis at the site of successful fibrinolysis, though, is the most likely pathological aetiology of subsequent ischaemic events in this population.

Subgroup analyses are always at risk of selection bias. The ECG substudy of ExTRACT-TIMI 25, however, was a prespecified substudy within a larger randomized double-blind, double-dummy clinical trial and was designed to include sequential patients at selected sites to reduce selection bias. While treatment assignment was not specifically randomized within this cohort, there were essentially equal numbers of patients randomized to ENOX and UFH in the ECG substudy with no significant differences in baseline characteristics, index presentation, or concomitant therapy between the two treatment arms. Moreover, all

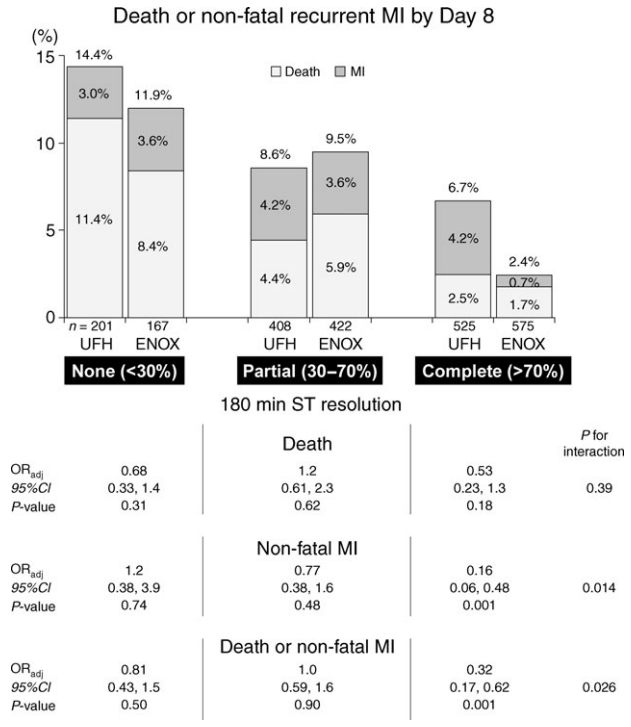

Figure 3 The rates of death or non-fatal recurrent MI at Day 8 or hospital discharge according to both STRes at 180 min and treatment strategy. OR_{adj}, odds ratio adjusted for treatment group; the type of fibrinolytic agent used (fibrin-specific vs. non-fibrin-specific); time from symptom onset to fibrinolysis and the location of the infarct; UFH, unfractionated heparin; ENOX, enoxaparin; MI, myocardial infarction.

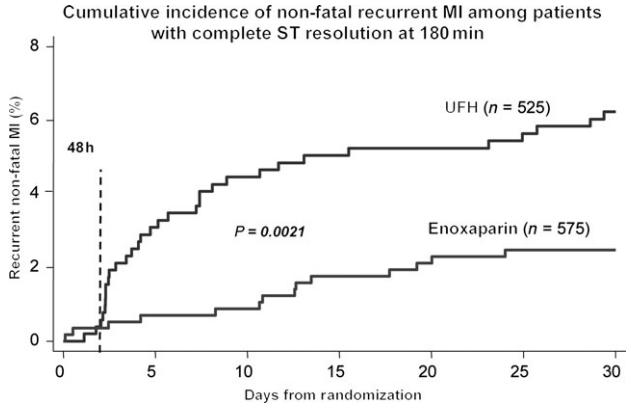

Figure 4 Cumulative incidence of non-fatal recurrent MI among patients who achieve complete STRes at 180 min according to treatment strategy. UFH, unfractionated heparin; ENOX, enoxaparin; MI, myocardial infarction.

analyses investigating the relationship between STRes, treatment, and outcomes were adjusted for potential confounders. However, these results must be interpreted in the context of the population studied, particularly in relation to baseline risk and concomitant treatment.

Clinical implications

The hours and days after fibrinolysis are the highest risk period for acute re-occlusion of the infarct-related artery. Extended and reliable anticoagulation with ENOX significantly reduces the risk of death or recurrent MI[18] and should be strongly considered for all patients without contraindications who receive fibrinolytic therapy. The greatest benefit of ENOX, when given with fibrinolytic therapy, is most likely the result of maintaining arterial patency among patients who have achieved reperfusion as detected by STRes at 180 min. Therefore, STRes should be closely monitored after fibrinolysis. Failure to achieve STRes should prompt immediate referral for revascularization, regardless of the initial treatment. Conversely, patients who achieve reperfusion with fibrinolytic therapy and are treated with intensive medical therapy are at very low risk for recurrent ischaemic complications and may be safely monitored until they are electively referred for catheterization or risk-stratified for medical management.

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References

1. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA 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 (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;**110**:e82–e292.
2. Clemmensen P, Ohman EM, Sevilla DC, Peck S, Wagner NB, Quigley PS, Grande P, Lee KL, Wagner GS. Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. *Am J Cardiol* 1990;**66**:1407–1411.
3. Mauri F, Maggioni AP, Franzosi MG, de Vita C, Santoro E, Santoro L, Giannuzzi P, Tognoni G. A simple electrocardiographic predictor of the outcome of patients with acute myocardial infarction treated with a thrombolytic agent. A Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2)-Derived Analysis. *J Am Coll Cardiol* 1994;**24**:600–607.
4. Doevendans PA, Gorgels AP, van der Zee R, Partouns J, Bar FW, Wellens HJ. Electrocardiographic diagnosis of reperfusion during thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1995;**75**:1206–1210.
5. de Lemos JA. ST-Segment resolution as a marker of epicardial and myocardial reperfusion after thrombolysis: insights from the TIMI 14 and In TIME-II trials. *J Electrocardiol* 2000;**33**(suppl.):67–72.
6. Zeymer U, Schroder R, Tebbe U, Molhoek GP, Wegscheider K, Neuhaus KL. Non-invasive detection of early infarct vessel patency by resolution of ST-segment elevation in patients with thrombolysis for acute myocardial infarction; results of the angiographic substudy of the Hirudin for Improvement of Thrombolysis (HIT)-4 trial. *Eur Heart J* 2001;**22**:769–775.
7. Schroder R, Dissmann R, Bruggemann T, Wegscheider K, Linderer T, Tebbe U, Neuhaus KL. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol* 1994;**24**:384–391.
8. de Lemos JA, Antman EM, Gibson CM, McCabe CH, Giugliano RP, Murphy SA, Coulter SA, Anderson K, Scherer J, Frey MJ, Van Der Wieken R, Van De Werf F, Braunwald E. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction. Observations from the TIMI 14 trial. *Circulation* 2000;**101**:239–243.

9. Schroder K, Wegscheider K, Zeymer U, Tebbe U, Schroder R. 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.
10. Schroder K, Wegscheider K, Zeymer U, Schroder R. Prediction of long-term outcome by the extent of existing ST-segment deviation in a single electrocardiographic lead shortly after thrombolysis in acute myocardial infarction. *Am J Cardiol* 2003;**91**:454–457.
11. de Lemos JA, Antman EM, Giugliano RP, McCabe CH, Murphy SA, Van de Werf F, Gibson CM, Braunwald E. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Thrombolysis In Myocardial Infarction (TIMI) 14 Investigators. *Am J Cardiol* 2000;**85**:299–304.
12. de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. *J Am Coll Cardiol* 2001;**38**: 1283–1294.
13. Schroder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. *Circulation* 2004;**110**:e506–e510.
14. Hudson MP, Granger CB, Topol EJ, Pieper KS, Armstrong PW, Barbash GI, Guerci AD, Vahanian A, Califf RM, Ohman EM. Early reinfarction after fibrinolysis: experience from the global utilization of streptokinase and tissue plasminogen activator (alteplase) for occluded coronary arteries (GUSTO I) and global use of strategies to open occluded coronary arteries (GUSTO III) trials. *Circulation* 2001;**104**:1229–1235.
15. Mueller HS, Forman SA, Menegus MA, Cohen LS, Knatterud GL, Braunwald E, for the TIMI Investigators.Prognostic significance of nonfatal reinfarction during 3-year follow-up: results of the Thrombolysis In Myocardial Infarction (TIMI) phase II clinical trial. *J Am Coll Cardiol* 1995;**26**:900–907.
16. Gibson CM, Karha J, Murphy SA, James D, Morrow DA, Cannon CP, Giugliano RP, Antman EM, Braunwald E. Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the Thrombolysis In Myocardial Infarction trials. *J Am Coll Cardiol* 2003;**42**:7–16.
17. Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, Sigmon KN, Kereiakes D, George B, Stack R. TAMI Study Group. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990;**82**:781–791.
18. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, Lopez-Sendon JL, Guneri S, Jiang F, White HD, Fox KA, Braunwald E. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;**354**: 1477–1488.
19. Simoons M, Krzeminska-Pakula M, Alonso A, Goodman S, Kali A, Loos U, Gosset F, Louer V, Bigonzi F. Improved reperfusion and clinical outcome with enoxaparin as an adjunct to streptokinase thrombolysis in acute myocardial infarction. The AMI-SK study. *Eur Heart J* 2002;**23**:1282–1290.
20. Antman EM, Morrow DA, McCabe CH, Jiang F, White HD, Fox KA, Sharma D, Chew P, Braunwald E. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). *Am Heart J* 2005;**149**:217–226.
21. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: an Intravenous NPA for Treatment of Infarcting Myocardium Early II trial substudy. *Circulation* 2000; **102**:2031–2037.
22. Morrow DA, Antman EM, Parsons L, de Lemos JA, Cannon CP, Giugliano RP, McCabe CH, Barron HV, Braunwald E. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA* 2001;**286**:1356–1359.
23. Antman EM, Louwerenburg HW, Baars HF, Wesdorp JC, Hamer B, Bassand JP, Bigonzi F, Pisapia G, Gibson CM, Heidbuchel H, Braunwald E, Van de Werf F. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis In Myocardial Infarction (TIMI) 23 Trial. *Circulation* 2002; **105**:1642–1649.
24. Armstrong PW, Wagner G, Goodman SG, Van de Werf F, Granger C, Wallentin L, Fu Y. ST segment resolution in ASSENT 3: insights into the role of three different treatment strategies for acute myocardial infarction. *Eur Heart J* 2003;**24**:1515–1522.
25. Antman EM, Van de Werf F. Pharmacoinvasive therapy: the future of treatment for ST-elevation myocardial infarction. *Circulation* 2004; **109**:2480–2486.