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Streptokinase and Enoxaparin as an Alternative to Fibrin-Specific Lytic-Based Regimens

An ExTRACT-TIMI 25 Analysis

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Abstract

Background: Enoxaparin was superior to unfractionated heparin (UFH), regardless of fibrinolytic agent in ST-elevation myocardial infarction (STEMI) patients receiving fibrinolytic therapy in ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction 25) trial.

Objective: This *post hoc* analysis compared outcomes with streptokinase plus enoxaparin to the standard regimen of fibrin-specific lytic (FSL) plus UFH and to the newer combination of FSL plus enoxaparin.

Methods: In ExTRACT-TIMI 25, STEMI patients received either streptokinase or a FSL (alteplase, reteplase or tenecteplase) at the physician's discretion and were randomized to enoxaparin or UFH, stratified by fibrinolytic type. Thirty-day outcomes were adjusted for baseline characteristics, region, in-hospital percutaneous coronary intervention (PCI) and a propensity score for the choice of lytic.

Results: The primary trial endpoint of 30-day death/myocardial infarction (MI) occurred in fewer patients in the streptokinase-enoxaparin cohort (n = 2083) compared with FSL-UFH (n = 8141) [10.2% vs 12.0%, adjusted odds ratio [OR_{adj}] 0.76; 95% CI 0.62, 0.93; p = 0.008]. Major bleeding was significantly increased with streptokinase-enoxaparin compared with FSL-UFH (OR_{adj} 2.74; 95% CI 1.81; 4.14; p < 0.001) but intracranial haemorrhage (ICH) was similar (OR_{adj} 0.90; 95% CI 0.40, 2.01; p = 0.79). Net clinical outcomes, defined as either death/MI/major bleeding or as death/MI/ICH tended to favour streptokinase-enoxaparin compared with FSL-UFH (OR_{adj} 0.88; 95% CI 0.73, 1.06; p = 0.17; and OR_{adj} 0.77; 95% CI 0.63, 0.93; p = 0.008, respectively). Patients receiving FSL-enoxaparin (n = 8142) and streptokinase-enoxaparin therapies experienced similar adjusted rates of the primary endpoint (OR_{adj} 1.08; 95% CI 0.87, 1.32; p = 0.49) and net clinical outcomes.

Conclusions: Our results suggest that fibrinolytic therapy with the combination of streptokinase and the potent anticoagulant agent enoxaparin resulted in similar adjusted outcomes compared with more costly regimens utilizing a FSL.

Background

Globally, fibrinolysis remains the most common method of reperfusion for patients with ST-elevation myocardial infarction (STEMI). Early and sustained coronary patency is the mainstay of reperfusion therapy. The combination of fibrinolytic and anticoagulant agents plays a key role in successful reperfusion. While the use of fibrinolytics has been associated with restoration of coronary flow, adjuvant anticoagulant therapy helps maintain coronary patency.[1]

The fibrin-specific agent alteplase in combination with unfractionated heparin (UFH) has been demonstrated to reduce mortality compared with streptokinase.[2] Subsequently, second-generation fibrin-specific compounds such as reteplase and tenecteplase were shown to be noninferior to alteplase.[3,4] Therefore, the efficacious combination of fibrin-specific lytics (FSLs) and UFH became the standard of therapy for fibrinolysis in STEMI. However, more recent studies have shown that the outcomes of patients treated with streptokinase might be improved with the use of more potent anticoagulant agents, raising the question that this combination might rival or even improve on current standard therapy with FSLs and UFH.[5-8]

The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction 25) trial demonstrated that a strategy of adjunctive anticoagulant therapy with the low molecular weight heparin enoxaparin for the duration of the index hospitalization was superior to the standard 2-day UFH regimen in patients with STEMI treated with fibrinolytic therapy.[9] In this trial, STEMI patients received the FSLs alteplase, tenecteplase or reteplase or the systemic agent streptokinase at the discretion of the treating physician and were randomized to UFH or enoxaparin stratified by type of fibrinolytic. While a previous analysis from this group has demonstrated the superiority of adjuvant anticoagulant therapy with enoxaparin over UFH regardless of the fibrinolytic agents utilized,[5] this novel study compares the efficacy of different pharmacological reperfusion regimens. The current article examines the outcomes of patients treated with the combination of streptokinase plus enoxaparin compared with standard FSLs plus UFH and FSLs plus enoxaparin.

Methods

Patient Population and Study Protocol

The design of the ExTRACT-TIMI 25 trial has been reported previously.[10] In brief, patients 18 years or older presenting within 6 hours of the onset of symptoms of STEMI scheduled to undergo fibrinolysis were treated with a fibrinolytic agent (alteplase, tenecteplase, reteplase, streptokinase) selected by the treating physician and administered according to the package insert for the treatment of STEMI. Patients were to receive aspirin (recommended dose of 150–325 mg in a nonenteric formulation orally or 500 mg intravenously on the first day, and 75–325 mg daily thereafter for at least 30 days). Clopidogrel could be added to aspirin at the treating physician's discretion. Patients were randomly assigned in a 1 : 1 ratio to receive enoxaparin or UFH in a double-blind fashion with a double-dummy design. UFH or matching placebo was given as an intravenous bolus of 60 U/kg (maximum 4000 U) followed by a continuous infusion at 12 U/kg/h (maximum 1000 U/h) initiated within 15 minutes after the bolus and continued for 48 hours The dose of UFH was adjusted to maintain an activated partial thromboplastin time of 1.5–2.0 times the control value. The enoxaparin regimen

was dose-adjusted according to the patient's age and renal function,[10] and continued until hospital discharge or for a maximum of 8 days, whichever came first.

Patients were monitored for clinical outcomes and adverse events during their hospitalization and through day 30 in person or by telephone.

Efficacy and Safety Outcomes

The primary efficacy endpoint of the trial and of the present analysis was the composite of all-cause mortality or nonfatal recurrent myocardial infarction (MI) in the first 30 days after randomization. The primary safety endpoint was TIMI major bleeding at 30 days. The main secondary endpoint was the composite of death from any cause, nonfatal reinfarction or recurrent myocardial ischaemia leading to urgent revascularization in the first 30 days. Net clinical outcomes, including death from any cause, nonfatal reinfarction or nonfatal disabling stroke, were additional secondary endpoints. Two other net clinical outcome endpoints incorporating safety were also prespecified for ExTRACT-TIMI 25 and were evaluated: (i) death, nonfatal recurrent MI or a nonfatal episode of major bleeding; and (ii) death, nonfatal MI or nonfatal intracranial haemorrhage (ICH). Since the duration of treatment with enoxaparin and UFH differed (by design), we also performed a sensitivity analysis at 48 hours.

Statistical Analysis

The population used for this analysis included patients randomized in the trial and treated with the combinations streptokinase-enoxaparin, FSL-UFH and FSL-enoxaparin. The comparison of baseline characteristics between treatment groups was performed using *t* tests or Wilcoxon rank sum tests for normally or non-normally distributed continuous variables, respectively, and chi-square (χ^2) tests were applied for categorical variables. All efficacy comparisons were analyzed according to the intent-to-treat principle. The χ^2 test was used to compare the primary and secondary endpoints between groups. All safety analyses were performed according to the treatment actually received by the patient.

Multivariable analyses for the evaluation of efficacy, safety and composite endpoints stratified by treatment group included components of the TIMI risk score for STEMI (age, weight, anterior location of the MI or new left bundle branch block, previous angina pectoris, history of hypertension or diabetes mellitus, time to fibrinolysis, systolic blood pressure <100 mmHg, heart rate >100 beats/min and Killip class ≥2 upon admission), as well as sex, race, smoking, history of MI, prior coronary-artery bypass graft surgery and baseline serum creatinine.[11] Adjustment was also performed for the different regions of the world as local practice might have influenced outcomes, in-hospital non-urgent percutaneous coronary intervention (PCI), and for a propensity score for streptokinase use. Since the choice of type of fibrinolytic was non-randomized, a propensity score was utilized to adjust for potential selection bias.[12] The propensity score was constructed using the clinical baseline variables considered to be clinically relevant for the choice of fibrinolytic and related to clinical outcomes including demographics, geographical region, traditional cardiovascular risk factors, prior cardiac disease and procedures, time to presentation, infarct location, Killip class at admission, creatinine level and region of enrolment. A p-value of <0.05 was the threshold for nominal significance for all endpoints.

Analyses were performed using Stata/SE version 9.2 (StataCorp LP, College Station, TX, USA).[13]

Results

A total of 18 366 patients of the ExTRACT-TIMI 25 population were included in this analysis (90% of total). Overall, 2083 were treated with the streptokinase-enoxaparin combination while 8141 received the FSL-UFH and 8142 FSL-enoxaparin combinations.

Baseline characteristics stratified by treatment are shown in table I. Patients who received streptokinase were older and more often female. They had higher prevalence of diabetes but

Table I. Population baseline characteristics stratified by treatment[a]

Characteristic	All patients (n = 18 366)	Treatment groups				
		SK-ENOX (n = 2083)	FSL-UFH (n = 8141)	p-value[b]	FSL-ENOX (n = 8142)	p-value[c]
Baseline characteristics						
Median age (y)	59	60	59	<0.001	59	<0.001
Age ≥75 y (%)	12.0	14.3	11.9	0.004	11.6	0.001
Males (%)	76.9	74.8	77.4	0.01	76.9	0.04
White[d] (%)	87.5	84.3	87.9	<0.001	88.0	<0.001
Median weight (kg)	76	76	76	0.52	76	0.80
Hypertension (%)	44.3	42.3	44.1	0.15	45.0	0.03
Hyperlipidaemia (%)	18.3	18.0	18.2	0.81	18.4	0.67
Current smoker (%)	47.9	42.7	48.6	<0.001	48.6	<0.001
Diabetes mellitus (%)	15.0	17.1	14.8	0.01	14.7	0.007
Prior MI (%)	13.4	11.1	13.6	0.003	13.7	0.002
History of PAD (%)	3.2	3.7	3.0	0.08	3.3	0.31
Prior PCI (%)	3.2	3.7	3.1	0.14	3.2	0.28
Prior CABG (%)	1.3	1.8	1.2	0.02	1.2	0.05
Index presentation and prior medications						
Anterior MI (%)	44.7	35.7	46.1	<0.001	45.6	<0.001
Killip class ≥ II[e] (%)	11.2	10.0	11.2	0.12	11.5	0.06
TIMI risk score (>3%)	35.5	36.1	35.3	0.52	35.4	0.57
Median creatinine clearance (mL/min)	82.5	80.2	82.8	0.004	82.9	<0.001
Creatine clearance <30 mL/min (%)	1.1	1.4	1.0	0.10	1.1	0.30
Median time to fibrinolysis (h)	3.1	3.2	3.2	0.44	3.1	0.43
In-hospital treatment						
Aspirin (%)	95.3	94.8	95.7	0.08	94.9	0.85
Clopidogrel (%)	27.8	28.4	28.6	0.89	26.8	0.14
β-Blocker (%)	86.0	86.0	86.0	1.00	85.9	0.95
ACE inhibitors or ARBs (%)	79.9	76.3	79.7	0.001	81.0	<0.001
Statins (%)	68.4	80.7	67.0	<0.001	66.6	<0.001
PCI during index hospitalization (%)	19.0	20.2	19.7	0.64	18.0	0.02
Region of the World				<0.001		<0.001
North America (%)	0.9	0.0	1.0		1.0	
South America (%)	8.1	9.2	7.9		8.1	
Australia, Asia, and Africa (%)	13.3	24.1	11.8		11.9	
Western Europe (%)	24.2	19.9	24.9		24.6	
Eastern Europe (%)	53.6	46.9	54.4		54.5	

a Results are expressed as a percentage of total patients with available information for the baseline characteristic.

b p-Value compares SK-ENOX and FSL-UFH (reference).

c p-Value compares FSL-ENOX and SK-ENOX (reference).

d Race was self-reported.

e Killip class II was defined as the presence of rales and/or jugular venous distension, class III as the presence of pulmonary oedema, and class IV as cardiogenic shock.

ARB = angiotensin receptor antagonist (blocker); **CABG** = coronary artery bypass graft surgery; **ENOX** = enoxaparin; **FSL** = fibrin-specific lytic; **MI** = myocardial infarction; **PAD** = peripheral vascular disease; **PCI** = percutaneous coronary intervention; **SK** = streptokinase; **TIMI** = thrombolysis in myocardial infarction; **UFH** = unfractionated heparin.

smoked less frequently. Patients treated with FSLs had higher incidence of anterior MI. The rates of performing PCI during hospitalization were similar in the streptokinase-enoxaparin and FSL-UFH cohorts, but lower in the FSL-enoxaparin group.

Efficacy Outcomes Stratified by Treatment

The rate of the primary efficacy endpoint (death or nonfatal MI) in the streptokinase-enoxaparin cohort at 30 days was 10.2% versus 12.0% in the FSL-UFH group (adjusted odds ratio [OR_{adj}] 0.76; 95% CI 0.62, 0.93; p = 0.008)

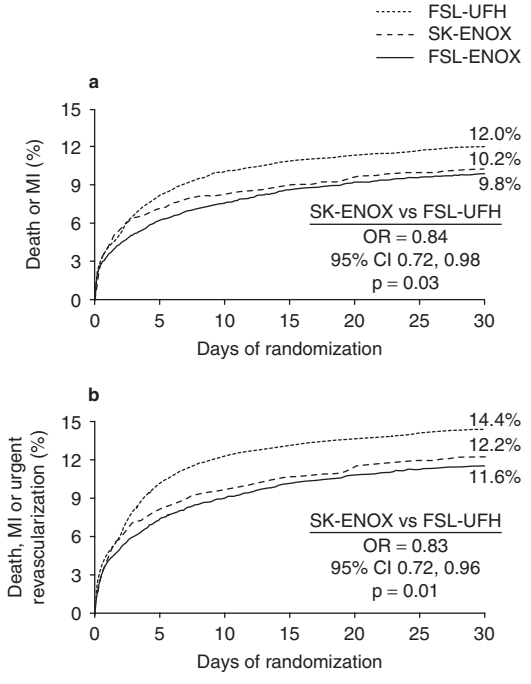

Fig. 1. Cumulative incidence of the primary endpoint (**a**) and secondary endpoint (**b**) in ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction 25). The crude rate of the primary endpoint (death, or nonfatal myocardial infarction [MI]) at 30 days was significantly lower in patients treated with streptokinase and enoxaparin (SK-ENOX) compared with fibrin-specific lytics plus unfractionated heparin (FSL-UFH). Unadjusted outcomes were similar for the SK-ENOX cohort and fibrin-specific lytics plus enoxaparin (FSL-ENOX) group (odds ratio [OR] 0.96; 95% CI 0.82, 1.12; p = 0.60) [**a**]. Crude rates of the main secondary endpoint (death, nonfatal MI or urgent revascularization) were significantly lower in the SK-ENOX compared to FSL-UFH group. Unadjusted outcomes of the secondary endpoint were similar with FSL-ENOX and SK-ENOX (OR 0.94; 95% CI 0.81, 1.09; p = 0.39) [**b**].

[figures 1a and 2; table II]. Lower rates of re-infarction in the streptokinase-enoxaparin cohort accounted for the difference observed in the primary endpoint (2.7% vs 4.6%; OR_{adj} 0.49; 95% CI 0.35, 0.69; p < 0.001) (figure 2 and table II). A regimen of streptokinase-enoxaparin also significantly reduced the prespecified principal secondary endpoint of all-cause mortality, nonfatal MI or urgent revascularization as compared with FSL-UFH (figures 1b and 2; table II). A significant 41% reduction in the OR_{adj} of recurrent myocardial ischaemia leading to urgent target vessel revascularization in the streptokinase-enoxaparin cohort contributed to the improved outcomes of these patients (p = 0.01) [table II]. The rate of rescue PCI with streptokinase-enoxaparin was 2.9%, similar to that observed with FSL-UFH (2.9%; p = 0.92) and with FSL-enoxaparin (2.5%; p = 0.37).

In the FSL-enoxaparin group, the primary endpoint of death or nonfatal MI occurred in 9.8% of patients. The adjusted OR for the primary endpoint indicates similar outcomes to patients in the streptokinase-enoxaparin cohort (OR_{adj} 1.08; 95% CI 0.87, 1.32; p = 0.49) despite a statistically significant higher rate of nonfatal recurrent MI in the FSL-enoxaparin group (OR_{adj} 1.43; 95% CI 1.01, 2.04; p = 0.05) [figures 1a and 3; table II]. Adjusted outcomes for the secondary endpoint were also similar between the FSL-enoxaparin group and the streptokinase-enoxaparin cohort (OR_{adj} 1.08; 95% CI 0.89, 1.31; p = 0.41) [figures 1b and 3; table II].

Safety Outcomes Stratified by Treatment

The rate of TIMI major bleeding (including ICH) at 30 days in patients treated with the combination streptokinase-enoxaparin was 2.4% as compared with 1.2% in those receiving FSL-UFH (OR_{adj} 2.74; 95% CI 1.81, 4.14; p < 0.001) [figure 2; table III]. Major bleeding without ICH was also increased in the streptokinase-enoxaparin cohort (1.9% vs 0.6%; OR_{adj} 4.97; 95% CI 2.94, 8.38; p < 0.001) [table III] as ICH was not different between streptokinase-enoxaparin and FSL-UFH (0.5% and 0.6%, respectively). Minor bleeding was increased in the streptokinase-enoxaparin cohort (table III).

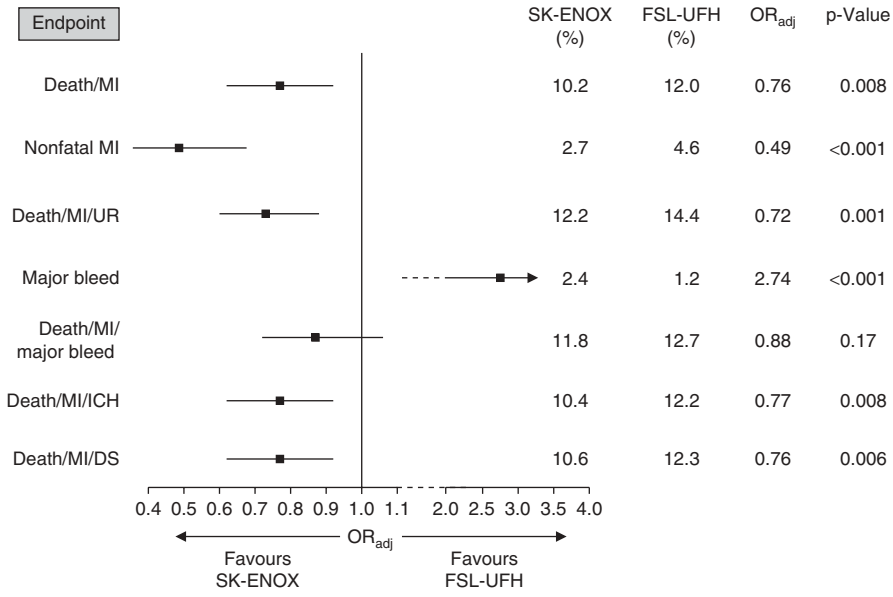

Fig. 2. Adjusted comparison of the primary efficacy, safety and net clinical benefit of streptokinase plus enoxaparin (SK-ENOX) versus fibrin-specific lytics plus unfractionated heparin (FSL-UFH). For each subgroup, the square represents the point estimate of the treatment effect; the horizontal lines represent the 95% confidence intervals. A significant reduction in death or myocardial infarction (MI) [primary endpoint], and death, MI or urgent revascularization (secondary endpoint) due to a reduction in MI was observed in patients treated with the combination of SK-ENOX versus FSL-UFH. Major bleeding was increased in the SK-ENOX cohort, resulting in a similar net clinical outcome defined as the composite of death, nonfatal MI or major bleeding. Meanwhile, the net clinical outcome consisting of death, MI or intracranial haemorrhage favoured SK-ENOX. **DS** = disabling stroke; **ICH** = intracranial haemorrhage; **OR_{adj}** = adjusted odds ratio; **UR** = urgent revascularization.

Major bleeding including ICH occurred in 2.0% of the patients receiving FSL-enoxaparin therapy with a significant reduction compared with streptokinase-enoxaparin (OR_{adj} 0.69; 95% CI 0.48, 1.00; p = 0.05) [figure 3; table III]. The adjusted rates of major bleeding without ICH were also significantly decreased in the FSL-enoxaparin group (OR_{adj} 0.48; 95% CI 0.31, 0.74; p = 0.001). In contrast, the incidence of ICH was higher with FSL-enoxaparin as compared with streptokinase-enoxaparin (0.9% vs 0.5%; OR_{adj} 1.69; 95% CI 0.78, 3.64; p = 0.18), although not statistically significant (table III). Minor bleeding rates were lower in the FSL-enoxaparin group (table III).

Net Clinical Outcomes

The rates of the prespecified net clinical outcome of all-cause mortality, nonfatal reinfarction or disabling stroke (major secondary endpoint) were 10.6% in the streptokinase-enoxaparin cohort and 12.3% in the FSL-UFH group (OR_{adj} 0.76; 95% CI 0.62, 0.92; p = 0.006) [figure 2; table IV]. A second net clinical outcome calculated as death, reinfarction or nonfatal ICH rates was also significantly reduced in the streptokinase-enoxaparin cohort compared with the FSL-UFH group (10.4% vs 12.2%; p = 0.008) [figure 2; table IV]. A third measure of net clinical outcome that included death, recurrent MI or nonfatal major bleeding directionally favoured streptokinase-enoxaparin over FSL-UFH (OR_{adj} 0.88; 95% CI 0.73, 1.06; p = 0.17) [figure 2; table IV], but was not statistically different. The adjusted net clinical outcomes were similar in patients treated with FSL-enoxaparin and streptokinase-enoxaparin (figure 3 and table IV).

Results at 48 Hours

The rate of death or nonfatal MI at 48 hours was 5.6% in the streptokinase-enoxaparin group, which was similar to the rates in the FSL-UFH

(5.1%; OR_{adj} 0.94; 95% CI 0.71, 1.26; p = 0.70) and FSL-enoxaparin (4.4%; OR_{adj} 0.93; 95% CI 0.69, 1.24; p = 0.61) groups. Major bleeding at 48 hours was higher with streptokinase-enoxaparin (1.7%) compared with FSL-UFH (0.9%; OR_{adj} 2.67; 95% CI 1.60, 4.43; p < 0.001), but similar to that observed with FSL-enoxaparin (1.4%; OR_{adj} 0.66; 95% CI 0.42, 1.04; p = 0.076). There were no differences in any of the three adjusted net clinical outcomes at 48 hours between streptokinase-enoxaparin and either FSL-UFH or FSL-enoxaparin.

Discussion

Our findings suggest better 30-day efficacy and similar-to-improved net clinical outcomes with the combination of streptokinase and the anticoagulant enoxaparin administered throughout hospitalization compared with FSLs with standard UFH anticoagulation for 48 hours in STEMI patients undergoing pharmacological reperfusion after adjustment for baseline differences in this nonrandomized comparison. The primary trial endpoint (all-cause mortality or nonfatal recurrent MI) and the principal secondary endpoint (death, nonfatal reinfarction, or myocardial ischaemia leading to urgent revascularization) at 30 days were both significantly reduced by ~25% in patients treated with streptokinase-enoxaparin compared with a standard strategy of FSL-UFH. A 51% lower adjusted rate of reinfarction and 41% decrease in the odds of urgent revascularization accounted for the improved outcomes seen with streptokinase-enoxaparin.

However, major bleeding rates were significantly higher in the streptokinase-enoxaparin cohort compared with FSL-UFH. This elevation was secondary to an increase in non-ICH major bleeding, as haemorrhagic strokes were similar in both groups. These results correlate with findings of contemporary trials demonstrating increased noncerebral bleeding in patients treated with either streptokinase or enoxaparin separately.[2,14,15] Despite the distinctly higher rates of bleeding, the net clinical outcome including death, MI and major bleeding tended to favor streptokinase-enoxaparin.

The improved adjusted efficacy outcomes in patients treated with the combination streptokinase-enoxaparin compared with therapy with FSL-UFH highlights the importance of anticoagulation in STEMI undergoing fibrinolysis. Infusion of accelerated alteplase with UFH has been demonstrated to reduce mortality compared with streptokinase plus UFH by inducing earlier reperfusion and improved coronary flow.[2,16] Despite the observations that streptokinase is less efficacious than FSLs when used with similar

Table II. Efficacy outcomes at 30 days by treatment group[a]

Outcome	Treatment group						
	SK-ENOX (%)	FSL-UFH (%)	OR_{adj} (95% CI)	p-value[b]	FSL-ENOX (%)	OR_{adj} (95% CI)	p-value[c]
Death or nonfatal MI	10.2	12.0	0.76 (0.62, 0.93)	0.008	9.8	1.08 (0.87, 1.32)	0.49
death	7.5	7.3	1.03 (0.80, 1.31)	0.84	6.7	0.93 (0.72, 1.19)	0.55
nonfatal MI	2.7	4.6	0.49 (0.35, 0.69)	<0.001	3.1	1.43 (1.01, 2.04)	0.05
Urgent revascularization	2.2	2.7	0.59 (0.39, 0.89)	0.01	2.1	1.25 (0.82, 1.90)	0.30
Death, nonfatal MI or urgent revascularization	12.2	14.4	0.72 (0.60, 0.87)	0.001	11.6	1.08 (0.89, 1.31)	0.41

a Results are expressed as a percentage of events. Results are adjusted for the components of the TIMI risk score, sex, race, smoking, prior MI or coronary-artery bypass graft surgery, baseline serum creatinine, regions, percutaneous coronary intervention during hospitalization and a propensity score for the use of streptokinase.

b p-Value compares SK-ENOX and FSL-UFH (reference).

c p-Value compares FSL-ENOX and SK-ENOX (reference).

ENOX = enoxaparin; **FSL** = fibrin-specific lytic; **MI** = myocardial infarction; **OR_{adj}** = adjusted odds ratio; **SK** = streptokinase; **TIMI** = thrombolysis in myocardial infarction; **UFH** = unfractionated heparin.

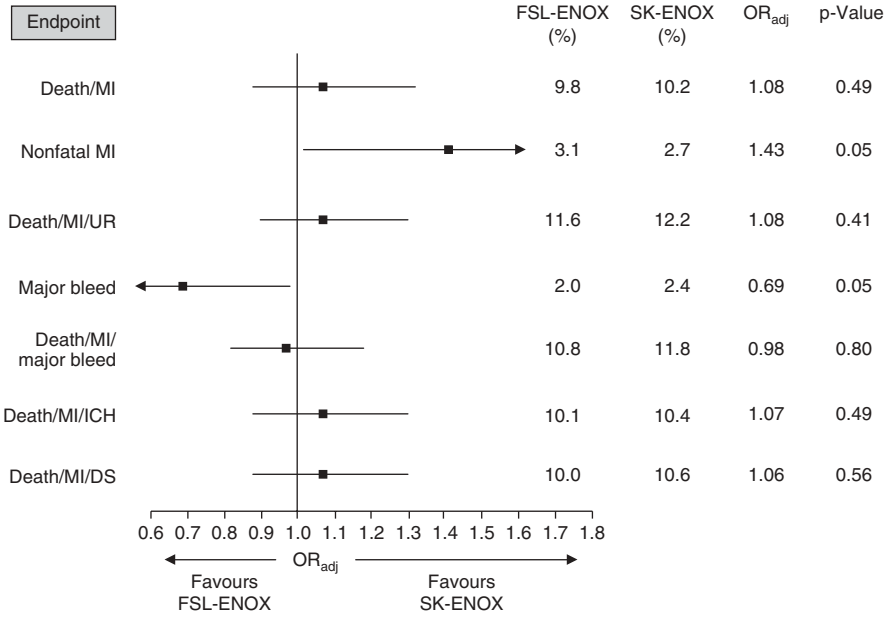

Fig. 3. Adjusted comparison of the primary efficacy, safety and net clinical benefit of fibrin-specific lytics plus enoxaparin (FSL-ENOX) versus streptokinase plus enoxaparin (SK-ENOX). For each subgroup, the square represents the point estimate of the treatment effect; the horizontal lines represent the 95% confidence intervals. Outcomes were largely similar for patients receiving SK-ENOX or FSL-ENOX, except for a 51% reduction in nonfatal myocardial infarction (MI) and a 2.7-fold increase in major bleeding in the SK-ENOX cohort. **DS** = disabling stroke; **ICH** = intracranial haemorrhage. **OR_{adj}** = adjusted odds ratio; **UR** = urgent revascularization.

anticoagulants, we observed that streptokinase plus the more potent anticoagulant enoxaparin was generally more effective than FSLs with UFH. Previous studies had also suggested that improved outcomes in STEMI patients treated with streptokinase were achieved when adjunctive anticoagulation was added to fibrinolytic therapy.[6-8] Although prevention of coronary reocclusion represents the main mechanism of action for anticoagulants as suggested by lower reinfarction and revascularization rates, it is possible that anticoagulant therapy also helps reestablish coronary flow in fibrinolysis.[17] Our results indicate that for every 1000 patients receiving fibrinolytic therapy, the combination of streptokinase-enoxaparin compared with FSL-UFH is expected to prevent 19 episodes of reinfarction while causing 12 additional major bleeds. Because streptokinase still is the most widely used fibrinolytic agent worldwide, the concomitant use of enoxaparin may be expected to introduce a significant improvement in outcomes of patients undergoing fibrinolytic therapy.[18] Also of significant importance are the economic implications of streptokinase-enoxaparin when compared with FSL-UFH. Enoxaparin has been shown to be more cost effective than UFH, while streptokinase is far less expensive than FSLs.[19-21] Therefore, the combination streptokinase-enoxaparin appears to have both efficacy and economic advantages over FSL-UFH. This might be of particular importance in countries with limited economic resources.

Crude rates of the primary and secondary endpoints at 30 days were lower in the FSL-enoxaparin group compared with the streptokinase-enoxaparin cohort, but these differences were not statistically different. The adjusted clinical efficacy also yielded similar results between these two regimens. However, there was a significant increase in major bleeding (specifically noncerebral bleeding) in the streptokinase-enoxaparin cohort. The most likely explanation for the increase in noncerebral bleeding with streptokinase-enoxaparin is the more sustained

Table III. Safety outcomes at 30 days by treatment group[a]

Outcome	Treatment group						
	SK-ENOX (%)	FSL-UFH (%)	OR_{adj} (95% CI)	p-value[b]	FSL-ENOX (%)	OR_{adj} (95% CI)	p-value[c]
Major bleeding (include ICH)[d]	2.4	1.2	2.74 (1.81, 4.14)	<0.001	2.0	0.69 (0.48, 1.00)	0.05
Major bleeding (exclude ICH)[d]	1.9	0.6	4.97 (2.94, 8.38)	<0.001	1.1	0.48 (0.31, 0.74)	0.001
ICH[d]	0.5	0.6	0.90 (0.40, 2.01)	0.79	0.9	1.69 (0.78, 3.64)	0.18
Minor bleeding[d]	3.8	1.5	2.66 (1.91, 3.71)	<0.001	2.2	0.58 (0.43, 0.79)	0.001

a Results are expressed as percent of events. Results are adjusted for the TIMI risk score, sex, race, smoking, prior MI or coronary-artery bypass graft surgery, baseline serum creatinine, region, percutaneous coronary intervention through 30 days, and a propensity score for the use of streptokinase.

b p-Value compares SK-ENOX and FSL-UFH (reference).

c p-Value compares FSL-ENOX and SK-ENOX (reference).

d Safety population.

ENOX = enoxaparin; **FSL** = fibrin-specific lytic; **ICH** = intracranial haemorrhage; **MI** = myocardial infarction; **OR_{adj}** = adjusted odds ratio; **SK** = streptokinase; **TIMI** = thrombolysis in myocardial infarction; **UFH** = unfractionated heparin.

fibrinogen depletion and general coagulopathy that occurs following administration of streptokinase.[22] A much larger, prospectively randomized study would be required to rigorously establish whether, on a background of enoxaparin, the two types of fibrinolytic are equivalent or not with respect to clinical efficacy and net clinical outcomes.

Limitations

Three main limitations of this analysis deserve consideration. First, patients were not randomized to the type of fibrinolytic therapy as the choice of fibrinolytic agent was left to the discretion of the treating physician. Therefore our results, while statistically robust, should be considered hypothesis generating. To adjust for imbalances between groups, we utilized multivariate models, including a large panel of baseline characteristics, region of enrolment, in-hospital therapy and a propensity score, but residual confounding cannot be excluded as we could not account for unmeasured confounders. Second, the relatively smaller number of patients included in the streptokinase-enoxaparin cohort does not allow for a robust comparison between groups, mostly between streptokinase-enoxaparin and

Table IV. Net clinical benefit outcomes at 30 days by treatment group[a]

Outcome at 30 days	Treatment group						
	SK-ENOX (%)	FSL-UFH (%)	OR_{adj} (95% CI)	p-value[b]	FSL-ENOX (%)	OR_{adj} (95% CI)	p-value[c]
Death, nonfatal MI or major bleeding	11.8	12.7	0.88 (0.73, 1.06)	0.17	10.8	0.98 (0.81, 1.18)	0.80
Death, nonfatal MI or ICH	10.4	12.2	0.77 (0.63, 0.93)	0.008	10.1	1.07 (0.88, 1.32)	0.49
Death, nonfatal MI or disabling stroke	10.6	12.3	0.76 (0.62, 0.92)	0.006	10.0	1.06 (0.87, 1.30)	0.56

a Results are expressed as percent of events. Results are adjusted for the TIMI risk score, sex, race, smoking, prior MI or coronary-artery bypass graft surgery, baseline serum creatinine, region, percutaneous coronary intervention through 30 days, and a propensity score for the use of streptokinase.

b p-Value compares SK-ENOX and FSL-UFH (reference).

c p-Value compares FSL-ENOX and SK-ENOX (reference).

ENOX = enoxaparin; **FSL** = fibrin-specific lytic; **ICH** = intracranial haemorrhage; **MI** = myocardial infarction; **OR_{adj}** = adjusted odds ratio; **SK** = streptokinase; **TIMI** = thrombolysis in myocardial infarction; **UFH** = unfractionated heparin.

FSL-enoxaparin. Finally, ExTRACT-TIMI 25 compared two anticoagulant strategies that included different durations of therapy. Whether longer therapy with enoxaparin (compared with UFH) in addition to greater anticoagulant activity played a role in our findings cannot be determined definitively from this analysis; however, analyses at 48 hours were supportive of our main findings.

Conclusions

In this nonrandomized analysis, we have demonstrated that STEMI patients undergoing pharmacological reperfusion with the combination of streptokinase and enoxaparin experience similar-to-improved adjusted net clinical outcomes compared with standard fibrinolysis with FSLs plus UFH. If confirmed in future prospective randomized trials, this finding would be expected to have far-reaching implications for the treatment of STEMI worldwide, as streptokinase remains the most frequently used fibrinolytic agent in the developing world,[18] and the use of streptokinase-enoxaparin represents substantial cost savings compared with a fibrin-specific-based regimen. Outcomes of patients treated with streptokinase-enoxaparin and FSL-enoxaparin were similar and larger studies would be necessary to determine the best fibrinolytic therapy for STEMI patients receiving enoxaparin.

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